



Clinical trial results:

A 24-month, multi-center, single arm, prospective study to evaluate renal function, efficacy, safety and tolerability of everolimus in combination with reduced exposure cyclosporine or tacrolimus in paediatric liver transplant recipients

Summary

EudraCT number	2011-003069-14
Trial protocol	HU SE DE ES GB DK IT BE FR
Global end of trial date	01 June 2016

Results information

Result version number	v1 (current)
This version publication date	16 December 2016
First version publication date	16 December 2016

Trial information

Trial identification

Sponsor protocol code	CRAD001H2305
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01598987
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)	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	01 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 June 2016
Global end of trial reached?	Yes
Global end of trial date	01 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the evolution of renal function assessed by estimated Glomerular Filtration Rate (eGFR) estimated by the Chronic Kidney Disease in Children (CKiD) Schwartz formula (Schwartz 2009) from start to Month 12 of an everolimus based regimen

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	09 October 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	Australia: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	56
EEA total number of subjects	43

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)	25
Children (2-11 years)	26
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Overall 62 patients were screened prior to the data monitoring committee (DMC) recommendation to terminate enrolment.

Six patients were screen failures. The other 56 patients were included and treated.

Period 1

Period 1 title	Period up to Month 12
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Everolimus based regimen
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Arm description:

Conversion at baseline from an immunosuppressive regimen which contains either cyclosporine (CsA) or tacrolimus (TAC) with or without mycophenolic acid (MPA), with or without corticosteroids in a regimen which contains everolimus combined reduced dose of either cyclosporine (CsA) or tacrolimus (TAC). The dosing schedule was twice daily, 12 hours apart.

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:

Everolimus 0.10 and 0.25 mg dispersible tablets and 0.25, 0.50, 0.75 and 1.0 mg tablets were provided for oral administration. At the start of everolimus treatment regimen, pediatric transplant recipients received a starting dose of 0.8 mg/m²/dose in combination with cyclosporine or 2.0 mg/m²/dose in combination with tacrolimus, twice-daily. Thereafter, doses were adjusted to achieve everolimus C-0h blood trough level between 3 to 8 ng/mL.

Number of subjects in period 1	Everolimus based regimen
Started	56
Completed	50
Not completed	6
Consent withdrawn by subject	4
Administrative problems	2

Period 2

Period 2 title	Period up to 24 month
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Everolimus based regimen
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Arm description:

Conversion at baseline from an immunosuppressive regimen which contains either cyclosporine (CsA) or tacrolimus (TAC) with or without mycophenolic acid (MPA), with or without corticosteroids in a regimen which contains everolimus combined reduced dose of either cyclosporine (CsA) or tacrolimus (TAC). The dosing schedule was twice daily, 12 hours apart.

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Number of subjects in period 2	Everolimus based regimen
Started	50
Completed	48
Not completed	2
Consent withdrawn by subject	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Everolimus based regimen
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Reporting group description:

Conversion at baseline from an immunosuppressive regimen which contains either cyclosporine (CsA) or tacrolimus (TAC) with or without mycophenolic acid (MPA), with or without corticosteroids in a regimen which contains everolimus combined reduced dose of either cyclosporine (CsA) or tacrolimus (TAC). The dosing schedule was twice daily, 12 hours apart.

Reporting group values	Everolimus based regimen	Total	
Number of subjects	56	56	
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)	25	25	
Children (2-11 years)	26	26	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	4.9		
standard deviation	± 4.59	-	
Gender, Male/Female			
Units: Subjects			
Female	25	25	
Male	31	31	

End points

End points reporting groups

Reporting group title	Everolimus based regimen
Reporting group description: Conversion at baseline from an immunosuppressive regimen which contains either cyclosporine (CsA) or tacrolimus (TAC) with or without mycophenolic acid (MPA), with or without corticosteroids in a regimen which contains everolimus combined reduced dose of either cyclosporine (CsA) or tacrolimus (TAC). The dosing schedule was twice daily, 12 hours apart.	
Reporting group title	Everolimus based regimen
Reporting group description: Conversion at baseline from an immunosuppressive regimen which contains either cyclosporine (CsA) or tacrolimus (TAC) with or without mycophenolic acid (MPA), with or without corticosteroids in a regimen which contains everolimus combined reduced dose of either cyclosporine (CsA) or tacrolimus (TAC). The dosing schedule was twice daily, 12 hours apart.	
Subject analysis set title	<=5% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Height	
Subject analysis set title	>5% - 25% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Height	
Subject analysis set title	>25% - 50% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Height	
Subject analysis set title	>50% - 75% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Height	
Subject analysis set title	>75% - 95% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Height	
Subject analysis set title	>95% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Height	
Subject analysis set title	Total
Subject analysis set type	Safety analysis
Subject analysis set description: The classified change from baseline in growth percentiles cross-tabulated against baseline categories of growth percentiles at 12 months	
Subject analysis set title	<=5% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Weight	
Subject analysis set title	>5% - 25% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Weight	

Subject analysis set title	>25% - 50% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Weight	
Subject analysis set title	>50% - 75% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Weight	
Subject analysis set title	>75% - 95% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Weight	
Subject analysis set title	>95% percentile
Subject analysis set type	Safety analysis
Subject analysis set description: Growth percentile category - Weight	
Subject analysis set title	Total
Subject analysis set type	Safety analysis
Subject analysis set description: The classified change from baseline in growth percentiles cross-tabulated against baseline categories of growth percentiles at 12 months	

Primary: Change from Baseline in Estimated Glomerular Filtration Rate - Month 12

End point title	Change from Baseline in Estimated Glomerular Filtration Rate - Month 12 ^[1]
End point description: Evolution of renal function assessed by estimated Glomerular Filtration Rate (eGFR) estimated by the Chronic Kidney Disease in Children (CKiD) Schwartz formula (Schwartz 2009), expressed in mean change in eGFR of CKiD between start of study (baseline assessment) and Month 12.	
End point type	Primary
End point timeframe: Baseline, Month 12	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were planned for this end point.

End point values	Everolimus based regimen			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: mL/min/1.73m ²				
arithmetic mean (standard deviation)	6.2 (± 19.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates for Failure rates of Efficacy Endpoints

End point title	Kaplan-Meier Estimates for Failure rates of Efficacy Endpoints
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End point description:

The proportion of patients with composite efficacy failure (treated biopsy proven acute rejection[tBPAR], graft loss [GL] , death [D]) before/at Month 12 and Month 24, estimated with Kaplan-Meier (KM) methods and the proportion of patients who experienced any of the components of composite efficacy failure (tBPAR, GL, D) before/at Month 12 and Month 24, separately for each component. AR: acute rejection; BPAR: biopsy proven acute rejection. Rate = Kaplan-Meier estimate for failure in %; CI = confidence interval for failure rate.

End point type	Secondary
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End point timeframe:

At 12-month and 24-month after start of study drug

End point values	Everolimus based regimen			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Percentages				
number (confidence interval 80%)				
Month 12: tBPAR,GL,or D	1.9 (0 to 4.2)			
Month 12: tBPAR,GL,D,or loss to follow-up	1.9 (0 to 4.2)			
Month 12: Treated BPAR	1.9 (0 to 4.2)			
Month 12: Graft loss	0 (0 to 0)			
Month 12: Death	0 (0 to 0)			
Month 12: Graft loss or death	0 (0 to 0)			
Month 12: BPAR	3.7 (0.4 to 7)			
Month 12: Treated AR	3.6 (0.4 to 6.9)			
Month 24: tBPAR,GL,or D	5.9 (0.3 to 11.5)			
Month 24: tBPAR,GL,D,or loss to follow-up	9.7 (2.5 to 16.9)			
Month 24: Treated BPAR	5.9 (0.3 to 11.5)			
Month 24: Graft Loss	0 (0 to 0)			
Month 24: Death	0 (0 to 0)			
Month 24: Graft loss or death	0 (0 to 0)			
Month 24: BPAR	11.9 (4.2 to 19.6)			
Month 24: Treated AR	7.7 (1.7 to 13.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Estimated Glomerular Filtration Rate - Month 24

End point title	Change from Baseline in Estimated Glomerular Filtration Rate - Month 24
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End point description:

Evolution of renal function assessed by estimated Glomerular Filtration Rate (eGFR) estimated by the Chronic Kidney Disease in Children (CKiD) Schwartz formula (Schwartz 2009), expressed in mean

change in eGFR of CKiD between start of study (baseline assessment) and Month 24.

End point type	Secondary
End point timeframe:	
Baseline, Month 24	

End point values	Everolimus based regimen			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: mL/min/1.73m ²				
arithmetic mean (standard deviation)	4.5 (± 19.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Growth development - Height at Baseline and Month 12

End point title	Growth development - Height at Baseline and Month 12
End point description:	
Individual growth measurements were compared with the gender and age-specific growth percentiles in the CDC growth charts for the US population. Each value observed is thus represented by the (approximated) percentage of subjects with a lower value in the reference population. Changes were calculated on this scale and thus express the change in growth measurements relative to the percentiles in the CDC growth charts. Patients were classified into growth percentile categories (<=5, >5-25, >25-50, >50-75, >75-95 and >95% percentile).	
End point type	Secondary
End point timeframe:	
Baseline, Month 12	

End point values	<=5% percentile	>5% - 25% percentile	>25% - 50% percentile	>50% - 75% percentile
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	15	6	7
Units: Percentages				
number (not applicable)				
Decrease	0	26.7	16.7	14.3
No Change	68.8	20	33.3	28.6
Increase >3 to 5%	12.5	6.7	0	0
Increase >5 to 10%	0	20	16.7	14.3
Increase >10%	18.8	26.7	33.3	42.9

End point values	>75% - 95% percentile	>95% percentile	Total	

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	2	50	
Units: Percentages				
number (not applicable)				
Decrease	25	0	14	
No Change	50	100	44	
Increase >3 to 5%	25	0	8	
Increase >5 to 10%	0	0	10	
Increase >10%	0	0	24	

Statistical analyses

No statistical analyses for this end point

Secondary: Growth development - Weight at Baseline and Month 12

End point title	Growth development - Weight at Baseline and Month 12
End point description:	Individual growth measurements were compared with the gender and age-specific growth percentiles in the CDC growth charts for the US population. Each value observed is thus represented by the (approximated) percentage of subjects with a lower value in the reference population. Changes were calculated on this scale and thus express the change in growth measurements relative to the percentiles in the CDC growth charts. Patients were classified into growth percentile categories (≤ 5 , $>5-25$, $>25-50$, $>50-75$, $>75-95$ and $>95\%$ percentile).
End point type	Secondary
End point timeframe:	Baseline, Month 12

End point values	$\leq 5\%$ percentile	$>5\% - 25\%$ percentile	$>25\% - 50\%$ percentile	$>50\% - 75\%$ percentile
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	10	7	11
Units: Percentages				
number (not applicable)				
Decrease	0	20	42.9	72.9
No Change	33.3	20	0	18.2
Increase >3 to 5%	0	0	0	0
Increase >5 to 10%	26.7	0	0	9.1
Increase >10%	40	60	57.1	0

End point values	$>75\% - 95\%$ percentile	$>95\%$ percentile	Total	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	1	22	
Units: Percentages				
number (not applicable)				
Decrease	16.7	0	28	

No Change	33.3	100	24	
Increase >3 to 5%	16.7	0	2	
Increase >5 to 10%	0	0	10	
Increase >10%	33.3	0	36	

Statistical analyses

No statistical analyses for this end point

Secondary: Growth development - Weight at Baseline and Month 24

End point title	Growth development - Weight at Baseline and Month 24
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End point description:

Individual growth measurements were compared with the gender and age-specific growth percentiles in the CDC growth charts for the US population. Each value observed is thus represented by the (approximated) percentage of subjects with a lower value in the reference population. Changes were calculated on this scale and thus express the change in growth measurements relative to the percentiles in the CDC growth charts. Patients were classified into growth percentile categories (<=5, >5-25, >25-50, >50-75, >75-95 and >95% percentile).

End point type	Secondary
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End point timeframe:

Baseline, Month 24

End point values	<=5% percentile	>5% - 25% percentile	>25% - 50% percentile	>50% - 75% percentile
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	5	2	8
Units: Percentages				
number (not applicable)				
Decrease	0	40	100	12.5
No Change	50	0	0	25
Increase >3 to 5%	16.7	0	0	12.5
Increase >5 to 10%	16.7	20	0	12.5
Increase >10%	16.7	40	0	37.5

End point values	>75% - 95% percentile	>95% percentile	Total
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0 ^[2]	1	22
Units: Percentages			
number (not applicable)			
Decrease		0	22.7
No Change		100	27.3
Increase >3 to 5%		0	9.1
Increase >5 to 10%		0	13.6
Increase >10%		0	27.3

Notes:

[2] - No patients were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Growth development - Height at Baseline and Month 24

End point title	Growth development - Height at Baseline and Month 24
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End point description:

Individual growth measurements were compared with the gender and age-specific growth percentiles in the CDC growth charts for the US population. Each value observed is thus represented by the (approximated) percentage of subjects with a lower value in the reference population. Changes were calculated on this scale and thus express the change in growth measurements relative to the percentiles in the CDC growth charts. Patients were classified into growth percentile categories (≤ 5 , $>5-25$, $>25-50$, $>50-75$, $>75-95$ and $>95\%$ percentile).

End point type	Secondary
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End point timeframe:

Baseline, Month 24

End point values	$\leq 5\%$ percentile	$>5\% - 25\%$ percentile	$>25\% - 50\%$ percentile	$>50\% - 75\%$ percentile
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	8	3	2
Units: Percentages				
number (not applicable)				
Decrease	0	12.5	33.3	0
No Change	50	12.5	0	0
Increase >3 to 5%	33.3	12.5	0	0
Increase >5 to 10%	0	0	33.3	0
Increase $>10\%$	16.7	62.5	33.3	100

End point values	$>75\% - 95\%$ percentile	$>95\%$ percentile	Total	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	1	22	
Units: Percentages				
number (not applicable)				
Decrease	0	0	9	
No Change	50	100	27.3	
Increase >3 to 5%	50	0	18.2	
Increase >5 to 10%	0	0	4.5	
Increase $>10\%$	0	0	40.9	

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.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	All Patients
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Reporting group description:

All Patients

Serious adverse events	All Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 56 (76.79%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Post transplant lymphoproliferative disorder			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	9 / 56 (16.07%)		
occurrences causally related to treatment / all	6 / 10		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transplant rejection			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Lung infiltration			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Organising pneumonia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stridor			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Psychiatric disorders			
Food aversion			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Body temperature increased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Drug level increased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Liver function test increased			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Weight decreased subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Biliary anastomosis complication subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Complications of transplanted liver subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibula fracture subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Incisional hernia subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Tibia fracture subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transplant failure subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Tachycardia subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Headache			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic lesion			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aphthous ulcer			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Internal hernia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal haemorrhage			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth ulceration			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Hepatic function abnormal			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic steatosis			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic vein occlusion			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatocellular injury			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Portal fibrosis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dermal cyst			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Swelling face			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Proteinuria			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Adenoviral upper respiratory infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Adenovirus infection			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Alpha haemolytic streptococcal infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial pyelonephritis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis infective			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Croup infectious			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea infectious			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis infectious			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterovirus infection			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Epstein-Barr viraemia			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Epstein-Barr virus infection			

subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Escherichia infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis adenovirus			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis sapovirus			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			

subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Mastoiditis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral candidiasis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oral viral infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paronychia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences causally related to treatment / all	5 / 7		
deaths causally related to treatment / all	0 / 0		
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Puncture site infection			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rhinovirus infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rotavirus infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scarlet fever			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			

subjects affected / exposed	3 / 56 (5.36%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Varicella zoster virus infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 56 (91.07%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences (all)	4		
Pain			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	22 / 56 (39.29%)		
occurrences (all)	41		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	8		
Epistaxis			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3		
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	7 / 56 (12.50%) 7		
Hepatic enzyme increased subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4 3 / 56 (5.36%) 5		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 9		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	6 / 56 (10.71%) 7 4 / 56 (7.14%) 5		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 4		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper	7 / 56 (12.50%) 10		

<p>subjects affected / exposed occurrences (all)</p>	<p>3 / 56 (5.36%) 3</p>		
<p>Constipation subjects affected / exposed occurrences (all)</p>	<p>3 / 56 (5.36%) 4</p>		
<p>Diarrhoea subjects affected / exposed occurrences (all)</p>	<p>22 / 56 (39.29%) 36</p>		
<p>Mouth ulceration subjects affected / exposed occurrences (all)</p>	<p>6 / 56 (10.71%) 8</p>		
<p>Nausea subjects affected / exposed occurrences (all)</p>	<p>4 / 56 (7.14%) 7</p>		
<p>Stomatitis subjects affected / exposed occurrences (all)</p>	<p>5 / 56 (8.93%) 5</p>		
<p>Vomiting subjects affected / exposed occurrences (all)</p>	<p>15 / 56 (26.79%) 22</p>		
<p>Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)</p>	<p>4 / 56 (7.14%) 4</p>		
<p>Rash subjects affected / exposed occurrences (all)</p>	<p>3 / 56 (5.36%) 4</p>		
<p>Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)</p>	<p>4 / 56 (7.14%) 4</p>		
<p>Infections and infestations Bronchitis subjects affected / exposed occurrences (all)</p>	<p>5 / 56 (8.93%) 7</p>		
<p>Conjunctivitis</p>			

subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	6		
Cytomegalovirus viraemia			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	7		
Diarrhoea infectious			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	5		
Ear infection			
subjects affected / exposed	6 / 56 (10.71%)		
occurrences (all)	11		
Epstein-Barr viraemia			
subjects affected / exposed	10 / 56 (17.86%)		
occurrences (all)	14		
Epstein-Barr virus infection			
subjects affected / exposed	7 / 56 (12.50%)		
occurrences (all)	10		
Eye infection			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Gastroenteritis			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	8		
Influenza			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	5		
Nasopharyngitis			
subjects affected / exposed	15 / 56 (26.79%)		
occurrences (all)	35		
Otitis media			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Rhinitis			
subjects affected / exposed	5 / 56 (8.93%)		
occurrences (all)	6		
Tonsillitis			

subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 5		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	14 / 56 (25.00%) 17		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 January 2014	The main purpose of this amendment was a) to introduce a 12 Month analysis in a subset of at least 20 patients for the purpose of regulatory data submission, and b) to introduce a standardized definition for the assessment of NODM which was applied to all ongoing and new RAD001 clinical trials.
13 February 2015	The main purpose of this amendment was to implement CRAD001H2305 DMC recommendations. DMC recommended to keep the enrollment closed (due to high rate of post-transplant lymphoproliferative disorder, high rate of related serious infections leading to prolonged hospitalization and high rate of premature discontinuation of study medication) and discontinue the study medication in patients younger than 7 years of age and switch those patients to standard of care immunosuppressive treatment. All patients who discontinued study medication, regardless of age, were required to remain in the study for safety follow-up up to 24 months, as per protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported