Clinical trial results:
A 12-month, multicenter, open label, randomized, controlled study to evaluate the efficacy, tolerability and safety of early introduction of everolimus, reduced CNI, and early steroid elimination compared to standard CNI, mycophenolate mofetil and steroid regimen in pediatric renal transplant recipients with a 24-month additional safety follow-up

Summary

EudraCT number	2010-024381-21
Trial protocol	HU BE FR DE NO IT Outside EU/EEA SE GB ES
Global end of trial date	24 September 2018

Results information

Result version number	v1 (current)
This version publication date	04 April 2019
First version publication date	04 April 2019

Trial information

Trial identification

Sponsor protocol code	CRAD001A2314

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01544491
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000019-PIP06-09
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this trial were :
1) To estimate the rate of the composite efficacy endpoint of BPAR, graft loss or death at 12 months post-transplantation in primary pediatric kidney transplant recipients, converted at 4-6 weeks post-transplantation from mycophenolate mofetil + standard TAC regimen and steroids (MMF+sTAC) to everolimus + reduced dose TAC regimen and Steroid withdrawal at 6 months (EVR+rTAC), versus continuation of MMF + standard TAC regimen and steroids.
2) To evaluate renal function, assessed by Glomerular Filtration Rate (eGFR) and estimated by the Schwartz formula (abbreviated) (Schwartz et al 2009), at Month 12.

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	17 August 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	Argentina: 3
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	106
EEA total number of subjects	79

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)	2
Children (2-11 years)	54
Adolescents (12-17 years)	49
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Full Analysis set (FAS) 106 enrolled and randomized patients except misrandomized
Per Protocol set (PPS) 90 patients in the FAS without major protocol deviations
Safety set (SAF) 106 randomized patients who received at least one dose of study drug

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	EVR+rTAC

Arm description:

Investigational arm : Conversion from MMF to everolimus plus reduced dose tacrolimus and steroids withdrawal at 6 months after transplant

Arm type	Experimental
Investigational medicinal product name	EverolimusRAD001
Investigational medicinal product code	
Other name	Certican, Zortress
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets, water-dispersible tablets of 0.1 and 0.25 mg or tablets of 0.25 mg, 0.5 mg, 0.75 mg, or 1.0 mg.
When prescribed with TAC: 2.0 mg/m2/dose (maximal initial dose: 0.75 mg bid). Subsequent doses were administered to maintain blood Level C0: 3-8 ng/mL. Given twice daily, 12 hours apart

Arm title	MMF+sTAC

Arm description:

Control arm : MMF continuation (in combination with tacrolimus and standard dose steroids)

Arm type	Active comparator
Investigational medicinal product name	Mycophenolate mofetil
Investigational medicinal product code	
Other name	CellCept
Pharmaceutical forms	Capsule, Buccal tablet, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Capsules; one capsule containing 250 mg, or tablets containing 500 mg.
Oral suspension containing 200 mg/mL.
Initial recommended dose: 1200 mg/m2/day (max. 1 gr/dose).
Subsequent doses were to be reduced to 900 mg/m2/day or lower. As of Month 12 as per center practice.
Twice daily, 12 hours apart.

Number of subjects in period 1	EVR+rTAC	MMF+sTAC
Started	52	54
Completed	47	51
Not completed	5	3
Consent withdrawn by subject	3	2
administrative problems	2	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	EVR+rTAC
Reporting group description:	
Investigational arm : Conversion from MMF to everolimus plus reduced dose tacrolimus and steroids withdrawal at 6 months after transplant	
Reporting group title	MMF+sTAC
Reporting group description:	
Control arm : MMF continuation (in combination with tacrolimus and standard dose steroids)	

Reporting group values	EVR+rTAC	MMF+sTAC	Total
Number of subjects	52	54	106
Age, Customized Units: Subjects			
1 to <11 years	26	27	53
11 <= 18 years	26	27	53
Age continuous Units: years			
arithmetic mean	10.7	10.8	
standard deviation	± 4.9	± 4.8	-
Sex/Gender, Customized Units: Subjects			
Male	29	31	60
Female	23	23	46
Race/Ethnicity, Customized Units: Subjects			
Caucasian	42	47	89
Black	1	0	1
Asian	3	2	5
Other	6	5	11

End points

End points reporting groups

Reporting group title	EVR+rTAC
Reporting group description:	
Investigational arm : Conversion from MMF to everolimus plus reduced dose tacrolimus and steroids withdrawal at 6 months after transplant	
Reporting group title	MMF+sTAC
Reporting group description:	
Control arm : MMF continuation (in combination with tacrolimus and standard dose steroids)	

Primary: number of participants having reached the composite efficacy endpoint of biopsy-proven acute rejection

End point title	number of participants having reached the composite efficacy endpoint of biopsy-proven acute rejection
End point description:	
To estimate the rate of the composite efficacy endpoint of biopsy-proven acute rejection (BPAR), graft loss or death at 12 months post transplantation in primary paediatric kidney transplant recipients converted at 4-6 weeks post-transplantation from MMF + standard TAC regimen and steroids, to everolimus + reduced dose TAC regimen and steroid withdrawal at 6 months, versus continuation of MMF + standard TAC regimen and steroids.	
End point type	Primary
End point timeframe:	
12 months, 36 months	

End point values	EVR+rTAC	MMF+sTAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: Participants				
12 months	5	3		
36 months	5	5		

Statistical analyses

Statistical analysis title	Composite efficacy endpoint analysis at 12 months
Statistical analysis description:	
at 12 months	
Comparison groups	EVR+rTAC v MMF+sTAC
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9712
Method	Logrank
Parameter estimate	Mean difference (final values)
Point estimate	0.1

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-6.6
upper limit	6.8
Variability estimate	Standard error of the mean
Dispersion value	5.25

Statistical analysis title	Composite efficacy endpoint analysis at 36 months
Statistical analysis description:	
36 months	
Comparison groups	EVR+rTAC v MMF+sTAC
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9634
Method	Logrank
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-7.3
upper limit	7.7
Variability estimate	Standard error of the mean
Dispersion value	5.84

Primary: To evaluate renal function, assessed by Glomerular Filtration Rate (eGFR) and estimated by the Schwartz formula (abbreviated), at Month 12 and 36

End point title	To evaluate renal function, assessed by Glomerular Filtration Rate (eGFR) and estimated by the Schwartz formula (abbreviated), at Month 12 and 36

End point description:

To evaluate renal function assessed by Glomerular Filtration Rate (eGFR) estimated by the Schwartz Formula (abbreviated) (Schwartz, 2009).

End point type	Primary

End point timeframe:

12 months and 36 months post-transplantation

End point values	EVR+rTAC	MMF+sTAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: mL/min/1.73m2				
arithmetic mean (standard error)				
12 months	76.7 (± 3.66)	71.7 (± 3.56)		
36 months	68.1 (± 3.45)	67.3 (± 3.54)		

Statistical analyses

Statistical analysis title	Renal function analysis at 12 months
Statistical analysis description: at 12 months	
Comparison groups	EVR+rTAC v MMF+sTAC
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3455
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	5
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.8
upper limit	11.8
Variability estimate	Standard error of the mean
Dispersion value	5.26

Statistical analysis title	Renal function analysis at 36 months
Statistical analysis description: 36 months	
Comparison groups	EVR+rTAC v MMF+sTAC
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8642
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-5.5
upper limit	7.2

Variability estimate	Standard error of the mean
Dispersion value	4.95

Secondary: Composite efficacy endpoint

End point title	Composite efficacy endpoint

End point description:

To evaluate the proportion of patients with the following efficacy events: Biopsy Proven Acute Rejection (BPAR), graft loss or death. The efficacy events will be descriptively summarized by treatment group.

End point type	Secondary

End point timeframe:

at 12 and 36 months post-transplantation

End point values	EVR+rTAC	MMF+sTAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: participants				
month 12 composite efficacy endpoint	5	3		
graft loss 12 months	0	0		
death 12 months	0	0		
acute rejection 12 months	5	4		
treated acute rejection 12 months	5	4		
Biopsy proven acute rejection 12 months	5	3		
treated Biopsy proven acute rejection 12 months	5	3		
month 36 composite efficacy endpoint	5	5		
graft loss 36 months	1	2		
death 36 months	0	0		
acute rejection 36 months	5	7		
Biopsy proven acute rejection 36 months	5	5		
treated Biopsy proven acute rejection 36 months	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate the severity of BPAR (all BPAR) (Banff 2009)

End point title	To evaluate the severity of BPAR (all BPAR) (Banff 2009)

End point description:

T-cell mediated rejection severity : Type IA - Significant interstitial infiltration (> 25% of parenchyma) and foci of moderate tubulitis (> 4 mononuclear cells/tubular cross section or group of 10 tubular cells). Type IB - Significant interstitial infiltration (> 25% of parenchyma) and foci of severe tubulitis (> 10 mononuclear cells/tubular cross section or group of 10 tubular cells). Type IIA - Mild to moderate intimal arteritis Type IIB - Severe intimal arteritis comprising > 25% of the lumenal area Type III - Transmural

(full vessel wall thickness) arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells (with accompanying lymphocytic inflammation)

End point type	Secondary

End point timeframe:

month 12, month 36

End point values	EVR+rTAC	MMF+sTAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: participants				
month 12 grade IA	3	1		
month 12 grade IB	1	0		
month 12 grade IIA	0	2		
month 12 grade IIB	0	0		
month 12 grade III	0	0		
month 36 grade IA	3	1		
month 36 grade IB	2	0		
month 36 grade IIA	0	1		
month 36 grade IIB	0	1		
month 36 grade III	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate the time to event of BPAR

End point title	To evaluate the time to event of BPAR

End point description:

Time to incidence of Event, given in terms of number of participants with an Event according to time interval up to 36 months

End point type	Secondary

End point timeframe:

36 months

End point values	EVR+rTAC	MMF+sTAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: participants				
day 1-7	0	0		
day 8-14	0	0		
day 15-28	1	0		
day 29-56	0	0		
day 57-84	0	0		

day 85-150	2	2		
day 151- 240	0	0		
day 241-330	1	2		
day 331- 510	0	1		
day 511-690	1	0		
day 691-870	0	0		
day 871-1050	0	0		
after day 1050	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of biopsy proven antibody mediated rejection.

End point title	Incidence of biopsy proven antibody mediated rejection.

End point description:

To evaluate the proportion of patients with the following efficacy events: biopsy proven antibody mediated rejection/Steroid resistant BPAR and BPAR treated with T cell depleting therapy.

End point type	Secondary

End point timeframe:

at 12 and 36 months post-transplantation

End point values	EVR+rTAC	MMF+sTAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: participants				
patients with BPAR at 12 months	7	8		
BPAR Steroid resistant,12 months	1	0		
BPAR, T Cell depleting therapy 12 months	1	1		
patients with BPAR at 36 months	6	12		
BPAR Steroid resistant,36 months	1	2		
BPAR, T Cell depleting therapy 36 months	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic allograft nephropathy / interstitial fibrosis and tubular atrophy

End point title	Chronic allograft nephropathy / interstitial fibrosis and tubular atrophy

End point description:

To evaluate the proportion of patients with chronic allograft nephropathy (interstitial fibrosis and tubular atrophy, IF/TA) by histopathology and its progression.The term chronic allograft nephropathy was used

inappropriately in the protocol and therefore, replaced by interstitial fibrosis and tubular atrophy

End point type	Secondary

End point timeframe:

at 12 and 36 months post-transplantation.

End point values	EVR+rTAC	MMF+sTAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: participants				
12 months	3	3		
36 months	11	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Proteinuria (urinary protein/creatinine ratio)

End point title	Proteinuria (urinary protein/creatinine ratio)

End point description:

The urinary protein/creatinine ratio will be descriptively summarized by treatment group at each visit. The incidence rate of patients with proteinuria will be categorized in <0.2 g/mg/mg, 0.2<2.0 mg/mg and ≥ 2.0 mg/mg and summarized by treatment groups at each visit.

End point type	Secondary

End point timeframe:

at 12 and 36 months post-transplantation

End point values	EVR+rTAC	MMF+sTAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: participants				
Baseline < 200mg/g	1	2		
Baseline 200 - < 2000 mg/g	12	12		
Baseline >= 2000 mg/g	14	15		
Month 12 < 200mg/g	19	28		
Month 12 200 - < 2000 mg/g	13	11		
Month 12 >= 2000 mg/g	0	0		
Month 36 < 200mg/g	23	23		
Month 36 200 - < 2000 mg/g	10	11		
Month 36 >= 2000 mg/g	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Growth/development : weight, height, BMI : change from baseline

End point title	Growth/development : weight, height, BMI : change from baseline

End point description:

evaluation of the potential effects upon the bone growth. The mean Z-score change from randomization is summarized. The Z-score represents the percentile Z(p) of the normal distribution where p denotes the percent of patients in the reference population (of same age and gender) with a value lower than or equal to the value measured.

End point type	Secondary

End point timeframe:

month 12 , month 36 post transplantation.

End point values	EVR+rTAC	MMF+sTAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: z score				
arithmetic mean (standard deviation)				
Height month 12	0.37 (± 0.625)	0.20 (± 0.537)		
Height month 36	0.72 (± 1.131)	0.39 (± 0.776)		
Weight month 12	0.30 (± 0.732)	0.42 (± 0.747)		
Weight month 36	0.61 (± 0.987)	0.82 (± 1.268)		
BMI month 12	0.00 (± 0.716)	0.24 (± 0.980)		
BMI month 36	0.02 (± 0.860)	0.47 (± 1.231)		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of evolution of renal allograft function over time

End point title	Evaluation of evolution of renal allograft function over time

End point description:

results given as eGFR values by time interval

End point type	Secondary

End point timeframe:

baseline, 6 months, 12 months , 24 months, 36 months

End point values	EVR+rTAC	MMF+sTAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: ml/min/1.73m2				
arithmetic mean (standard deviation)				
baseline	14.2 (± 11.38)	13.1 (± 15.62)		
month 6	76.6 (± 28.29)	68.3 (± 21.02)		
month 12	76.9 (± 21.61)	67.8 (± 23.57)		
month 24	72.9 (± 28.43)	68.6 (± 23.26)		
month 36	68.2 (± 21.60)	69.6 (± 20.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate renal function, assessed by Glomerular Filtration Rate (eGFR) and estimated by the Schwartz formula (extended), at Month 12

End point title	To evaluate renal function, assessed by Glomerular Filtration Rate (eGFR) and estimated by the Schwartz formula (extended), at Month 12

End point description:

To evaluate renal function assessed by Glomerular Filtration Rate (eGFR) estimated by the Schwartz Formula (extended) (Schwartz, 2009). Results given as change from randomization

End point type	Secondary

End point timeframe:

12 months post-transplantation

End point values	EVR+rTAC	MMF+sTAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: mL/min/1.73m2				
arithmetic mean (standard deviation)	4.6 (± 11.94)	-0.0 (± 23.92)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to 36 months	
Adverse event reporting additional description: AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	EVR+rTAC
Reporting group description: EVR+rTAC	
Reporting group title	MMF+sTAC
Reporting group description: MMF+sTAC	

Serious adverse events	EVR+rTAC	MMF+sTAC	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	0 / 54 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	EVR+rTAC	MMF+sTAC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 52 (88.46%)	48 / 54 (88.89%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 52 (1.92%)	3 / 54 (5.56%)	
occurrences (all)	1	4	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 52 (13.46%)	6 / 54 (11.11%)	
occurrences (all)	9	7	
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	14 / 52 (26.92%)	11 / 54 (20.37%)	
occurrences (all)	55	27	
Fatigue			
subjects affected / exposed	3 / 52 (5.77%)	2 / 54 (3.70%)	
occurrences (all)	3	4	
Pain			
subjects affected / exposed	3 / 52 (5.77%)	3 / 54 (5.56%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 52 (21.15%)	10 / 54 (18.52%)	
occurrences (all)	20	23	
Oropharyngeal pain			
subjects affected / exposed	3 / 52 (5.77%)	3 / 54 (5.56%)	
occurrences (all)	3	3	
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 52 (5.77%)	6 / 54 (11.11%)	
occurrences (all)	6	7	
Hepatic enzyme increased			
subjects affected / exposed	3 / 52 (5.77%)	1 / 54 (1.85%)	
occurrences (all)	3	1	
Weight decreased			
subjects affected / exposed	0 / 52 (0.00%)	5 / 54 (9.26%)	
occurrences (all)	0	7	
Weight increased			
subjects affected / exposed	5 / 52 (9.62%)	2 / 54 (3.70%)	
occurrences (all)	5	2	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 52 (19.23%)	11 / 54 (20.37%)	
occurrences (all)	17	13	
Tremor			

subjects affected / exposed	1 / 52 (1.92%)	4 / 54 (7.41%)	
occurrences (all)	1	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 52 (19.23%)	11 / 54 (20.37%)	
occurrences (all)	11	12	
Iron deficiency anaemia			
subjects affected / exposed	3 / 52 (5.77%)	0 / 54 (0.00%)	
occurrences (all)	4	0	
Leukopenia			
subjects affected / exposed	6 / 52 (11.54%)	6 / 54 (11.11%)	
occurrences (all)	8	7	
Neutropenia			
subjects affected / exposed	2 / 52 (3.85%)	10 / 54 (18.52%)	
occurrences (all)	2	12	
Polycythaemia			
subjects affected / exposed	3 / 52 (5.77%)	0 / 54 (0.00%)	
occurrences (all)	3	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	5 / 52 (9.62%)	5 / 54 (9.26%)	
occurrences (all)	6	5	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 52 (13.46%)	6 / 54 (11.11%)	
occurrences (all)	10	9	
Abdominal pain upper			
subjects affected / exposed	6 / 52 (11.54%)	5 / 54 (9.26%)	
occurrences (all)	8	11	
Aphthous ulcer			
subjects affected / exposed	9 / 52 (17.31%)	1 / 54 (1.85%)	
occurrences (all)	14	3	
Constipation			
subjects affected / exposed	3 / 52 (5.77%)	2 / 54 (3.70%)	
occurrences (all)	3	3	
Diarrhoea			

subjects affected / exposed	13 / 52 (25.00%)	16 / 54 (29.63%)	
occurrences (all)	23	31	
Mouth ulceration			
subjects affected / exposed	3 / 52 (5.77%)	2 / 54 (3.70%)	
occurrences (all)	7	2	
Nausea			
subjects affected / exposed	4 / 52 (7.69%)	4 / 54 (7.41%)	
occurrences (all)	6	4	
Vomiting			
subjects affected / exposed	10 / 52 (19.23%)	8 / 54 (14.81%)	
occurrences (all)	25	23	
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	3 / 52 (5.77%)	0 / 54 (0.00%)	
occurrences (all)	5	0	
Pruritus			
subjects affected / exposed	0 / 52 (0.00%)	4 / 54 (7.41%)	
occurrences (all)	0	6	
Rash			
subjects affected / exposed	5 / 52 (9.62%)	2 / 54 (3.70%)	
occurrences (all)	9	2	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 52 (5.77%)	3 / 54 (5.56%)	
occurrences (all)	3	3	
Proteinuria			
subjects affected / exposed	4 / 52 (7.69%)	2 / 54 (3.70%)	
occurrences (all)	4	2	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	4 / 52 (7.69%)	1 / 54 (1.85%)	
occurrences (all)	4	1	
Infections and infestations			
BK virus infection			
subjects affected / exposed	4 / 52 (7.69%)	8 / 54 (14.81%)	
occurrences (all)	6	9	

Bronchitis			
subjects affected / exposed	2 / 52 (3.85%)	4 / 54 (7.41%)	
occurrences (all)	2	6	
Cystitis			
subjects affected / exposed	3 / 52 (5.77%)	1 / 54 (1.85%)	
occurrences (all)	6	1	
Cytomegalovirus infection			
subjects affected / exposed	3 / 52 (5.77%)	3 / 54 (5.56%)	
occurrences (all)	4	4	
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 52 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	3	
Ear infection			
subjects affected / exposed	1 / 52 (1.92%)	5 / 54 (9.26%)	
occurrences (all)	1	5	
Epstein-Barr viraemia			
subjects affected / exposed	3 / 52 (5.77%)	2 / 54 (3.70%)	
occurrences (all)	3	2	
Epstein-Barr virus infection			
subjects affected / exposed	7 / 52 (13.46%)	2 / 54 (3.70%)	
occurrences (all)	8	2	
Gastroenteritis			
subjects affected / exposed	4 / 52 (7.69%)	5 / 54 (9.26%)	
occurrences (all)	5	6	
Influenza			
subjects affected / exposed	3 / 52 (5.77%)	1 / 54 (1.85%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	16 / 52 (30.77%)	6 / 54 (11.11%)	
occurrences (all)	45	20	
Oral herpes			
subjects affected / exposed	2 / 52 (3.85%)	3 / 54 (5.56%)	
occurrences (all)	2	4	
Otitis media			
subjects affected / exposed	4 / 52 (7.69%)	1 / 54 (1.85%)	
occurrences (all)	6	1	

Pharyngitis			
subjects affected / exposed	6 / 52 (11.54%)	1 / 54 (1.85%)	
occurrences (all)	6	1	
Rhinitis			
subjects affected / exposed	7 / 52 (13.46%)	5 / 54 (9.26%)	
occurrences (all)	15	10	
Sinusitis			
subjects affected / exposed	1 / 52 (1.92%)	3 / 54 (5.56%)	
occurrences (all)	1	3	
Tonsillitis			
subjects affected / exposed	3 / 52 (5.77%)	8 / 54 (14.81%)	
occurrences (all)	3	9	
Upper respiratory tract infection			
subjects affected / exposed	8 / 52 (15.38%)	6 / 54 (11.11%)	
occurrences (all)	10	9	
Urinary tract infection			
subjects affected / exposed	13 / 52 (25.00%)	15 / 54 (27.78%)	
occurrences (all)	20	30	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 52 (1.92%)	3 / 54 (5.56%)	
occurrences (all)	2	5	
Hypertriglyceridaemia			
subjects affected / exposed	4 / 52 (7.69%)	2 / 54 (3.70%)	
occurrences (all)	4	2	
Hypokalaemia			
subjects affected / exposed	3 / 52 (5.77%)	1 / 54 (1.85%)	
occurrences (all)	3	1	
Hypomagnesaemia			
subjects affected / exposed	0 / 52 (0.00%)	4 / 54 (7.41%)	
occurrences (all)	0	5	
Iron deficiency			
subjects affected / exposed	6 / 52 (11.54%)	0 / 54 (0.00%)	
occurrences (all)	7	0	
Metabolic acidosis			

subjects affected / exposed	3 / 52 (5.77%)	0 / 54 (0.00%)	
occurrences (all)	3	0	
Obesity			
subjects affected / exposed	2 / 52 (3.85%)	3 / 54 (5.56%)	
occurrences (all)	2	3	
Vitamin D deficiency			
subjects affected / exposed	3 / 52 (5.77%)	4 / 54 (7.41%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2013	The purpose of this amendment was a) to update inclusion / exclusion criteria, and b) to allow the choice between two induction options (Simulect or no induction) to optimize patient enrollment, c) to introduce an interim analysis for the purpose of regulatory data submission.
03 June 2014	The purpose of this amendment was a) to replace the analysis introduced in the protocol amendment v02, dated 19-Feb-2013 by a 12 Month analysis in a subset of at least 30 patients for the purpose of regulatory data submission, and b) to introduce a standardized definition for the assessment of New Onset Diabetes Mellitus (NODM) which will be applied to all ongoing and new RAD001 clinical trials.
11 February 2015	The purpose of this amendment was to comply with the European Medicines Agency request to amend all Novartis clinical trials where Cellcept® (mycophenolate mofetil - MMF) and Myfortic™ (enteric-coated formulation of mycophenolate sodium (EC-MPS)) are used as Investigational Medicinal Product (IMP). The following new warnings regarding the risks of hypogammaglobulinemia and bronchiectasis had to be provided to all investigators and patients participating in the study
14 July 2016	In response to the French Health Authorities (HA) request, the protocol was updated with the recent notifications for use of mycophenolate based on EMA's recommendation published on 23 Oct 2015, and the Dear Health Care Professional Letter (DHCPL) for CellCept that was distributed by F. Hoffmann-La Roche AG on 10-Nov-2015.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported