Clinical trial results:
A national, multi-center, randomized, open label study to evaluate the efficacy and safety of everolimus combined with enteric-coated mycophenolate sodium compared to the standard treatment combining tacrolimus and enteric-coated mycophenolate sodium in de novo liver transplant recipients

Summary

EudraCT number	2012-000137-39
Trial protocol	FR
Global end of trial date	26 March 2015

Results information

Result version number	v1 (current)
This version publication date	10 April 2016
First version publication date	10 April 2016

Trial information

Trial identification

Sponsor protocol code	CRAD001HFR02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01625377
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	26 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate whether Certican® combined with Myfortic® led to better kidney function, compared to standard treatment combining tacrolimus and Myfortic®, in de novo liver transplant patients, between randomization and 6 months after transplantation.
Renal function was assessed by the estimated glomerular filtration rate (eGFR) (abbreviated Modification of Diet in Renal Disease [aMDRD] formula).

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	07 December 2012
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	France: 188
Worldwide total number of subjects	188
EEA total number of subjects	188

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)	168
From 65 to 84 years	20

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 188 patients were randomized

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	Tacrolimus

Arm description:

From transplantation to randomization: Basiliximab (20mg) at Day 0 and Day 4 + tacrolimus (C0 6-10 ng/ml) from Day 3-Day 5 + mycophenolic acid 1440 mg/d ± oral corticosteroids. From randomization to month 6 : tacrolimus (C0 6-10 ng/ml) + mycophenolic acid 1440 mg/d ± oral corticosteroids

Arm type	Active comparator
Investigational medicinal product name	Basiliximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Basiliximab was supplied to the participating centers as marketed, i.e. in packs containing one vial of 20-mg powder, and water for injection (WFI). 20 mg at D0 and D4

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

Dosage and administration details:

Arm 1: tacrolimus (C06-10 ng/ml) from D3-D5 post-transplantation to month 6 post-transplantation.
Arm 2 : tacolimus (C0 6-10 ng/ml) from D3-D5 post-transplantation to month 6 post-transplantation.
Arm 2 : tacolimus (C0 6-10 ng/ml) from D3-D5 post-transplantation tomonth 6 post-transplantation.
Arm 2 : tacolimus (C0 6-10 ng/ml) from D3-D5 post-transplantation to

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Administration of oral corticosteroid therapy was at the discretion of the centers according to their usual practice

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

Dosage and administration details:

Dose of 1440 mg/day from transplantation to month 6 post-transplantation

Arm title	Everolimus (RAD001)

Arm description:

From transplantation to randomization: Basiliximab (20mg) at Day 0 and Day 4 + tacrolimus (C0 6-10 ng/ml) from Day 3-Day 5 + mycophenolic acid 1440 mg/d ± oral corticosteroids. From randomization to month 6 : everolimus (recommended starting dose of 2 mg/day, then adjusted to achieve the target 6 ≤ C0 ≤ 10 ng/mL, until W24) + mycophenolic acid 1440 mg/d ± oral corticosteroids. The dose of tacrolimus was reduced by 50% twice: at the introduction of everolimus and at week 8 post-transplantation. Tacrolimus had to be finally discontinued in week 12 post-transplantation (by week 16 at the latest).

Arm type	Experimental
Investigational medicinal product name	Basiliximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Basiliximab was supplied to the participating centers as marketed, i.e. in packs containing one vial of 20-mg powder, and water for injection (WFI). 20 mg at D0 and D4

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

Dosage and administration details:

everolimus (C0 6-10 ng/ml) from randomization to month 6 post-transplantation

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Administration of oral corticosteroid therapy was at the discretion of the centers according to their usual practice

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

Dosage and administration details:

Dose of 1440 mg/day from transplantation to month 6 post-transplantation

Number of subjects in period 1	Tacrolimus	Everolimus (RAD001)
Started	95	93
Safety set of population	94	90
Intent to treat population	93	90
Completed	88	71
Not completed	7	22
Adverse event, serious fatal	1	1
Administrative Problem	1	1
Graft loss	1	-
Adverse event, non-fatal	3	16
Unsatisfactory therapeutic effect	-	1
Abnormal laboratory values	1	-
Protocol deviation	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Tacrolimus
Reporting group description:	
From transplantation to randomization: Basiliximab (20mg) at Day 0 and Day 4 + tacrolimus (C0 6-10 ng/ml) from Day 3-Day 5 + mycophenolic acid 1440 mg/d ± oral corticosteroids. From randomization to month 6 : tacrolimus (C0 6-10 ng/ml) + mycophenolic acid 1440 mg/d ± oral corticosteroids	
Reporting group title	Everolimus (RAD001)
Reporting group description:	
From transplantation to randomization: Basiliximab (20mg) at Day 0 and Day 4 + tacrolimus (C0 6-10 ng/ml) from Day 3-Day 5 + mycophenolic acid 1440 mg/d ± oral corticosteroids. From randomization to month 6 : everolimus (recommended starting dose of 2 mg/day, then adjusted to achieve the target 6 ≤ C0 ≤ 10 ng/mL, until W24) + mycophenolic acid 1440 mg/d ± oral corticosteroids. The dose of tacrolimus was reduced by 50% twice: at the introduction of everolimus and at week 8 post-transplantation. Tacrolimus had to be finally discontinued in week 12 post-transplantation (by week 16 at the latest).	

Reporting group values	Tacrolimus	Everolimus (RAD001)	Total
Number of subjects	95	93	188
Age categorical Units: Subjects			
Adults (18-64 years)	85	83	168
From 65-84 years	10	10	20
Age Continuous | Units: Years			
arithmetic mean	55.5	56.5	
standard deviation	± 8.24	± 8.59	-
Gender, Male/Female Units: Participants			
Female	14	14	28
Male	81	79	160

End points

End points reporting groups

Reporting group title	Tacrolimus
Reporting group description:	
From transplantation to randomization: Basiliximab (20mg) at Day 0 and Day 4 + tacrolimus (C0 6-10 ng/ml) from Day 3-Day 5 + mycophenolic acid 1440 mg/d ± oral corticosteroids. From randomization to month 6 : tacrolimus (C0 6-10 ng/ml) + mycophenolic acid 1440 mg/d ± oral corticosteroids	
Reporting group title	Everolimus (RAD001)
Reporting group description:	
From transplantation to randomization: Basiliximab (20mg) at Day 0 and Day 4 + tacrolimus (C0 6-10 ng/ml) from Day 3-Day 5 + mycophenolic acid 1440 mg/d ± oral corticosteroids. From randomization to month 6 : everolimus (recommended starting dose of 2 mg/day, then adjusted to achieve the target 6 ≤ C0 ≤ 10 ng/mL, until W24) + mycophenolic acid 1440 mg/d ± oral corticosteroids. The dose of tacrolimus was reduced by 50% twice: at the introduction of everolimus and at week 8 post-transplantation. Tacrolimus had to be finally discontinued in week 12 post-transplantation (by week 16 at the latest).	

Primary: Change from baseline (randomization) in renal function

End point title	Change from baseline (randomization) in renal function
End point description:	
Change in renal function was measured by change in glomerular filtration rate (GFR). GFR calculated using the abbreviated modification of diet in renal disease (aMDRD) formula. GFR in mL/min/1.73m^2 for men of non-black ethnicity: 186 * [C/88]^-1.154 * [A]^-0.023*G*R ; C = serum creatinine (in µmol/L); A = Age (in years). G = 0.742 when the patient is a women; Otherwise G=1 R= 1.21 when the patient was of black ethnicity; Otherwise R = 1 Baseline was Day 28 visit.	
End point type	Primary
End point timeframe:	
Baseline, Week 24	

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	90		
Units: mL/min/1.73m^2				
least squares mean (standard error)	-13.29 (± 2.75)	1.05 (± 2.81)		

Statistical analyses

Statistical analysis title	Treatments comparison in eGFR change
Comparison groups	Everolimus (RAD001) v Tacrolimus

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-14.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.34
upper limit	-7.34

Secondary: Number of patients with treatment failures

End point title	Number of patients with treatment failures

End point description:

Incidence of treatment failures, assessed with composite criterion including treated biopsy proven acute rejection (tBPAR) with a rejection activity index (RAI) according to Banff classification >3, graft loss or death at 6 months. Biopsy proven acute rejection (BPAR) was defined as a clinically suspected acute rejection confirmed by biopsy. The Banff Rejection Activity Index (RAI) comprises 3 components scored from 0 to 3: venous endothelial inflammation; bile duct inflammation damage; and portal inflammation; the scores are combined to an overall score (the RAI) ranging from 0 to 9. An overall score of 0-3 is considered indeterminate, score of 4-5 is mild acute, score of 6-7 is moderate acute , and score of 8-9 is severe acute. Only the episode with the highest total RAI score for each participant was counted. The graft was presumed to be lost on the day the patient was registered again on the waiting list, or the day he/she received a new graft.

End point type	Secondary

End point timeframe:

At week 12 and week 24

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	90		
Units: Patients				
week 12, Treatment failures - NO	91	88		
week 12, Treatment failures - YES	2	2		
week 24, Treatment failures - NO	89	81		
week 24, Treatment failures - YES	4	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with treated or not treated Biopsy proven acute rejection (BPAR)

End point title	Number of patients with treated or not treated Biopsy proven

	acute rejection (BPAR)

End point description:

Biopsy proven acute rejection was defined as a clinically suspected acute rejection confirmed by biopsy.

End point type	Secondary

End point timeframe:

at 12 week and 24 week

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	90		
Units: Patients				
Week 12, Treated BPAR	2	2		
Week 12, Not treated BPAR	0	0		
Week 24, Treated BPAR	2	8		
Week 24, Not Treated BPAR	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients reported with different categories of severity of BPAR according to Banff classification

End point title	Number of patients reported with different categories of severity of BPAR according to Banff classification

End point description:

Biopsy proven acute rejection was defined as a clinically suspected acute rejection confirmed by biopsy. The severity of BPAR was categorized as : Mild (Banff grade I, RAI = 4 and 5) Moderate (Banff grade II, RAI = 6 and 7) Severe (Banff grade III, RAI = 8 and 9) Banff Rejection Activity Index (RAI) comprises 3 components scored from 0 to 3: venous endothelial inflammation; bile duct inflammation damage; and portal inflammation; the scores are combined to an overall score (the RAI) ranging from 0 to 9. An overall score of 0-3 is considered indeterminate, score of 4-5 is mild acute, score of 6-7 is moderate acute , and score of 8-9 is severe acute. Only the episode with the highest total RAI score for each participant was counted.

End point type	Secondary

End point timeframe:

at 12 week and 24 week

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	90		
Units: Patients				
Week 12: Mild	1	1		
Week 12: Moderate	1	1		
Week 12: Severe	0	0		
Week 24: Mild	1	5		

Week 24: Moderate	1	3		
Week 24: Sever	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with treated or untreated BPAR with RAI score greater than 3

End point title	Number of patients with treated or untreated BPAR with RAI score greater than 3

End point description:

Biopsy proven acute rejection (BPAR) was defined as a clinically suspected acute rejection confirmed by biopsy. The Banff Rejection Activity Index (RAI) comprises 3 components scored from 0 to 3: venous endothelial inflammation; bile duct inflammation damage; and portal inflammation; the scores are combined to an overall score (the RAI) ranging from 0 to 9. An overall score of 0-3 is considered indeterminate, score of 4-5 is mild acute, score of 6-7 is moderate acute , and score of 8-9 is severe acute. Only the episode with the highest total RAI score for each participant was counted. The patients with treated or untreated BPAR having RAI score > 3 were reported in this end point.

End point type	Secondary

End point timeframe:

At 24 weeks

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	90		
Units: Patients				
Not Treated BPAR: RAI score >3	0	0		
Not Treated BPAR: Missing RAI score	0	1		
Treated BPAR: RAI score >3	2	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with death or graft loss

End point title	Number of patients with death or graft loss

End point description:

The graft was presumed to be lost on the day the patient was registered again on the waiting list, or the day he/she received a new graft.

End point type	Secondary

End point timeframe:

at week 24

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	90		
Units: Patients				
Graft Loss	1	0		
Death	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline (randomization) in serum creatinine

End point title	Change from baseline (randomization) in serum creatinine

End point description:

Change in serum creatinine concentrations from baseline (randomization) to week 24 post-randomization was one of the efficacy assessments of renal function. Baseline was Day 28 visit.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	90		
Units: µmol/L				
arithmetic mean (standard deviation)	7.2 (± 36)	-1.3 (± 38.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline (randomization) in urine protein/creatinine ratio

End point title	Change from baseline (randomization) in urine protein/creatinine ratio

End point description:

Change in urine protein/creatinine ratio from baseline (randomization) to week 24 post-randomization was one of the efficacy assessments of renal function. Baseline was Day 28 visit.

End point type	Secondary

End point timeframe:

Baseline, week 24

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	61		
Units: mg/mmol				
arithmetic mean (standard deviation)	-2.3 (± 27.89)	21.9 (± 92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline (randomization) in Creatinine clearance estimated using the adjusted Cockcroft-Gault formula

End point title	Change from baseline (randomization) in Creatinine clearance estimated using the adjusted Cockcroft-Gault formula

End point description:

Creatinine clearance by the Cockcroft-Gault formula is computed in mL/min/1.73m^2 from the creatinine clearance in mL/min by multiplying it by 1.73 and dividing it by the body surface area Baseline was Day 28 visit.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	90		
Units: mL/min/1.73m^2				
arithmetic mean (standard deviation)	-9 (± 30.63)	0.7 (± 25.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline (randomization) in glomerular filtration rate estimated by abbreviated modification of diet in renal disease (MDRD) formula

End point title	Change from baseline (randomization) in glomerular filtration rate estimated by abbreviated modification of diet in renal disease (MDRD) formula

End point description:

Change in glomerular filtration rate was calculated using the MDRD abbreviated formula. GFR in mL/min/1.73m^2 for men of non-black ethnicity: 186 * [C/88]^-1.154 * [A]^-0.023*G*R ; C = serum creatinine (in µmol/L); A = Age (in years). G = 0.742 when the patient is a women; Otherwise G=1 R=

1.21 when the patient was of black ethnicity; Otherwise R = 1 Baseline was Day 28 visit.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	90		
Units: mL/min/1.73m^2				
arithmetic mean (standard deviation)	-11.8 (± 34.01)	0.1 (± 32.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline (randomization) in glomerular filtration rate estimated by CKD-EPI formula

End point title	Change from baseline (randomization) in glomerular filtration rate estimated by CKD-EPI formula

End point description:

GFR estimated by using the Chronic kidney disease- epidemiology (CKD-EPI) formula: eGFR (mL/min/1.73m^2) = 141 * min(C/K,1)^ α * max(C/K,1)^-1.209 * 0.993^A * 1.1018 (if male) * 1.159 (if black) where C = serum creatinine (in mg/dL) ; A = Age (in years); K = 0.7 for women and 0.9 for men; α = -0.329 for women and -0.411 for men. Baseline was Day 28 visit.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	90		
Units: mL/min/1.73m^2				
arithmetic mean (standard deviation)	-6.9 (± 20.11)	2.4 (± 22.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients in different stages of chronic kidney diseases according to the K/DOQI classification system

End point title	Number of patients in different stages of chronic kidney diseases according to the K/DOQI classification system

End point description:

Kidney disease outcomes quality initiative (K/DOQI) classification is based on glomerular filtration rate (GFR), abbreviated MDRD formula (mL/min/1.73m^2) : Stage 1 : GFR >= 90; Stage 2 = GFR was between 60-89; Stage 3 = GFR was between 30-59 ; Stage 4 = GFR was between 15-29; Stage 5 = GFR was < 15 (or dialysis)

End point type	Secondary

End point timeframe:

At Week 24

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	74		
Units: Patients				
Stage 1	24	41		
Stage 2	34	29		
Stage 3	28	4		
Stage 4	0	0		
Stage 5	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with any adverse events, serious adverse events, death and premature discontinuation

End point title	Number of patients with any adverse events, serious adverse events, death and premature discontinuation

End point description:

Baseline was Day 28 visit. This endpoint reports patients with total adverse events (any), serious adverse events, death and premature discontinuation.

End point type	Secondary

End point timeframe:

Baseline to 24 weeks

End point values	Tacrolimus	Everolimus (RAD001)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	90		
Units: Patients				
Any Adverse events	85	81		
Serious Adverse events	28	42		
Death	1	2		

At least one AE led to premature discontinuation	4	18		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Everolimus (RAD001)

Reporting group description:

From transplantation to randomization: Basiliximab (20mg) at Day 0 and Day 4 + tacrolimus (C0 6-10 ng/ml) from Day 3-Day 5 + mycophenolic acid 1440 mg/d ± oral corticosteroids. From randomization to month 6 : everolimus (recommended starting dose of 2 mg/day, then adjusted to achieve the target 6 ≤ C0 ≤ 10 ng/mL, until W24) + mycophenolic acid 1440 mg/d ± oral corticosteroids. The dose of tacrolimus was reduced by 50% twice: at the introduction of everolimus and at week 8 post transplantation. Tacrolimus had to be finally discontinued in week 12 post-transplantation (by week 16 at the latest).

Reporting group title	Tacrolimus

Reporting group description:

From transplantation to randomization: Basiliximab (20mg) at Day 0 and Day 4 + tacrolimus (C0 6-10 ng/ml) from Day 3-Day 5 + mycophenolic acid 1440 mg/d ± oral corticosteroids. From randomization to month 6 : tacrolimus (C0 6-10 ng/ml) + mycophenolic acid 1440 mg/d ± oral corticosteroids

Serious adverse events	Everolimus (RAD001)	Tacrolimus	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 90 (46.67%)	28 / 94 (29.79%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Arterial stenosis			
subjects affected / exposed	2 / 90 (2.22%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lymphoedema			
subjects affected / exposed	2 / 90 (2.22%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Diabetes mellitus management			
subjects affected / exposed	1 / 90 (1.11%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drain removal			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia repair			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 90 (2.22%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	

Pyrexia			
subjects affected / exposed	1 / 90 (1.11%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Liver transplant rejection			
subjects affected / exposed	5 / 90 (5.56%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	3 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			
subjects affected / exposed	2 / 90 (2.22%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Physical disability			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asphyxia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	2 / 90 (2.22%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	2 / 90 (2.22%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications				
Anastomotic stenosis				
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Biliary anastomosis complication				
subjects affected / exposed	5 / 90 (5.56%)	4 / 94 (4.26%)		
occurrences causally related to treatment / all	0 / 5	0 / 4		
deaths causally related to treatment / all	0 / 0	0 / 0		
Overdose				
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Liver graft loss				
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Post procedural bile leak				
subjects affected / exposed	1 / 90 (1.11%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Rib fracture				
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Spinal fracture				
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vascular pseudoaneurysm				
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Wound evisceration				

subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
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			
Agranulocytosis			
subjects affected / exposed	1 / 90 (1.11%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 90 (2.22%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombotic microangiopathy			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 90 (1.11%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 90 (1.11%)	4 / 94 (4.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 90 (1.11%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 90 (1.11%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiolitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biloma			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic artery stenosis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (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	1 / 90 (1.11%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic vein stenosis			

subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic vein thrombosis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis cholestatic			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	2 / 90 (2.22%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodular regenerative hyperplasia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Purpura			

subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 90 (3.33%)	4 / 94 (4.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 90 (2.22%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 90 (2.22%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess oral			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cholangitis suppurative			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 90 (1.11%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	1 / 90 (1.11%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral infection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal infection			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 90 (5.56%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic arthritis staphylococcal			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 90 (1.11%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis aspergillus			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			

subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 90 (1.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Everolimus (RAD001)	Tacrolimus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 90 (71.11%)	68 / 94 (72.34%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 90 (7.78%)	12 / 94 (12.77%)	
occurrences (all)	7	13	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 90 (13.33%)	7 / 94 (7.45%)	
occurrences (all)	12	7	
Neutropenia			
subjects affected / exposed	9 / 90 (10.00%)	14 / 94 (14.89%)	
occurrences (all)	11	15	
Lymphopenia			
subjects affected / exposed	4 / 90 (4.44%)	6 / 94 (6.38%)	
occurrences (all)	4	7	
Leukopenia			
subjects affected / exposed	10 / 90 (11.11%)	8 / 94 (8.51%)	
occurrences (all)	10	9	
Pancytopenia			
subjects affected / exposed	5 / 90 (5.56%)	1 / 94 (1.06%)	
occurrences (all)	5	1	
Thrombocytopenia			
subjects affected / exposed	8 / 90 (8.89%)	10 / 94 (10.64%)	
occurrences (all)	8	10	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	7 / 90 (7.78%)	6 / 94 (6.38%)	
occurrences (all)	7	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 90 (6.67%)	16 / 94 (17.02%)	
occurrences (all)	7	18	
Aphthous stomatitis			
subjects affected / exposed	8 / 90 (8.89%)	0 / 94 (0.00%)	
occurrences (all)	9	0	
Abdominal pain			
subjects affected / exposed	3 / 90 (3.33%)	5 / 94 (5.32%)	
occurrences (all)	3	5	
Hepatobiliary disorders			
Cholestasis			

subjects affected / exposed	24 / 90 (26.67%)	12 / 94 (12.77%)	
occurrences (all)	24	13	
Hepatocellular injury			
subjects affected / exposed	16 / 90 (17.78%)	4 / 94 (4.26%)	
occurrences (all)	16	4	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 90 (3.33%)	11 / 94 (11.70%)	
occurrences (all)	4	12	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 90 (5.56%)	6 / 94 (6.38%)	
occurrences (all)	6	7	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	7 / 90 (7.78%)	1 / 94 (1.06%)	
occurrences (all)	7	1	
Hyperglycaemia			
subjects affected / exposed	6 / 90 (6.67%)	5 / 94 (5.32%)	
occurrences (all)	6	5	
Hyperkalaemia			
subjects affected / exposed	7 / 90 (7.78%)	3 / 94 (3.19%)	
occurrences (all)	7	6	
Hypokalaemia			
subjects affected / exposed	11 / 90 (12.22%)	2 / 94 (2.13%)	
occurrences (all)	13	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 May 2012	- The study design was amended to have a more gradual elimination of tacrolimus in the everolimus (RAD001) group: the dose of tacrolimus was reduced by 50% twice (D0 and in W8 post-transplantation). Tacrolimus had to be fully discontinued in W12 post-transplantation when the everolimus (RAD001) C0 was within the target ranges or by Visit 10 (W16) at the latest. Prior to protocol amendment 1, the dose of tacrolimus was reduced by 50% upon everolimus (RAD001) initiation, then fully discontinued when the everolimus (RAD001) C0 was within the target ranges (when possible at Visit 6, W6), and by Visit 7 (W8) at the latest. - The exclusion/non-eligibility criteria were modified or completed based on the investigators' comments, to focus more precisely the concerned patient population: henceforth, patients transplanted for primary biliary cirrhosis were excluded; patients with BMI ≥35 (formely, ≥32) were excluded; patients with platelet count <50,000 /mm3 (formely, <75,000 /mm3) were non eligible for randomization.
19 September 2013	- Following investigators' request, the day of initiation of tacrolimus was modified from D5 post-transplantation to D3-D5 post-transplantation, to ensure the patients' best healthcare. - The exclusion criterion 7, alpha-fetoprotein > 1000 ng/mL was restricted to patients with hepatocellular carcinoma, as the dosage of this parameter was not medically relevant for all patients. Both above changes were to apply only to patients who did not already started tacrolimus treatment (Visit 3, D5 post-transplantation) or did not have completed already the laboratory assessments of the screening visit (Visit 1, D-7 pre-transplantation).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported