Clinical trial results:
Multicenter, prospective, open-label, controlled, randomized, parallel groups study to evaluate the renal function of adult liver transplant recipients treated with two everolimus-based immunosuppressive regimens (tacrolimus withdrawal vs. minimization) until 12 months post-transplant, with a 6-months follow-up

Summary

EudraCT number	2013-004325-91
Trial protocol	IT
Global end of trial date	30 September 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	CRAD001HIT34

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02115113
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare, at Month 12 post-transplantation, renal function measured by estimated GFR (MDRD-4) between a tacrolimus withdrawal regimen and an early tacrolimus minimization regimen, both facilitated by everolimus introduction 4 weeks after liver transplantation.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2014
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	Italy: 78
Worldwide total number of subjects	78
EEA total number of subjects	78

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	69
From 65 to 84 years	9

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included a run-in period and a randomization period. Run-in started 4 weeks post-transplant and ended at 5 months post randomization. After run-in, eligible participants were randomized in a 1:1 ratio to tacrolimus elimination or tacrolimus minimization.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Group A (Tacrolimus Elimination Arm)

Arm description:

At study start, participants received an Everolimus starting dose of 1.0 mg twice daily in combination with Tacrolimus. Tacrolimus was administered as per center practice. Thereafter, Everolimus doses were adjusted to achieve Everolimus C-0h blood trough levels between 3-8 ng/mL by week 1 after drug initiation until 5 months after transplant. At 5 months after transplant, Everolimus doses were adjusted to achieve C-0h blood trough level target ranges 6-10 ng/mL. Tacrolimus withdrawal was completed by 6 months after transplant.

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

Dosage and administration details:

At study start, participants received an Everolimus starting dose of 1.0 mg twice daily in combination with Tacrolimus. Thereafter, Everolimus doses were adjusted to achieve Everolimus C-0h blood trough levels between 3-8 ng/mL by week 1 after drug initiation until 5 months after transplant. At 5 months after transplant, Everolimus doses were adjusted to achieve C-0h blood trough level target ranges 6-10 ng/mL.

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

Dosage and administration details:

At study start, participants received an Everolimus starting dose of 1.0 mg twice daily in combination with Tacrolimus. Tacrolimus was administered as per center practice. Tacrolimus withdrawal was completed by 6 months after transplant.

Arm title	Group B (Tacrolimus Minimization Arm)

Arm description:

At study start, participants received an Everolimus starting dose of 1.0 mg twice daily in combination with Tacrolimus. Tacrolimus was administered as per center practice. Thereafter, Everolimus doses were adjusted to achieve Everolimus C-0h blood trough levels between 3-8 ng/mL by week 1 after drug initiation until 5 months after transplant. At 5 months after transplant, Everolimus doses continued to be adjusted to achieve C-0h blood trough level target ranges 3-8 ng/mL and Tacrolimus doses were adjusted to achieve C-0h blood trough level target ranges 3-5 ng/mL.

Arm type	Experimental

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

Dosage and administration details:

At study start, participants received an Everolimus starting dose of 1.0 mg twice daily in combination with Tacrolimus. Thereafter, Everolimus doses were adjusted to achieve Everolimus C-0h blood trough levels between 3-8 ng/mL by week 1 after drug initiation until 5 months after transplant. At 5 months after transplant, Everolimus doses continued to be adjusted to achieve C-0h blood trough level target ranges 3-8 ng/mL.

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

Dosage and administration details:

At study start, participants received an Everolimus starting dose of 1.0 mg twice daily in combination with Tacrolimus. Tacrolimus was administered as per center practice. At 5 months after transplant, Tacorlimus doses were adjusted to achieve C-0h blood trough level target ranges 3-5 ng/mL.

Arm title	Total enrolled at run-in

Arm description:

Participants, who had a successful liver transplantation and who had initiated a tacrolimus-based regimen and possible induction therapy or intravenous (i.v.) steroids according to local practice, were enrolled into the study 4 weeks (+/- 7 days) after transplantation and started on a everolimus-based regimen with tacrolimus minimization up until 5 months post transplantation.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

At study start, participants received an Everolimus starting dose of 1.0 mg twice daily in combination with Tacrolimus. Tacrolimus was administered as per center practice.

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

Dosage and administration details:

At study start, participants received an Everolimus starting dose of 1.0 mg twice daily in combination with Tacrolimus. Thereafter, Everolimus doses were adjusted to achieve Everolimus C-0h blood trough levels between 3-8 ng/mL by week 1 after drug initiation until 5 months after transplant.

Number of subjects in period 1	Group A (Tacrolimus Elimination Arm)	Group B (Tacrolimus Minimization Arm)	Total enrolled at run-in
Started	24	26	78
Completed	22	26	68
Not completed	2	0	10
Consent withdrawn by subject	-	-	3

Death	1	-	1
Administrative problems	-	-	1
Lost to follow-up	1	-	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	78	78	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	69	69	
From 65-84 years	9	9	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	53.73		
standard deviation	± 9.69	-	
Gender, Male/Female Units: Subjects			
Female	19	19	
Male	59	59	

End points

End points reporting groups

Reporting group title	Group A (Tacrolimus Elimination Arm)

Reporting group description:

At study start, participants received an Everolimus starting dose of 1.0 mg twice daily in combination with Tacrolimus. Tacrolimus was administered as per center practice. Thereafter, Everolimus doses were adjusted to achieve Everolimus C-0h blood trough levels between 3-8 ng/mL by week 1 after drug initiation until 5 months after transplant. At 5 months after transplant, Everolimus doses were adjusted to achieve C-0h blood trough level target ranges 6-10 ng/mL. Tacrolimus withdrawal was completed by 6 months after transplant.

Reporting group title	Group B (Tacrolimus Minimization Arm)

Reporting group description:

At study start, participants received an Everolimus starting dose of 1.0 mg twice daily in combination with Tacrolimus. Tacrolimus was administered as per center practice. Thereafter, Everolimus doses were adjusted to achieve Everolimus C-0h blood trough levels between 3-8 ng/mL by week 1 after drug initiation until 5 months after transplant. At 5 months after transplant, Everolimus doses continued to be adjusted to achieve C-0h blood trough level target ranges 3-8 ng/mL and Tacrolimus doses were adjusted to achieve C-0h blood trough level target ranges 3-5 ng/mL.

Reporting group title	Total enrolled at run-in

Reporting group description:

Participants, who had a successful liver transplantation and who had initiated a tacrolimus-based regimen and possible induction therapy or intravenous (i.v.) steroids according to local practice, were enrolled into the study 4 weeks (+/- 7 days) after transplantation and started on a everolimus-based regimen with tacrolimus minimization up until 5 months post transplantation.

Primary: Renal function assessed by estimated glomerular filtartion rate (eGFR)

End point title	Renal function assessed by estimated glomerular filtartion rate (eGFR)[1]

End point description:

Renal function was assessed by eGFR using the MDRD-4 formula at 12 months after transplant: eGFR = 186.3 * (serum creatinine)-1.154 * age-0.203 * (0.742 for women) * (1.21 if African American) where serum creatinine was in mg/dL and age in years.

End point type	Primary

End point timeframe:

At 12 months post-transplant

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the statistical analysis.

End point values	Group A (Tacrolimus Elimination Arm)	Group B (Tacrolimus Minimization Arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: mL/min/1.73m^2				
least squares mean (standard error)	85.5 (± 3.97)	80.26 (± 3.87)		

Statistical analyses

Statistical analysis title	Renal function assessed by eGFR
Comparison groups	Group A (Tacrolimus Elimination Arm) v Group B (Tacrolimus Minimization Arm)
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3013
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	5.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.86
upper limit	15.34
Variability estimate	Standard error of the mean
Dispersion value	5.01

Secondary: Percentage of participants with treated biopsy proven acute rejection (tBPAR) acute rejection (AR), Graft Loss (GL) or Death (D)

End point title	Percentage of participants with treated biopsy proven acute rejection (tBPAR) acute rejection (AR), Graft Loss (GL) or Death (D)[2]

End point description:

Participants were assessed for tBPAR, AR, GL or death. For all suspected rejection episodes, regardless of initiation of anti-rejection treatment, a liver biopsy was to be performed preferably within 24 hours, latest within 48 hours whenever clinically possible. A treated biopsy proven acute rejection was considered an episode of acute rejection when demonstrated by local pathology reading with a rejection activity index of at least 3 or greater of acute rejection index and when treated with anti-rejection therapy. The allograft was considered lost on the day the subject was re-transplanted or died due to liver failure.

End point type	Secondary

End point timeframe:

At 12 and 18 months post-transplant

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis does not apply to this end point.

End point values	Group A (Tacrolimus Elimination Arm)	Group B (Tacrolimus Minimization Arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: Number of participants				
tBPAR, 12 months	2	1		
AR, 12 months	2	1		
GL, 12 months	0	0		
Death, 12 months	1	0		
tBPAR, 18 months	2	1		
AR, 18 months	2	1		
GL, 18 months	0	0		

Death, 18 months	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline (randomization) in serum creatinine at 12 months post-transplant

End point title	Change from baseline (randomization) in serum creatinine at 12 months post-transplant[3]

End point description:

Blood samples were collected to assess serum creatinine.

End point type	Secondary

End point timeframe:

baseline, 12 months post-transplant

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis does not apply to this end point.

End point values	Group A (Tacrolimus Elimination Arm)	Group B (Tacrolimus Minimization Arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: mg/dL				
least squares mean (standard error)	-0.11 (± 0.04)	-0.05 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Run-in population Total
Reporting group description:	
Run-in population Total	
Reporting group title	Run-in population Tacrolimus Elimination
Reporting group description:	
Run-in population Tacrolimus Elimination	
Reporting group title	Run-in population Tacrolimus Minimization
Reporting group description:	
Run-in population Tacrolimus Minimization	
Reporting group title	Randomization treatment period Tacrolimus Elimination
Reporting group description:	
Randomization treatment period Tacrolimus Elimination	
Reporting group title	Randomization treatment period Tacrolimus Minimization
Reporting group description:	
Randomization treatment period Tacrolimus Minimization	

Serious adverse events	Run-in population Total	Run-in population Tacrolimus Elimination	Run-in population Tacrolimus Minimization
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 78 (32.05%)	4 / 24 (16.67%)	9 / 26 (34.62%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metastases to bone			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schwannoma			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Lymphocele			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (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
Surgical and medical procedures			
Biliary anastomosis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (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
Oedema peripheral			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	5 / 78 (6.41%)	0 / 24 (0.00%)	2 / 26 (7.69%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Transplant rejection			
subjects affected / exposed	2 / 78 (2.56%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 78 (6.41%)	1 / 24 (4.17%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	1 / 6	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 78 (8.97%)	2 / 24 (8.33%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	1 / 8	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 78 (2.56%)	1 / 24 (4.17%)	0 / 26 (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
Blood bilirubin increased			

subjects affected / exposed	6 / 78 (7.69%)	1 / 24 (4.17%)	2 / 26 (7.69%)
occurrences causally related to treatment / all	1 / 7	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 78 (2.56%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight increased			
subjects affected / exposed	1 / 78 (1.28%)	1 / 24 (4.17%)	0 / 26 (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
White blood cell count increased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (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
Injury, poisoning and procedural complications			
Biliary anastomosis complication			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			

subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cranial nerve disorder			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 78 (1.28%)	1 / 24 (4.17%)	0 / 26 (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
Intestinal obstruction			

subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (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
Melaena			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	3 / 78 (3.85%)	2 / 24 (8.33%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic artery stenosis			
subjects affected / exposed	2 / 78 (2.56%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	3 / 78 (3.85%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	1 / 78 (1.28%)	1 / 24 (4.17%)	0 / 26 (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
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			

subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (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
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (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 infection			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	2 / 78 (2.56%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes virus infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (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
Liver abscess			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (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
Pneumonia			
subjects affected / exposed	3 / 78 (3.85%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (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

Serious adverse events	Randomization treatment period Tacrolimus Elimination	Randomization treatment period Tacrolimus Minimization	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 24 (16.67%)	9 / 26 (34.62%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 24 (4.17%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 24 (4.17%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Schwannoma			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Lymphocele			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Biliary anastomosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 24 (4.17%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Transplant rejection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			

subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Biliary anastomosis complication			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericarditis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cranial nerve disorder			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			

subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic artery stenosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			

subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Herpes virus infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Run-in population Total	Run-in population Tacrolimus Elimination	Run-in population Tacrolimus Minimization
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 78 (73.08%)	20 / 24 (83.33%)	21 / 26 (80.77%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 78 (7.69%)	1 / 24 (4.17%)	1 / 26 (3.85%)
occurrences (all)	6	1	1
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 78 (3.85%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	3	0	1
Blood bilirubin increased			
subjects affected / exposed	6 / 78 (7.69%)	2 / 24 (8.33%)	1 / 26 (3.85%)
occurrences (all)	10	2	2
Gamma-glutamyltransferase increased			

subjects affected / exposed	4 / 78 (5.13%)	1 / 24 (4.17%)	2 / 26 (7.69%)
occurrences (all)	4	1	2
Transaminases increased			
subjects affected / exposed	9 / 78 (11.54%)	4 / 24 (16.67%)	4 / 26 (15.38%)
occurrences (all)	9	4	4
Weight increased			
subjects affected / exposed	2 / 78 (2.56%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	2	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 78 (7.69%)	3 / 24 (12.50%)	2 / 26 (7.69%)
occurrences (all)	6	3	2
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 78 (10.26%)	3 / 24 (12.50%)	1 / 26 (3.85%)
occurrences (all)	8	3	1
Tremor			
subjects affected / exposed	5 / 78 (6.41%)	2 / 24 (8.33%)	1 / 26 (3.85%)
occurrences (all)	5	2	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 78 (6.41%)	0 / 24 (0.00%)	3 / 26 (11.54%)
occurrences (all)	6	0	4
Leukopenia			
subjects affected / exposed	6 / 78 (7.69%)	0 / 24 (0.00%)	4 / 26 (15.38%)
occurrences (all)	6	0	4
Thrombocytopenia			
subjects affected / exposed	5 / 78 (6.41%)	1 / 24 (4.17%)	3 / 26 (11.54%)
occurrences (all)	5	1	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 78 (8.97%)	4 / 24 (16.67%)	1 / 26 (3.85%)
occurrences (all)	8	5	1
Oedema peripheral			
subjects affected / exposed	3 / 78 (3.85%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	3	0	1

Pyrexia			
subjects affected / exposed	14 / 78 (17.95%)	4 / 24 (16.67%)	4 / 26 (15.38%)
occurrences (all)	17	5	5
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 78 (7.69%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	6	0	1
Gastritis			
subjects affected / exposed	2 / 78 (2.56%)	2 / 24 (8.33%)	0 / 26 (0.00%)
occurrences (all)	2	2	0
Mouth ulceration			
subjects affected / exposed	4 / 78 (5.13%)	1 / 24 (4.17%)	2 / 26 (7.69%)
occurrences (all)	4	1	2
Nausea			
subjects affected / exposed	8 / 78 (10.26%)	3 / 24 (12.50%)	2 / 26 (7.69%)
occurrences (all)	8	3	2
Stomatitis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	3 / 78 (3.85%)	0 / 24 (0.00%)	2 / 26 (7.69%)
occurrences (all)	3	0	2
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 78 (3.85%)	2 / 24 (8.33%)	0 / 26 (0.00%)
occurrences (all)	3	2	0
Myalgia			
subjects affected / exposed	3 / 78 (3.85%)	2 / 24 (8.33%)	1 / 26 (3.85%)
occurrences (all)	3	2	1
Infections and infestations			

Cytomegalovirus infection			
subjects affected / exposed	4 / 78 (5.13%)	1 / 24 (4.17%)	1 / 26 (3.85%)
occurrences (all)	4	1	1
Dermo-hypodermitis			
subjects affected / exposed	2 / 78 (2.56%)	0 / 24 (0.00%)	2 / 26 (7.69%)
occurrences (all)	2	0	2
Epstein-Barr virus infection			
subjects affected / exposed	2 / 78 (2.56%)	0 / 24 (0.00%)	2 / 26 (7.69%)
occurrences (all)	2	0	2
Hepatitis C			
subjects affected / exposed	3 / 78 (3.85%)	1 / 24 (4.17%)	0 / 26 (0.00%)
occurrences (all)	3	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	2 / 78 (2.56%)	2 / 24 (8.33%)	0 / 26 (0.00%)
occurrences (all)	2	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 78 (6.41%)	1 / 24 (4.17%)	2 / 26 (7.69%)
occurrences (all)	5	1	2
Diabetes mellitus			
subjects affected / exposed	6 / 78 (7.69%)	1 / 24 (4.17%)	4 / 26 (15.38%)
occurrences (all)	6	1	4
Dyslipidaemia			
subjects affected / exposed	3 / 78 (3.85%)	2 / 24 (8.33%)	0 / 26 (0.00%)
occurrences (all)	3	2	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Hypercreatininaemia			
subjects affected / exposed	4 / 78 (5.13%)	1 / 24 (4.17%)	3 / 26 (11.54%)
occurrences (all)	4	1	3
Hypertriglyceridaemia			

subjects affected / exposed	5 / 78 (6.41%)	2 / 24 (8.33%)	3 / 26 (11.54%)
occurrences (all)	5	2	3

Non-serious adverse events	Randomization treatment period Tacrolimus Elimination	Randomization treatment period Tacrolimus Minimization	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 24 (66.67%)	15 / 26 (57.69%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 24 (12.50%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 24 (16.67%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Blood bilirubin increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 24 (16.67%)	2 / 26 (7.69%)	
occurrences (all)	4	2	
Transaminases increased			
subjects affected / exposed	2 / 24 (8.33%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Weight increased			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Tremor			

subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 24 (0.00%)	5 / 26 (19.23%)	
occurrences (all)	0	5	
Leukopenia			
subjects affected / exposed	1 / 24 (4.17%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Thrombocytopenia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Oedema peripheral			
subjects affected / exposed	5 / 24 (20.83%)	1 / 26 (3.85%)	
occurrences (all)	6	2	
Pyrexia			
subjects affected / exposed	3 / 24 (12.50%)	4 / 26 (15.38%)	
occurrences (all)	3	7	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Stomatitis			

subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Dermo-hypodermitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Epstein-Barr virus infection			
subjects affected / exposed	1 / 24 (4.17%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Hepatitis C			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Pharyngitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Diabetes mellitus			
subjects affected / exposed	1 / 24 (4.17%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Dyslipidaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Hypercholesterolaemia			
subjects affected / exposed	1 / 24 (4.17%)	3 / 26 (11.54%)	
occurrences (all)	1	3	
Hypercreatininaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported