Clinical trial results:
An Open-Label, Prospective, Randomized, Controlled, Multi-Center Study Assessing Fixed Dose Versus Concentration Controlled Cellcept® Regimens for Patients Following a Single Organ Renal Transplantation in Combination With Full Dose and Reduced Dose Calcineurin Inhibitors

Summary

EudraCT number	2016-001043-39
Trial protocol	Outside EU/EEA
Global end of trial date	22 September 2007

Results information

Result version number	v1 (current)
This version publication date	01 January 2017
First version publication date	01 January 2017

Trial information

Trial identification

Sponsor protocol code	ML17225

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00087581
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 March 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 September 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study were to compare the efficacy at 12 months post-transplant and the effects on renal function of a regimen of reduced concentration of calcineurin inhibitor (CNI), either cyclosporine or tacrolimus, and monitored mycophenolate mofetil (MMF/CellCept) to a regimen of standard concentrations of CNI and fixed-dose MMF.

Protection of trial subjects:

The investigators have ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study has fully adhered to the principles outlined in "Guideline for Good Clinical Practice" International Council for Harmonisation Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the participant. The investigators have additionally ensured that the basic principles of "Good Clinical Practice" as outlined in the current version of 21 Code of Federal Regulations, subchapter D, part 312, "Responsibilities of Sponsors and Investigators"; part 50, "Protection of Human Subjects"; and part 56, "Institutional Review Boards" were adhered to.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 June 2004
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 720
Worldwide total number of subjects	720
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

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

Adolescents (12-17 years)	2
Adults (18-64 years)	635
From 65 to 84 years	83
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened for study participation starting 1 week prior through 24 hours following the transplantation procedure and were then randomized to one of the three treatment regimens (Group A, B, or C) in a 1:1:1 ratio within 24 hours after transplantation. Randomization was to be balanced within each center.

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	Group A: Monitored MMF + Reduced CNI

Arm description:

Group A received concentration-controlled/monitored MMF with an oral CNI, either cyclosporine or tacrolimus, at reduced blood concentration. The initial dose of MMF was at least 1 gram twice a day (BID) in adults and 600 milligrams per meter-squared (mg/m^2) in pediatrics. Subsequent doses were adjusted to maintain blood mycophenolic acid (MPA) levels greater than or equal to (≥) 1.3 micrograms per milliliter (µg/mL) with cyclosporine or ≥1.9 µg/mL with tacrolimus, not to exceed 4 grams total per day. The selected CNI was dosed to maintain reduced blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 nanograms per milliliter (ng/mL); Days 30–90, 125–165 ng/mL; Days 90 through end of study, 95–145 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 4–6 ng/mL; Days 90 through end of study, 3–5 ng/mL.

Arm type	Experimental
Investigational medicinal product name	Mycophenolate mofetil
Investigational medicinal product code	
Other name	CellCept®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The initial dose was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics. In Groups A and B, subsequent doses were adjusted to maintain blood MPA levels ≥1.3 µg/mL with cyclosporine or ≥1.9 µg/mL with tacrolimus. In Group C, subsequent doses were not to be adjusted, except in the case of unacceptable toxicity.

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Prograf®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tacrolimus was given as 1-mg and 5-mg capsules and dosed to maintain either reduced (Group A) or standard/full (Groups B and C) blood concentrations. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 4–6 ng/mL (reduced), 8–10 ng/mL (full); Days 90 through end of study, 3–5 ng/mL (reduced), 6–8 ng/mL (full).

Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	Neoral®
Pharmaceutical forms	Capsule, soft

Routes of administration	Oral use

Dosage and administration details:

Cyclosporine was given as 100-mg soft gelatin capsules and dosed to maintain either reduced (Group A) or standard/full (Groups B and C) blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 125–165 ng/mL (reduced) or 250–270 ng/mL (full); Days 90 through end of study, 95–145 ng/mL (reduced) or 190–220 ng/mL (full).

Arm title	Group B: Monitored MMF + Full CNI

Arm description:

Group B received concentration-controlled/monitored MMF with an oral CNI, either cyclosporine or tacrolimus, at a standard/full blood concentration. The initial dose of MMF was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics. Subsequent doses were adjusted to maintain blood MPA levels ≥1.3 µg/mL with cyclosporine or ≥1.9 µg/mL with tacrolimus, not to exceed 4 grams total per day. The selected CNI was dosed to maintain standard/full blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 250–270 ng/mL; Days 90 through end of study, 190–220 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 8–10 ng/mL; Days 90 through end of study, 6–8 ng/mL.

Arm type	Experimental
Investigational medicinal product name	Mycophenolate mofetil
Investigational medicinal product code	
Other name	CellCept®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The initial dose was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics. In Groups A and B, subsequent doses were adjusted to maintain blood MPA levels ≥1.3 µg/mL with cyclosporine or ≥1.9 µg/mL with tacrolimus. In Group C, subsequent doses were not to be adjusted, except in the case of unacceptable toxicity.

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Prograf®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tacrolimus was given as 1-mg and 5-mg capsules and dosed to maintain either reduced (Group A) or standard/full (Groups B and C) blood concentrations. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 4–6 ng/mL (reduced), 8–10 ng/mL (full); Days 90 through end of study, 3–5 ng/mL (reduced), 6–8 ng/mL (full).

Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	Neoral®
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Cyclosporine was given as 100-mg soft gelatin capsules and dosed to maintain either reduced (Group A) or standard/full (Groups B and C) blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 125–165 ng/mL (reduced) or 250–270 ng/mL (full); Days 90 through end of study, 95–145 ng/mL (reduced) or 190–220 ng/mL (full).

Arm title	Group C: Fixed MMF + Full CNI

Arm description:

Group C received fixed-dose MMF with an oral CNI, either cyclosporine or tacrolimus, at a standard/full blood concentration. The dose of MMF was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics, not to exceed 4 grams total per day. Subsequent doses were not to be adjusted, except in the case of unacceptable toxicity. The selected CNI was dosed to maintain standard/full blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 250–270 ng/mL; Days 90 through end of study, 190–220 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 8–10 ng/mL; Days 90 through end of study, 6–8 ng/mL.

Arm type	Experimental

Investigational medicinal product name	Mycophenolate mofetil
Investigational medicinal product code	
Other name	CellCept®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The initial dose was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics. In Groups A and B, subsequent doses were adjusted to maintain blood MPA levels ≥1.3 µg/mL with cyclosporine or ≥1.9 µg/mL with tacrolimus. In Group C, subsequent doses were not to be adjusted, except in the case of unacceptable toxicity.

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Prograf®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tacrolimus was given as 1-mg and 5-mg capsules and dosed to maintain either reduced (Group A) or standard/full (Groups B and C) blood concentrations. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 4–6 ng/mL (reduced), 8–10 ng/mL (full); Days 90 through end of study, 3–5 ng/mL (reduced), 6–8 ng/mL (full).

Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	Neoral®
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Cyclosporine was given as 100-mg soft gelatin capsules and dosed to maintain either reduced (Group A) or standard/full (Groups B and C) blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 125–165 ng/mL (reduced) or 250–270 ng/mL (full); Days 90 through end of study, 95–145 ng/mL (reduced) or 190–220 ng/mL (full).

Number of subjects in period 1	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI
Started	243	237	240
Completed Treatment	180	150	153
Completed 24-Month Follow-Up	20	36	41
Completed	20	36	41
Not completed	223	201	199
Consent withdrawn by subject	18	24	15
Death	10	7	8
Refused treatment	3	-	4
Unspecified	144	117	131
Lost to follow-up	21	31	29
Administrative reason/other	24	17	12
Adverse event or intercurrent illness	3	5	-

Baseline characteristics

Reporting groups	
Reporting group title	Group A: Monitored MMF + Reduced CNI

Reporting group description:

Group A received concentration-controlled/monitored MMF with an oral CNI, either cyclosporine or tacrolimus, at reduced blood concentration. The initial dose of MMF was at least 1 gram twice a day (BID) in adults and 600 milligrams per meter-squared (mg/m^2) in pediatrics. Subsequent doses were adjusted to maintain blood mycophenolic acid (MPA) levels greater than or equal to (≥) 1.3 micrograms per milliliter (µg/mL) with cyclosporine or ≥1.9 µg/mL with tacrolimus, not to exceed 4 grams total per day. The selected CNI was dosed to maintain reduced blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 nanograms per milliliter (ng/mL); Days 30–90, 125–165 ng/mL; Days 90 through end of study, 95–145 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 4–6 ng/mL; Days 90 through end of study, 3–5 ng/mL.

Reporting group title	Group B: Monitored MMF + Full CNI

Reporting group description:

Group B received concentration-controlled/monitored MMF with an oral CNI, either cyclosporine or tacrolimus, at a standard/full blood concentration. The initial dose of MMF was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics. Subsequent doses were adjusted to maintain blood MPA levels ≥1.3 µg/mL with cyclosporine or ≥1.9 µg/mL with tacrolimus, not to exceed 4 grams total per day. The selected CNI was dosed to maintain standard/full blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 250–270 ng/mL; Days 90 through end of study, 190–220 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 8–10 ng/mL; Days 90 through end of study, 6–8 ng/mL.

Reporting group title	Group C: Fixed MMF + Full CNI

Reporting group description:

Group C received fixed-dose MMF with an oral CNI, either cyclosporine or tacrolimus, at a standard/full blood concentration. The dose of MMF was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics, not to exceed 4 grams total per day. Subsequent doses were not to be adjusted, except in the case of unacceptable toxicity. The selected CNI was dosed to maintain standard/full blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 250–270 ng/mL; Days 90 through end of study, 190–220 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 8–10 ng/mL; Days 90 through end of study, 6–8 ng/mL.

Reporting group values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI
Number of subjects	243	237	240
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	48.3	48.8	49.6
standard deviation	± 12.8	± 13.55	± 13.2
Gender categorical			
Units: Subjects			
Female	80	78	77
Male	163	159	163

Reporting group values	Total		
Number of subjects	720		
Age categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	235		
Male	485		

End points

End points reporting groups

Reporting group title	Group A: Monitored MMF + Reduced CNI

Reporting group description:

Group A received concentration-controlled/monitored MMF with an oral CNI, either cyclosporine or tacrolimus, at reduced blood concentration. The initial dose of MMF was at least 1 gram twice a day (BID) in adults and 600 milligrams per meter-squared (mg/m^2) in pediatrics. Subsequent doses were adjusted to maintain blood mycophenolic acid (MPA) levels greater than or equal to (≥) 1.3 micrograms per milliliter (µg/mL) with cyclosporine or ≥1.9 µg/mL with tacrolimus, not to exceed 4 grams total per day. The selected CNI was dosed to maintain reduced blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 nanograms per milliliter (ng/mL); Days 30–90, 125–165 ng/mL; Days 90 through end of study, 95–145 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 4–6 ng/mL; Days 90 through end of study, 3–5 ng/mL.

Reporting group title	Group B: Monitored MMF + Full CNI

Reporting group description:

Group B received concentration-controlled/monitored MMF with an oral CNI, either cyclosporine or tacrolimus, at a standard/full blood concentration. The initial dose of MMF was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics. Subsequent doses were adjusted to maintain blood MPA levels ≥1.3 µg/mL with cyclosporine or ≥1.9 µg/mL with tacrolimus, not to exceed 4 grams total per day. The selected CNI was dosed to maintain standard/full blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 250–270 ng/mL; Days 90 through end of study, 190–220 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 8–10 ng/mL; Days 90 through end of study, 6–8 ng/mL.

Reporting group title	Group C: Fixed MMF + Full CNI

Reporting group description:

Group C received fixed-dose MMF with an oral CNI, either cyclosporine or tacrolimus, at a standard/full blood concentration. The dose of MMF was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics, not to exceed 4 grams total per day. Subsequent doses were not to be adjusted, except in the case of unacceptable toxicity. The selected CNI was dosed to maintain standard/full blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 250–270 ng/mL; Days 90 through end of study, 190–220 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 8–10 ng/mL; Days 90 through end of study, 6–8 ng/mL.

Primary: Percentage of Participants with Treatment Failure During 12 Months Post-Transplantation

End point title	Percentage of Participants with Treatment Failure During 12 Months Post-Transplantation

End point description:

Treatment failure was defined as any one event of biopsy-proven acute rejection (BPAR), graft loss (characterized as initiation of chronic dialysis, transplant nephrectomy, re-transplantation, or death with functioning graft), death, or loss to follow-up. BPAR was defined as oral temperature greater than (>) 100 degrees Fahrenheit, graft swelling/tenderness, serum creatinine rise >0.3 milligrams per deciliter (mg/dL), rising blood pressure, oliguria, reduced renal flow, and ultrasound findings consistent with rejection, in addition to histologic findings of tubular invasion obtained from renal allograft biopsy. The percentage of participants who experienced treatment failure at any time during the first 12 months post-transplantation was reported. The 95 percent (%) confidence interval (CI) was calculated using the exact method. Intent-to-Treat (ITT) Population: All participants randomized into the study.

End point type	Primary

End point timeframe:

Month 12

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: percentage of participants				
number (confidence interval 95%)	22.6 (17.5 to 28.4)	28.3 (22.6 to 34.5)	27.9 (22.3 to 34.1)	

Statistical analyses

Statistical analysis title	Difference at 12 Months (Group A vs Group C)
Statistical analysis description:	
Analysis stratified by CNI type. Non-inferiority was determined on the basis of the upper limit of the 90% CI. The regimen administered to Group A was considered statistically non-inferior to the regimen in Group C if the upper limit of the CI was less than (<) 10.	
Comparison groups	Group C: Fixed MMF + Full CNI v Group A: Monitored MMF + Reduced CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1825
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-5.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.8
upper limit	1.3

Primary: Percent Change from Baseline in Calculated Glomerular Filtration Rate (GFR) at 12 Months Post-Transplantation

End point title	Percent Change from Baseline in Calculated Glomerular Filtration Rate (GFR) at 12 Months Post-Transplantation
End point description:	
GFR was calculated using the Nankivell equation: [6.7 divided by (÷) serum creatinine in millimoles per liter (mmol/L)] plus (+) [body weight in kilograms ÷ 4] + [serum urea in mmol/L ÷ 2] + [100 ÷ height in meters] + a value of 35 for males or 25 for females. The percent change in GFR from Baseline to Month 12 was calculated as [GFR at Month 12 minus (–) GFR at Baseline] divided by GFR at Baseline, multiplied by 100. The result was averaged among all participants. ITT Population.	
End point type	Primary
End point timeframe:	
Baseline to Month 12	

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: percent change				
arithmetic mean (standard deviation)	12.3 (± 47.43)	5.4 (± 30.65)	8.2 (± 35.88)	

Statistical analyses

Statistical analysis title	Difference at 12 Months (Group A vs Group C)
Statistical analysis description: Analysis performed with terms for treatment and CNI type as factors.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3469
Method	ANOVA
Parameter estimate	Difference in least squares means
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.46
upper limit	12.66

Statistical analysis title	Difference at 12 Months (Group A vs Group B)
Statistical analysis description: Analysis performed with terms for treatment and CNI type as factors.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1077
Method	ANOVA
Parameter estimate	Difference in least squares means
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	14.95

Secondary: Percentage of Participants with Treatment Failure During 6 and 20-24 Months Post-Transplantation

End point title	Percentage of Participants with Treatment Failure During 6 and 20-24 Months Post-Transplantation

End point description:

Treatment failure was defined as any one event of BPAR, graft loss (characterized as initiation of chronic dialysis, transplant nephrectomy, re-transplantation, or death with functioning graft), death, or loss to follow-up. BPAR was defined as oral temperature >100 degrees Fahrenheit, graft swelling/tenderness, serum creatinine rise >0.3 mg/dL, rising blood pressure, oliguria, reduced renal flow, and ultrasound findings consistent with rejection, in addition to histologic findings of tubular invasion obtained from renal allograft biopsy. The percentage of participants who experienced treatment failure at any time during the first 6 and 20-24 months post-transplantation was reported. ITT Population.

End point type	Secondary

End point timeframe:

Months 6, 20-24

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: percentage of participants				
number (not applicable)				
6 Months	18.9	21.5	21.7	
20-24 Months	30.5	40.5	35	

Statistical analyses

Statistical analysis title	Difference at 6 Months (Group A vs Group C)

Statistical analysis description:

Analysis stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.4599
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-2.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.8
upper limit	3.3

Notes:

[1] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 6 Months (Group B vs Group C)

Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.9362
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-0.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.3
upper limit	6.1

Notes:

[2] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 6 Months (Group A vs Group B)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.4961
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-2.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.6
upper limit	3.4

Notes:

[3] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group C)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.2895
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-4.5

Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.6
upper limit	2.5

Notes:

[4] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 20-24 Months (Group B vs Group C)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.237
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	5.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.8
upper limit	12.8

Notes:

[5] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group B)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0225
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-10.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-17.2
upper limit	-2.9

Notes:

[6] - Mantel-Haenszel general association test was performed.

Secondary: Percentage of Participants with BPAR During 6, 12, and 20-24 Months Post-Transplantation

End point title	Percentage of Participants with BPAR During 6, 12, and 20-24

	Months Post-Transplantation

End point description:

BPAR was defined as oral temperature >100 degrees Fahrenheit, graft swelling/tenderness, serum creatinine rise >0.3 mg/dL, rising blood pressure, oliguria, reduced renal flow, and ultrasound findings consistent with rejection, in addition to histologic findings of tubular invasion obtained from renal allograft biopsy. The percentage of participants with at least one BPAR episode during the first 6, 12, and 20-24 months post-transplantation was reported. ITT Population.

End point type	Secondary

End point timeframe:

Months 6, 12, 20-24

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: percentage of participants				
number (not applicable)				
6 Months	6.2	7.6	7.5	
12 Months	6.2	9.7	9.6	
20-24 Months	6.6	11	10	

Statistical analyses

Statistical analysis title	Difference at 6 Months (Group A vs Group C)

Statistical analysis description:

Analysis stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.5675
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	3.2

Notes:

[7] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 6 Months (Group B vs Group C)

Statistical analysis description:

Analysis stratified by CNI type.

Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF +

	Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.9929
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	4.8

Notes:

[8] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 6 Months (Group A vs Group B)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.5616
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	3.1

Notes:

[9] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 12 Months (Group A vs Group C)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.1663
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-3.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	1.4

Notes:

[10] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 12 Months (Group B vs Group C)
Statistical analysis description: Analysis stratified by CNI type.	
Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.9938
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	5.4

Notes:

[11] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 12 Months (Group A vs Group B)
Statistical analysis description: Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.1714
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	1.3

Notes:

[12] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group C)

Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.1754
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	1.5

Notes:

[13] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 20-24 Months (Group B vs Group C)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.7782
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	6.5

Notes:

[14] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group B)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.105
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-4.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.4
upper limit	0.7

Notes:

[15] - Mantel-Haenszel general association test was performed.

Secondary: Percentage of Participants by Number of BPAR Episodes During 6, 12, and 20-24 Months Post-Transplantation

End point title	Percentage of Participants by Number of BPAR Episodes During 6, 12, and 20-24 Months Post-Transplantation

End point description:

BPAR was defined as oral temperature >100 degrees Fahrenheit, graft swelling/tenderness, serum creatinine rise >0.3 mg/dL, rising blood pressure, oliguria, reduced renal flow, and ultrasound findings consistent with rejection, in addition to histologic findings of tubular invasion obtained from renal allograft biopsy. The percentage of participants with 0, 1, 2, or 3 BPAR episodes during the first 6, 12, and 20-20-24 months post-transplantation was reported. ITT Population.

End point type	Secondary

End point timeframe:

Months 6, 12, 20-24

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: percentage of participants				
number (not applicable)				
6 Months, 0 Episodes	93.8	92.4	92.5	
6 Months, 1 Episode	5.8	6.8	7.1	
6 Months, 2 Episodes	0.4	0.8	0.4	
12 Months, 0 Episodes	93.8	90.3	90.4	
12 Months, 1 Episode	5.3	8.9	8.8	
12 Months, 2 Episodes	0	0.8	0.8	
12 Months, 3 Episodes	0.8	0	0	
20-24 Months, 0 Episodes	93.4	89	90	
20-24 Months, 1 Episode	5.8	9.7	8.3	
20-24 Months, 2 Episodes	0	0.8	1.3	
20-24 Months, 3 Episodes	0.8	0.4	0.4	

Statistical analyses

Statistical analysis title	Difference at 6 Months (Group A vs Group C)

Statistical analysis description:

Analysis stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI

Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.8419
Method	Cochran-Mantel-Haenszel

Notes:

[16] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 6 Months (Group B vs Group C)

Statistical analysis description:

Analysis stratified by CNI type.

Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.8157
Method	Cochran-Mantel-Haenszel

Notes:

[17] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 6 Months (Group A vs Group B)

Statistical analysis description:

Analysis stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.7703
Method	Cochran-Mantel-Haenszel

Notes:

[18] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Overall Treatment Effect at 6 Months

Statistical analysis description:

Analysis performed with terms for treatment and CNI type as factors.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	720
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.5921
Method	Poisson regression model

Notes:

[19] - Generalized linear modeling assuming Poisson distribution was performed.

Statistical analysis title	Difference at 12 Months (Group A vs Group C)

Statistical analysis description:

Analysis stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.105
Method	Cochran-Mantel-Haenszel

Notes:

[20] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 12 Months (Group B vs Group C)

Statistical analysis description:

Analysis stratified by CNI type.

Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.9989
Method	Cochran-Mantel-Haenszel

Notes:

[21] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 12 Months (Group A vs Group B)

Statistical analysis description:

Analysis stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.1013
Method	Cochran-Mantel-Haenszel

Notes:

[22] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Overall Treatment Effect at 12 Months

Statistical analysis description:

Analysis performed with terms for treatment and CNI type as factors.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	720
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.35
Method	Poisson regression model

Notes:

[23] - Generalized linear modeling assuming Poisson distribution was performed.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group C)

Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.2008
Method	Cochran-Mantel-Haenszel

Notes:

[24] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 20-24 Months (Group B vs Group C)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.9437
Method	Cochran-Mantel-Haenszel

Notes:

[25] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group B)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	= 0.1848
Method	Cochran-Mantel-Haenszel

Notes:

[26] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Overall Treatment Effect at 20-24 Months
Statistical analysis description:	
Analysis performed with terms for treatment and CNI type as factors.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	720
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.1912
Method	Poisson regression model

Notes:

[27] - Generalized linear modeling assuming Poisson distribution was performed.

Secondary: Percentage of Participants Treated for Acute Rejection (AR) During 6, 12, and 20-24 Months Post-Transplantation

End point title	Percentage of Participants Treated for Acute Rejection (AR) During 6, 12, and 20-24 Months Post-Transplantation

End point description:

AR was defined as oral temperature >100 degrees Fahrenheit, graft swelling/tenderness, serum creatinine rise >0.3 mg/dL, rising blood pressure, oliguria, reduced renal flow, and ultrasound findings consistent with rejection, but without confirmation from biopsy. The percentage of participants who received treatment for AR during the first 6, 12, and 20-24 months post-transplantation was reported. ITT Population. (99999 = endpoint not analyzed because no data were available from any participants.)

End point type	Secondary

End point timeframe:

Months 6, 12, 20-24

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: percentage of participants				
number (not applicable)				
6 Months	99999	99999	99999	
12 Months	99999	99999	99999	
20-24 Months	99999	99999	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced Graft Loss During 6, 12, and 20-24 Months Post-Transplantation

End point title	Percentage of Participants Who Experienced Graft Loss During 6, 12, and 20-24 Months Post-Transplantation

End point description:

Graft loss was characterized as initiation of chronic dialysis, transplant nephrectomy, re-transplantation, or death with functioning graft. The percentage of participants who experienced graft loss at any time during the first 6, 12, and 20-24 months post-transplantation was reported. ITT Population.

End point type	Secondary

End point timeframe:

Months 6, 12, 20-24

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: percentage of participants				
number (not applicable)				
6 Months	3.7	2.1	2.5	
12 Months	4.9	3.4	5	
20-24 Months	6.2	5.9	5.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died During 6, 12, and 20-24 Months Post-Transplantation

End point title	Percentage of Participants Who Died During 6, 12, and 20-24 Months Post-Transplantation

End point description:

The percentage of participants who died from any cause during the first 6, 12, and 20-24 months post-transplantation was reported. ITT Population.

End point type	Secondary

End point timeframe:

Months 6, 12, 20-24

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: percentage of participants				
number (not applicable)				
6 Months	2.1	0.4	1.3	
12 Months	3.3	1.7	3.3	
20-24 Months	4.5	3	3.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Discontinued Treatment with MMF or Were Lost to Follow-Up During 6, 12, and 20-24 Months Post-Transplantation

End point title	Percentage of Participants Who Discontinued Treatment with MMF or Were Lost to Follow-Up During 6, 12, and 20-24 Months Post-Transplantation

End point description:

The collective percentage of participants who discontinued treatment with MMF and/or were lost to follow-up during the first 6, 12, and 20-24 months post-transplantation was reported. ITT Population.

End point type	Secondary

End point timeframe:

Months 6, 12, 20-24

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: percentage of participants				
number (not applicable)				
6 Months	19.3	28.3	30	
12 Months	23.5	36.3	36.3	
20-24 Months	23.9	36.7	36.7	

Statistical analyses

Statistical analysis title	Difference at 6 Months (Group A vs Group C)

Statistical analysis description:

Analysis stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	= 0.0068
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.3
upper limit	-3

Notes:

[28] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 6 Months (Group B vs Group C)

Statistical analysis description:

Analysis stratified by CNI type.

Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI

Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.6777
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	6.4

Notes:

[29] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 6 Months (Group A vs Group B)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.0206
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.5
upper limit	-1.3

Notes:

[30] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 12 Months (Group A vs Group C)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.0022
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-12.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.9
upper limit	-4.7

Notes:

[31] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 12 Months (Group B vs Group C)
Statistical analysis description: Analysis stratified by CNI type.	
Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.98
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	8.7

Notes:

[32] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 12 Months (Group A vs Group B)
Statistical analysis description: Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.0018
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.9
upper limit	-4.7

Notes:

[33] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group C)

Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.0023
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.9
upper limit	-4.7

Notes:

[34] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 20-24 Months (Group B vs Group C)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.977
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	8.7

Notes:

[35] - Mantel-Haenszel general association test was performed.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group B)
Statistical analysis description:	
Analysis stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	= 0.0018
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-12.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-21
upper limit	-4.7

Notes:

[36] - Mantel-Haenszel general association test was performed.

Secondary: Time to First BPAR Episode During 6, 12, and 20-24 Months Post-Transplantation

End point title	Time to First BPAR Episode During 6, 12, and 20-24 Months Post-Transplantation

End point description:

Time to first BPAR episode was defined as the time from transplantation to the first documented BPAR episode. BPAR was defined as oral temperature >100 degrees Fahrenheit, graft swelling/tenderness, serum creatinine rise >0.3 mg/dL, rising blood pressure, oliguria, reduced renal flow, and ultrasound findings consistent with rejection, in addition to histologic findings of tubular invasion obtained from renal allograft biopsy. Median time to first BPAR episode during the first 6, 12, and 20-24 months post-transplantation was estimated by Kaplan-Meier analysis and expressed in days. ITT Population. Values entered as "99999" indicate that data could not be reported due to a high number of censored observations.

End point type	Secondary

End point timeframe:

Months 6, 12, 20-24

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: days				
median (confidence interval 95%)				
6 Months	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	
12 Months	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	
20-24 Months	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

Statistical analysis title	Difference at 6 Months (Group A vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI

Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.5395
Method	Logrank

Notes:

[37] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 6 Months (Group B vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[38]
P-value	= 0.961
Method	Logrank

Notes:

[38] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 6 Months (Group A vs Group B)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.5659
Method	Logrank

Notes:

[39] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 12 Months (Group A vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	= 0.159
Method	Logrank

Notes:

[40] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 12 Months (Group B vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.9595
Method	Logrank

Notes:

[41] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 12 Months (Group A vs Group B)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[42]
P-value	= 0.1724
Method	Logrank

Notes:

[42] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0.1686
Method	Logrank

Notes:

[43] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 20-24 Months (Group B vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[44]
P-value	= 0.8016
Method	Logrank

Notes:

[44] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group B)

Statistical analysis description:	
Analysis comparing survival curves for treatment groups, stratified by CNI type.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	= 0.0958
Method	Logrank

Notes:

[45] - Survival curves were plotted and compared by the log rank test.

Secondary: Time to Treatment Failure During 6, 12, and 20-24 Months Post-Transplantation

End point title	Time to Treatment Failure During 6, 12, and 20-24 Months Post-Transplantation

End point description:

Time to treatment failure was defined as time from transplantation to the first documented treatment failure event. Treatment failure was defined as any one event of BPAR, graft loss (characterized as initiation of chronic dialysis, transplant nephrectomy, re-transplantation, or death with functioning graft), death, or loss to follow-up. BPAR was defined as oral temperature >100 degrees Fahrenheit, graft swelling/tenderness, serum creatinine rise >0.3 mg/dL, rising blood pressure, oliguria, reduced renal flow, and ultrasound findings consistent with rejection, in addition to histologic findings of tubular invasion obtained from renal allograft biopsy. Median time to treatment failure during the first 6, 12, and 20-24 months post-transplantation was estimated by Kaplan-Meier analysis and expressed in days. ITT Population. Values entered as "99999" indicate that data could not be reported due to a high number of censored observations.

End point type	Secondary

End point timeframe:

Months 6, 12, 20-24

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: days				
median (confidence interval 95%)				
6 Months	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	
12 Months	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	
20-24 Months	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

Statistical analysis title	Difference at 6 Months (Group A vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF

	+ Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[46]
P-value	= 0.4827
Method	Logrank

Notes:

[46] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 6 Months (Group B vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 0.8816
Method	Logrank

Notes:

[47] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 6 Months (Group A vs Group B)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[48]
P-value	= 0.5702
Method	Logrank

Notes:

[48] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 12 Months (Group A vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	= 0.2243
Method	Logrank

Notes:

[49] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 12 Months (Group B vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[50]
P-value	= 0.9133
Method	Logrank

Notes:

[50] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 12 Months (Group A vs Group B)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	= 0.1835
Method	Logrank

Notes:

[51] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other[52]
P-value	= 0.3022
Method	Logrank

Notes:

[52] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 20-24 Months (Group B vs Group C)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0.3349
Method	Logrank

Notes:

[53] - Survival curves were plotted and compared by the log rank test.

Statistical analysis title	Difference at 20-24 Months (Group A vs Group B)

Statistical analysis description:

Analysis comparing survival curves for treatment groups, stratified by CNI type.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	other[54]
P-value	= 0.0397
Method	Logrank

Notes:

[54] - Survival curves were plotted and compared by the log rank test.

Secondary: Percent Change from Baseline in Calculated GFR at 3, 6, and 20-24 Months Post-Transplantation

End point title	Percent Change from Baseline in Calculated GFR at 3, 6, and 20-24 Months Post-Transplantation

End point description:

GFR was calculated using the Nankivell equation: [6.7 ÷ serum creatinine in mmol/L] + [body weight in kilograms ÷ 4] + [serum urea in mmol/L ÷ 2] + [100 ÷ height in meters] + a value of 35 for males or 25 for females. The percent change in GFR from Baseline to Months 3, 6, and 20-24 was calculated as [GFR at Month 3, 6, or 20-24 – GFR at Baseline] divided by GFR at Baseline, multiplied by 100. The result was averaged among all participants. ITT Population

End point type	Secondary

End point timeframe:

Baseline to Months 3, 6, 20-24

End point values	Group A: Monitored MMF + Reduced CNI	Group B: Monitored MMF + Full CNI	Group C: Fixed MMF + Full CNI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	243	237	240	
Units: percent change				
arithmetic mean (standard deviation)				
3 Months	10.5 (± 43.63)	3.8 (± 22.75)	8.4 (± 26.67)	
6 Months	11.5 (± 45.91)	5.5 (± 24.45)	8.6 (± 27.26)	
20-24 Months	8.3 (± 47.27)	0.6 (± 31.79)	4.6 (± 37.89)	

Statistical analyses

Statistical analysis title	Difference at 3 Months (Group A vs Group C)

Statistical analysis description:

Analysis performed with terms for treatment and CNI type as factors.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI

Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5783
Method	ANOVA
Parameter estimate	Difference in least squares means
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.15
upper limit	9.21

Statistical analysis title	Difference at 3 Months (Group A vs Groups B+C)
Statistical analysis description:	
Analysis performed with terms for treatment and CNI type as factors.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	720
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1369
Method	ANOVA
Parameter estimate	Difference in least squares means
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	9.74

Statistical analysis title	Difference at 6 Months (Group A vs Group C)
Statistical analysis description:	
Analysis performed with terms for treatment and CNI type as factors.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4797
Method	ANOVA
Parameter estimate	Difference in least squares means
Point estimate	2.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	10.82

Statistical analysis title	Difference at 6 Months (Group A vs Group B+C)
Statistical analysis description:	
Analysis performed with terms for treatment and CNI type as factors.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	720
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1836
Method	ANOVA
Parameter estimate	Difference in least squares means
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.05
upper limit	10.36

Statistical analysis title	Difference at 20-24 Months (Group A vs Group C)
Statistical analysis description:	
Analysis performed with terms for treatment and CNI type as factors.	
Comparison groups	Group A: Monitored MMF + Reduced CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4533
Method	ANOVA
Parameter estimate	Difference in least squares means
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.92
upper limit	13.24

Statistical analysis title	Difference at 20-24 Months (Group A vs Group B+C)

Statistical analysis description:

Analysis performed with terms for treatment and CNI type as factors.

Comparison groups	Group A: Monitored MMF + Reduced CNI v Group B: Monitored MMF + Full CNI v Group C: Fixed MMF + Full CNI
Number of subjects included in analysis	720
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1491
Method	ANOVA
Parameter estimate	Difference in least squares means
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	13.27

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline until up to 30 days after the last dose (maximum up to 24 months)

Adverse event reporting additional description:

Safety Population: All participants who received at least one dose of study medication and had at least one post-baseline safety assessment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	Group A: Monitored MMF + Reduced CNI

Reporting group description:

Group A received concentration-controlled/monitored MMF with an oral CNI, either cyclosporine or tacrolimus, at reduced blood concentration. The initial dose of MMF was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics. Subsequent doses were adjusted to maintain blood MPA levels ≥1.3 µg/mL with cyclosporine or ≥1.9 µg/mL with tacrolimus, not to exceed 4 grams total per day. The selected CNI was dosed to maintain reduced blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 125–165 ng/mL; Days 90 through end of study, 95–145 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 4–6 ng/mL; Days 90 through end of study, 3–5 ng/mL.

Reporting group title	Group C: Fixed MMF + Full CNI

Reporting group description:

Group C received fixed-dose MMF with an oral CNI, either cyclosporine or tacrolimus, at a standard/full blood concentration. The dose of MMF was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics, not to exceed 4 grams total per day. Subsequent doses were not to be adjusted, except in the case of unacceptable toxicity. The selected CNI was dosed to maintain standard/full blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 250–270 ng/mL; Days 90 through end of study, 190–220 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 8–10 ng/mL; Days 90 through end of study, 6–8 ng/mL.

Reporting group title	Group B: Monitored MMF + Full CNI

Reporting group description:

Group B received concentration-controlled/monitored MMF with an oral CNI, either cyclosporine or tacrolimus, at a standard/full blood concentration. The initial dose of MMF was at least 1 gram BID in adults and 600 mg/m^2 in pediatrics. Subsequent doses were adjusted to maintain blood MPA levels ≥1.3 µg/mL with cyclosporine or ≥1.9 µg/mL with tacrolimus, not to exceed 4 grams total per day. The selected CNI was dosed to maintain standard/full blood concentrations. Cyclosporine target concentrations were as follows: Days 1–30, 250–325 ng/mL; Days 30–90, 250–270 ng/mL; Days 90 through end of study, 190–220 ng/mL. Tacrolimus target concentrations were as follows: Days 1–30, 8–12 ng/mL; Days 30–90, 8–10 ng/mL; Days 90 through end of study, 6–8 ng/mL.

Serious adverse events	Group A: Monitored MMF + Reduced CNI	Group C: Fixed MMF + Full CNI	Group B: Monitored MMF + Full CNI
Total subjects affected by serious adverse events			
subjects affected / exposed	116 / 238 (48.74%)	141 / 238 (59.24%)	118 / 233 (50.64%)
number of deaths (all causes)	11	9	7
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			

subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (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
Multiple myeloma			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Bladder cancer			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Ovarian epithelial cancer			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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 of lung			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Diffuse large B-cell lymphoma stage III			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Lung cancer metastatic			

subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Lung squamous cell carcinoma stage unspecified			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Prostate cancer			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Vascular disorders			
Lymphocele			
subjects affected / exposed	4 / 238 (1.68%)	4 / 238 (1.68%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	3 / 238 (1.26%)	1 / 238 (0.42%)	4 / 233 (1.72%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 238 (0.00%)	3 / 238 (1.26%)	4 / 233 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	3 / 233 (1.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	2 / 238 (0.84%)	1 / 238 (0.42%)	0 / 233 (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
Thrombosis			

subjects affected / exposed	1 / 238 (0.42%)	2 / 238 (0.84%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrosis ischaemic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Peripheral ischaemia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Aneurysm			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aneurysm ruptured			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Arterial disorder			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Extremity necrosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Iliac artery thrombosis			

subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemia			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
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 arterial occlusive disease			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Thrombophlebitis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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			
Wound drainage			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrectomy			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 238 (1.68%)	7 / 238 (2.94%)	4 / 233 (1.72%)
occurrences causally related to treatment / all	1 / 4	1 / 8	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chest pain			
subjects affected / exposed	3 / 238 (1.26%)	3 / 238 (1.26%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Asthenia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Catheter thrombosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Generalised oedema			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Hernia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Soft tissue inflammation			

subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Iodine allergy			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Anaphylactic reaction			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Pancreas transplant rejection			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
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 rejection			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Epididymitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Prostatitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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

Vaginal haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 238 (0.42%)	2 / 238 (0.84%)	3 / 233 (1.29%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Pulmonary oedema			
subjects affected / exposed	4 / 238 (1.68%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	3 / 233 (1.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Pulmonary congestion			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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 arrest			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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

Respiratory distress			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Acute respiratory failure			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Asthma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Atelectasis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Status asthmaticus			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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			
Mental status changes			
subjects affected / exposed	2 / 238 (0.84%)	0 / 238 (0.00%)	0 / 233 (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
Anxiety			

subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Mania			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Bipolar disorder			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Confusional state			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	18 / 238 (7.56%)	13 / 238 (5.46%)	9 / 233 (3.86%)
occurrences causally related to treatment / all	5 / 23	4 / 17	4 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose increased			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	0 / 233 (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
Blood potassium increased			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine output decreased			

subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus antigen positive			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus test			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug level below therapeutic			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
International normalised ratio increased			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
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			
Graft dysfunction			
subjects affected / exposed	7 / 238 (2.94%)	16 / 238 (6.72%)	8 / 233 (3.43%)
occurrences causally related to treatment / all	0 / 7	1 / 16	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	4 / 238 (1.68%)	2 / 238 (0.84%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perinephric collection			

subjects affected / exposed	1 / 238 (0.42%)	2 / 238 (0.84%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous haematoma			
subjects affected / exposed	2 / 238 (0.84%)	1 / 238 (0.42%)	0 / 233 (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
Seroma			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complications of transplanted kidney			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Therapeutic agent toxicity			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Graft thrombosis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirenal haematoma			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			

subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	0 / 233 (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
Ureteric anastomosis complication			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary anastomotic leak			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	0 / 233 (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
Post procedural urine leak			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Fall			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Incision site haematoma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Post procedural haematoma			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			

subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Radiation pneumonitis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Tendon rupture			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Urostomy complication			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Wound secretion			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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			
Myocardial infarction			
subjects affected / exposed	7 / 238 (2.94%)	0 / 238 (0.00%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	6 / 233 (2.58%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	2 / 238 (0.84%)	2 / 238 (0.84%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 1
Cardiac failure congestive			
subjects affected / exposed	1 / 238 (0.42%)	2 / 238 (0.84%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 238 (0.42%)	2 / 238 (0.84%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Tachycardia			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	3 / 233 (1.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 238 (0.84%)	0 / 238 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Cardiomegaly			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Arrhythmia			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiogenic shock			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intracardiac thrombus			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Palpitations			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Convulsion			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Depressed level of consciousness			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Encephalitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Neurotoxicity			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Presyncope			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Anoxic encephalopathy			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Complex regional pain syndrome			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
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			
Anaemia			
subjects affected / exposed	4 / 238 (1.68%)	5 / 238 (2.10%)	4 / 233 (1.72%)
occurrences causally related to treatment / all	0 / 4	1 / 5	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	3 / 238 (1.26%)	5 / 238 (2.10%)	5 / 233 (2.15%)
occurrences causally related to treatment / all	3 / 3	5 / 5	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 238 (0.42%)	2 / 238 (0.84%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	1 / 1	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic uraemic syndrome			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	1 / 233 (0.43%)
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 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Pancytopenia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Visual disturbance			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 238 (0.84%)	4 / 238 (1.68%)	4 / 233 (1.72%)
occurrences causally related to treatment / all	0 / 2	4 / 4	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 238 (0.42%)	5 / 238 (2.10%)	3 / 233 (1.29%)
occurrences causally related to treatment / all	1 / 1	4 / 5	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	3 / 238 (1.26%)	3 / 238 (1.26%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	1 / 3	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 238 (0.42%)	3 / 238 (1.26%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	2 / 238 (0.84%)	0 / 238 (0.00%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 238 (0.84%)	1 / 238 (0.42%)	0 / 233 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 238 (0.84%)	1 / 238 (0.42%)	0 / 233 (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
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	3 / 233 (1.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erosive oesophagitis			
subjects affected / exposed	2 / 238 (0.84%)	0 / 238 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	0 / 233 (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
Food poisoning			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Gastrointestinal necrosis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Pancreatitis acute			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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 haemorrhagic			

subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Dysphagia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Haemorrhoids			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising oesophagitis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal spasm			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal effusion			

subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal effusion			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haematoma			
subjects affected / exposed	1 / 238 (0.42%)	2 / 238 (0.84%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary tract disorder			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Cholecystitis chronic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Bile duct stone			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Ischaemic hepatitis			

subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
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	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (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
Dry gangrene			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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 and urinary disorders			
Renal failure acute			
subjects affected / exposed	2 / 238 (0.84%)	3 / 238 (1.26%)	6 / 233 (2.58%)
occurrences causally related to treatment / all	0 / 2	3 / 4	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular necrosis			
subjects affected / exposed	4 / 238 (1.68%)	5 / 238 (2.10%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	1 / 4	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	4 / 238 (1.68%)	2 / 238 (0.84%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 4	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	3 / 233 (1.29%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract disorder			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	4 / 233 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			

subjects affected / exposed	1 / 238 (0.42%)	3 / 238 (1.26%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal artery stenosis			
subjects affected / exposed	2 / 238 (0.84%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	2 / 238 (0.84%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis interstitial			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal segmental glomerulosclerosis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Azotaemia			

subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Dysuria			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Glomerulonephritis membranoproliferative			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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 vein thrombosis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Bladder neck obstruction			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Cystitis haemorrhagic			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oliguria			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
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 artery thrombosis			

subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
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 infarct			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 238 (0.84%)	1 / 238 (0.42%)	0 / 233 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Osteoarthritis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Arthritis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Flank pain			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
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			
Urinary tract infection			
subjects affected / exposed	16 / 238 (6.72%)	12 / 238 (5.04%)	6 / 233 (2.58%)
occurrences causally related to treatment / all	10 / 20	8 / 15	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	6 / 238 (2.52%)	8 / 238 (3.36%)	5 / 233 (2.15%)
occurrences causally related to treatment / all	2 / 7	6 / 9	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	2 / 238 (0.84%)	3 / 238 (1.26%)	6 / 233 (2.58%)
occurrences causally related to treatment / all	1 / 2	3 / 3	2 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	4 / 238 (1.68%)	2 / 238 (0.84%)	4 / 233 (1.72%)
occurrences causally related to treatment / all	0 / 4	0 / 2	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 238 (0.84%)	5 / 238 (2.10%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 2	1 / 5	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 238 (0.42%)	2 / 238 (0.84%)	6 / 233 (2.58%)
occurrences causally related to treatment / all	0 / 1	1 / 2	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 238 (0.84%)	4 / 238 (1.68%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 2	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	2 / 238 (0.84%)	1 / 238 (0.42%)	3 / 233 (1.29%)
occurrences causally related to treatment / all	2 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	2 / 238 (0.84%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyomavirus-associated nephropathy			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	3 / 233 (1.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BK virus infection			

subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	0 / 233 (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
Gangrene			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	0 / 233 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	0 / 233 (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
Localised infection			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	0 / 233 (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
Subcutaneous abscess			

subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	0 / 233 (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
Abdominal sepsis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Bacterial pyelonephritis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Clostridial infection			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Escherichia sepsis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Genital herpes			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Herpes zoster			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Lung infection pseudomonal			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Perinephric abscess			

subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Peritonitis bacterial			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Abdominal wall abscess			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Abscess			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Abscess neck			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Arteriovenous graft site infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Bacillary angiomatosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Bronchitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Catheter related infection			

subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Catheter site cellulitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Cellulitis staphylococcal			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema infectiosum			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Escherichia urinary tract infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Gastroenteritis pseudomonas			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Groin abscess			

subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Hepatitis B			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes virus infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Human polyomavirus infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Infected skin ulcer			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Infective thrombosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Klebsiella infection			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Nocardiosis			

subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal candidiasis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Orchitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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 infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Tuberculosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Wound infection pseudomonas			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	6 / 238 (2.52%)	6 / 238 (2.52%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 6	1 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 238 (0.00%)	6 / 238 (2.52%)	6 / 233 (2.58%)
occurrences causally related to treatment / all	0 / 0	1 / 6	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	1 / 238 (0.42%)	4 / 238 (1.68%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	2 / 238 (0.84%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	1 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 238 (0.00%)	2 / 238 (0.84%)	2 / 233 (0.86%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 238 (0.84%)	0 / 238 (0.00%)	0 / 233 (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
Diabetic ketoacidosis			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 238 (0.42%)	1 / 238 (0.42%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Hypomagnesaemia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 238 (0.00%)	0 / 233 (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
Hypocalcaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 238 (0.42%)	0 / 233 (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
Metabolic acidosis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 238 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
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	Group A: Monitored MMF + Reduced CNI	Group C: Fixed MMF + Full CNI	Group B: Monitored MMF + Full CNI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	224 / 238 (94.12%)	227 / 238 (95.38%)	222 / 233 (95.28%)
Vascular disorders			
Hypertension			
subjects affected / exposed	51 / 238 (21.43%)	49 / 238 (20.59%)	51 / 233 (21.89%)
occurrences (all)	60	51	54
Hypotension			
subjects affected / exposed	30 / 238 (12.61%)	26 / 238 (10.92%)	24 / 233 (10.30%)
occurrences (all)	35	32	28
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	79 / 238 (33.19%)	90 / 238 (37.82%)	82 / 233 (35.19%)
occurrences (all)	99	121	104
Fatigue			

subjects affected / exposed	38 / 238 (15.97%)	41 / 238 (17.23%)	38 / 233 (16.31%)
occurrences (all)	40	46	40
Oedema peripheral			
subjects affected / exposed	33 / 238 (13.87%)	29 / 238 (12.18%)	29 / 233 (12.45%)
occurrences (all)	40	37	41
Pyrexia			
subjects affected / exposed	26 / 238 (10.92%)	28 / 238 (11.76%)	26 / 233 (11.16%)
occurrences (all)	30	35	30
Pain			
subjects affected / exposed	24 / 238 (10.08%)	19 / 238 (7.98%)	20 / 233 (8.58%)
occurrences (all)	34	26	26
Asthenia			
subjects affected / exposed	16 / 238 (6.72%)	18 / 238 (7.56%)	10 / 233 (4.29%)
occurrences (all)	19	18	11
Chest pain			
subjects affected / exposed	12 / 238 (5.04%)	9 / 238 (3.78%)	17 / 233 (7.30%)
occurrences (all)	14	10	18
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	30 / 238 (12.61%)	26 / 238 (10.92%)	28 / 233 (12.02%)
occurrences (all)	33	31	30
Cough			
subjects affected / exposed	21 / 238 (8.82%)	24 / 238 (10.08%)	22 / 233 (9.44%)
occurrences (all)	23	27	23
Pharyngolaryngeal pain			
subjects affected / exposed	10 / 238 (4.20%)	14 / 238 (5.88%)	11 / 233 (4.72%)
occurrences (all)	12	17	11
Psychiatric disorders			
Insomnia			
subjects affected / exposed	46 / 238 (19.33%)	41 / 238 (17.23%)	35 / 233 (15.02%)
occurrences (all)	49	46	37
Anxiety			
subjects affected / exposed	12 / 238 (5.04%)	11 / 238 (4.62%)	11 / 233 (4.72%)
occurrences (all)	12	11	12
Depression			

subjects affected / exposed	11 / 238 (4.62%)	9 / 238 (3.78%)	13 / 233 (5.58%)
occurrences (all)	11	9	13
Investigations			
Blood creatinine increased			
subjects affected / exposed	43 / 238 (18.07%)	33 / 238 (13.87%)	45 / 233 (19.31%)
occurrences (all)	50	48	55
Weight increased			
subjects affected / exposed	31 / 238 (13.03%)	29 / 238 (12.18%)	24 / 233 (10.30%)
occurrences (all)	31	32	25
Urine output decreased			
subjects affected / exposed	8 / 238 (3.36%)	8 / 238 (3.36%)	12 / 233 (5.15%)
occurrences (all)	8	8	12
Injury, poisoning and procedural complications			
Graft dysfunction			
subjects affected / exposed	23 / 238 (9.66%)	20 / 238 (8.40%)	13 / 233 (5.58%)
occurrences (all)	23	20	13
Incision site pain			
subjects affected / exposed	15 / 238 (6.30%)	14 / 238 (5.88%)	12 / 233 (5.15%)
occurrences (all)	16	14	12
Nervous system disorders			
Tremor			
subjects affected / exposed	38 / 238 (15.97%)	47 / 238 (19.75%)	46 / 233 (19.74%)
occurrences (all)	44	52	52
Headache			
subjects affected / exposed	25 / 238 (10.50%)	33 / 238 (13.87%)	30 / 233 (12.88%)
occurrences (all)	29	47	33
Dizziness			
subjects affected / exposed	22 / 238 (9.24%)	19 / 238 (7.98%)	15 / 233 (6.44%)
occurrences (all)	25	25	18
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	81 / 238 (34.03%)	80 / 238 (33.61%)	59 / 233 (25.32%)
occurrences (all)	92	90	62
Leukopenia			
subjects affected / exposed	54 / 238 (22.69%)	65 / 238 (27.31%)	56 / 233 (24.03%)
occurrences (all)	72	77	81

Thrombocytopenia			
subjects affected / exposed	9 / 238 (3.78%)	13 / 238 (5.46%)	6 / 233 (2.58%)
occurrences (all)	9	13	6
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	97 / 238 (40.76%)	94 / 238 (39.50%)	101 / 233 (43.35%)
occurrences (all)	130	122	138
Constipation			
subjects affected / exposed	54 / 238 (22.69%)	65 / 238 (27.31%)	65 / 233 (27.90%)
occurrences (all)	63	74	69
Nausea			
subjects affected / exposed	51 / 238 (21.43%)	53 / 238 (22.27%)	48 / 233 (20.60%)
occurrences (all)	61	75	56
Vomiting			
subjects affected / exposed	48 / 238 (20.17%)	37 / 238 (15.55%)	40 / 233 (17.17%)
occurrences (all)	54	48	50
Abdominal pain			
subjects affected / exposed	27 / 238 (11.34%)	29 / 238 (12.18%)	34 / 233 (14.59%)
occurrences (all)	29	41	37
Dyspepsia			
subjects affected / exposed	16 / 238 (6.72%)	26 / 238 (10.92%)	30 / 233 (12.88%)
occurrences (all)	16	28	31
Abdominal distension			
subjects affected / exposed	11 / 238 (4.62%)	14 / 238 (5.88%)	9 / 233 (3.86%)
occurrences (all)	11	14	9
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	12 / 238 (5.04%)	17 / 238 (7.14%)	23 / 233 (9.87%)
occurrences (all)	13	18	25
Rash			
subjects affected / exposed	14 / 238 (5.88%)	16 / 238 (6.72%)	19 / 233 (8.15%)
occurrences (all)	14	17	20
Alopecia			
subjects affected / exposed	8 / 238 (3.36%)	12 / 238 (5.04%)	8 / 233 (3.43%)
occurrences (all)	8	13	8
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	24 / 238 (10.08%)	20 / 238 (8.40%)	27 / 233 (11.59%)
occurrences (all)	25	21	28
Renal tubular necrosis			
subjects affected / exposed	15 / 238 (6.30%)	10 / 238 (4.20%)	13 / 233 (5.58%)
occurrences (all)	15	10	13
Dysuria			
subjects affected / exposed	19 / 238 (7.98%)	13 / 238 (5.46%)	14 / 233 (6.01%)
occurrences (all)	20	13	15
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	21 / 238 (8.82%)	24 / 238 (10.08%)	19 / 233 (8.15%)
occurrences (all)	21	27	19
Pain in extremity			
subjects affected / exposed	21 / 238 (8.82%)	21 / 238 (8.82%)	15 / 233 (6.44%)
occurrences (all)	21	22	18
Muscle spasms			
subjects affected / exposed	12 / 238 (5.04%)	15 / 238 (6.30%)	18 / 233 (7.73%)
occurrences (all)	12	18	22
Osteopenia			
subjects affected / exposed	14 / 238 (5.88%)	8 / 238 (3.36%)	11 / 233 (4.72%)
occurrences (all)	15	8	12
Arthralgia			
subjects affected / exposed	15 / 238 (6.30%)	9 / 238 (3.78%)	5 / 233 (2.15%)
occurrences (all)	17	11	5
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	29 / 238 (12.18%)	25 / 238 (10.50%)	35 / 233 (15.02%)
occurrences (all)	44	34	54
Upper respiratory tract infection			
subjects affected / exposed	21 / 238 (8.82%)	15 / 238 (6.30%)	12 / 233 (5.15%)
occurrences (all)	23	15	12
Nasopharyngitis			
subjects affected / exposed	16 / 238 (6.72%)	13 / 238 (5.46%)	13 / 233 (5.58%)
occurrences (all)	18	18	13
Metabolism and nutrition disorders			

Hypophosphataemia			
subjects affected / exposed	56 / 238 (23.53%)	59 / 238 (24.79%)	61 / 233 (26.18%)
occurrences (all)	61	64	67
Hyperkalaemia			
subjects affected / exposed	58 / 238 (24.37%)	60 / 238 (25.21%)	51 / 233 (21.89%)
occurrences (all)	70	81	66
Hypomagnesaemia			
subjects affected / exposed	53 / 238 (22.27%)	52 / 238 (21.85%)	53 / 233 (22.75%)
occurrences (all)	56	62	62
Hyperglycaemia			
subjects affected / exposed	32 / 238 (13.45%)	33 / 238 (13.87%)	30 / 233 (12.88%)
occurrences (all)	34	38	31
Hypokalaemia			
subjects affected / exposed	26 / 238 (10.92%)	25 / 238 (10.50%)	36 / 233 (15.45%)
occurrences (all)	26	29	38
Hyperlipidaemia			
subjects affected / exposed	28 / 238 (11.76%)	27 / 238 (11.34%)	18 / 233 (7.73%)
occurrences (all)	28	29	20
Hypocalcaemia			
subjects affected / exposed	16 / 238 (6.72%)	18 / 238 (7.56%)	25 / 233 (10.73%)
occurrences (all)	17	19	25
Diabetes mellitus			
subjects affected / exposed	19 / 238 (7.98%)	12 / 238 (5.04%)	19 / 233 (8.15%)
occurrences (all)	19	12	19
Hypercholesterolaemia			
subjects affected / exposed	14 / 238 (5.88%)	15 / 238 (6.30%)	8 / 233 (3.43%)
occurrences (all)	14	15	8
Hypoglycaemia			
subjects affected / exposed	13 / 238 (5.46%)	14 / 238 (5.88%)	8 / 233 (3.43%)
occurrences (all)	17	18	8
Hyperphosphataemia			
subjects affected / exposed	13 / 238 (5.46%)	4 / 238 (1.68%)	9 / 233 (3.86%)
occurrences (all)	13	4	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2004	The definition of treatment failure was modified in the first protocol amendment. Additionally, a last observation carried forward approach would be used for GFR analysis for participants who discontinued or were lost to follow-up before the planned end of study. Planned interim analyses were added. The schedule of a few laboratory collections was also modified and exclusion criteria regarding concomitant medication use and cold ischemia time were changed.
18 August 2004	The method for GFR assessment was changed from direct measurement with cold iothalmate to a calculated estimate using the Nankivell equation. Additionally, the CNI trough ranges were modified to allow for greater exposure in the early post-transplantation period. Dosing and treatment guidelines were updated, specifically regarding corticosteroid use and management of cyclosporine and MMF dosing.
15 November 2005	Clarifications were added for the handling of discontinued participants as well as the length of Sponsor provision of study drug. Plans for validation of the electronic Case Report Form database were specified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported