Clinical trial results:
Multicenter, open-label, single-arm, safety, tolerability, efficacy and pharmacokinetic study of RAD001 in pediatric de novo renal transplant patients (12-month analysis)

Summary

EudraCT number	2005-002372-16
Trial protocol	ES
Global end of trial date	21 March 2007

Results information

Result version number	v1 (current)
This version publication date	04 January 2017
First version publication date	04 January 2017
Summary attachment (see zip file)	CRAD001B351_NovCTR (CRAD001B351_NovCTR.pdf)

Trial information

Trial identification

Sponsor protocol code	CRAD001AB351

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	21 March 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2007
Global end of trial reached?	Yes
Global end of trial date	21 March 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study was conducted in 2 parts: Cohort 1 and Cohort 2.
Cohort 1: The main objective of the study was to evaluate the safety and tolerability of RAD001 (everolimus) administered in combination with cyclosporine and corticosteroids in pediatric de novo renal transplant subjects.
Cohort 2: The main objective of the study was to evaluate safety and tolerability of concentration-controlled everolimus administered in combination with reduced cyclosporine and corticosteroids in pediatric de novo renal transplant subjects.

Protection of trial subjects:

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

Background therapy:

Background immunosuppressive therapy was cyclosporine and corticosteroids. Cyclosporine [6 to 12 milligrams (mg)/Kilograms (kg)/day]was started within 24 hours post-transplantation or pre-transplantation according to the local standard of care. Intravenous (IV) corticosteroids were given pre- or intra-operatively according to local practice at each center. Oral prednisone (or equivalent) (0.1 mg/kg/day)was given according to local practice from Day 1, and continued for at least 6 months.

Evidence for comparator: -

Actual start date of recruitment	18 August 2004
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	37
EEA total number of subjects	19

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)	18
Adolescents (12-17 years)	19
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at: Cohort I - 15 centers [United States (6), France (2), Germany (2), Spain (2), Belgium (1), Brazil (1) and United Kingdom (1)]; Cohort II - 3 centers (United States).

Pre-assignment

Screening details:

A total of 37 subjects were enrolled in the study.

Period 1

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

Blinding implementation details:

The study was open label study, hence no blinding was performed

Arms

Are arms mutually exclusive?	No
Arm title	Everolimus (fixed dose), subjects <10 years

Arm description:

All subjects aged less than 10 years and undergone renal transplantation were administered with fixed-dose everolimus 0.8 milligram (mg)/metre (m) ^2 body surface area (BSA) (maximum 1.5 mg) twice-daily (bid), 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner. Cyclosporine was dosed according to trough blood levels based on a conventional down-titration of exposure.

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

Dosage and administration details:

Subjects were administered with fixed-dose everolimus 0.8 mg/ m^2 BSA (maximum 1.5 mg) bid, 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner.

Arm title	Everolimus (fixed dose), subjects 10 to 16 years

Arm description:

All subjects aged 10 to 16 years and undergone renal transplantation were administered with 0.8 mg/m^2 BSA of everolimus (not to exceed 1.5 mg as a single dose independent of BSA) bid, 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner. Cyclosporine was dosed according to trough blood levels based on a conventional down-titration of exposure.

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

Dosage and administration details:

Subjects were administered with fixed-dose everolimus 0.8 mg/ m^2 BSA (maximum 1.5 mg) bid, 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner.

Arm title	Everolimus (concentration-controlled), subjects <10 years

Arm description:

All subjects aged less than 10 years and undergone renal transplantation were administered with initial doses of everolimus at 0.8 mg/ m^2 BSA bid, 12 hours apart, in combination with cyclosporine and corticosteroids followed by administration of everolimus by therapeutic drug monitoring, targeting a blood trough level of > 3 nanogram (ng)/milliliter (mL). Cyclosporine was administered bid by therapeutic drug monitoring targeting reduced cyclosporine trough levels.

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

Dosage and administration details:

Subjects were administered with fixed-dose everolimus 0.8 mg/ m^2 BSA (maximum 1.5 mg) bid, 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner.

Arm title	Everolimus (concentration-controlled), subjects 10 to 16 years

Arm description:

All subjects aged between 10 to 16 years and undergone renal transplantation were administered with initial doses of everolimus at 0.8 mg/m^2 BSA bid, 12 hours apart, in combination with cyclosporine and corticosteroids followed by administration of everolimus by therapeutic drug monitoring, targeting a blood trough level of > 3ng/mL. Cyclosporine was administered targeting reduced cyclosporine trough levels.

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

Dosage and administration details:

Subjects were administered with fixed-dose everolimus 0.8 mg/ m^2 BSA (maximum 1.5 mg) bid, 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner.

Number of subjects in period 1	Everolimus (fixed dose), subjects <10 years	Everolimus (fixed dose), subjects 10 to 16 years	Everolimus (concentration-controlled), subjects <10 years
Started	10	9	6
Completed	10	9	6

Number of subjects in period 1	Everolimus (concentration-controlled), subjects 10 to 16 years
Started	12
Completed	12

Baseline characteristics

Reporting groups

Reporting group title	Everolimus (fixed dose), subjects <10 years

Reporting group description:

All subjects aged less than 10 years and undergone renal transplantation were administered with fixed-dose everolimus 0.8 milligram (mg)/metre (m) ^2 body surface area (BSA) (maximum 1.5 mg) twice-daily (bid), 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner. Cyclosporine was dosed according to trough blood levels based on a conventional down-titration of exposure.

Reporting group title	Everolimus (fixed dose), subjects 10 to 16 years

Reporting group description:

All subjects aged 10 to 16 years and undergone renal transplantation were administered with 0.8 mg/m^2 BSA of everolimus (not to exceed 1.5 mg as a single dose independent of BSA) bid, 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner. Cyclosporine was dosed according to trough blood levels based on a conventional down-titration of exposure.

Reporting group title	Everolimus (concentration-controlled), subjects <10 years

Reporting group description:

All subjects aged less than 10 years and undergone renal transplantation were administered with initial doses of everolimus at 0.8 mg/ m^2 BSA bid, 12 hours apart, in combination with cyclosporine and corticosteroids followed by administration of everolimus by therapeutic drug monitoring, targeting a blood trough level of > 3 nanogram (ng)/milliliter (mL). Cyclosporine was administered bid by therapeutic drug monitoring targeting reduced cyclosporine trough levels.

Reporting group title	Everolimus (concentration-controlled), subjects 10 to 16 years

Reporting group description:

All subjects aged between 10 to 16 years and undergone renal transplantation were administered with initial doses of everolimus at 0.8 mg/m^2 BSA bid, 12 hours apart, in combination with cyclosporine and corticosteroids followed by administration of everolimus by therapeutic drug monitoring, targeting a blood trough level of > 3ng/mL. Cyclosporine was administered targeting reduced cyclosporine trough levels.

Reporting group values	Everolimus (fixed dose), subjects <10 years	Everolimus (fixed dose), subjects 10 to 16 years	Everolimus (concentration-controlled), subjects <10 years
Number of subjects	10	9	6
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	10	0	6
Adolescents (12-17 years)	0	9	0
Age continuous Units: years			
arithmetic mean	5.7	13.2	5.2
standard deviation	± 2.54	± 1.72	± 2.32
Gender categorical Units: Subjects			
Female	6	4	3
Male	4	5	3

Reporting group values	Everolimus (concentration-controlled), subjects 10 to 16 years	Total	
Number of subjects	12	37	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	16	
Adolescents (12-17 years)	12	21	
Age continuous			
Units: years			
arithmetic mean	13.8		
standard deviation	± 2.08	-	
Gender categorical			
Units: Subjects			
Female	2	15	
Male	10	22	

End points

End points reporting groups

Reporting group title	Everolimus (fixed dose), subjects <10 years

Reporting group description:

All subjects aged less than 10 years and undergone renal transplantation were administered with fixed-dose everolimus 0.8 milligram (mg)/metre (m) ^2 body surface area (BSA) (maximum 1.5 mg) twice-daily (bid), 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner. Cyclosporine was dosed according to trough blood levels based on a conventional down-titration of exposure.

Reporting group title	Everolimus (fixed dose), subjects 10 to 16 years

Reporting group description:

All subjects aged 10 to 16 years and undergone renal transplantation were administered with 0.8 mg/m^2 BSA of everolimus (not to exceed 1.5 mg as a single dose independent of BSA) bid, 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner. Cyclosporine was dosed according to trough blood levels based on a conventional down-titration of exposure.

Reporting group title	Everolimus (concentration-controlled), subjects <10 years

Reporting group description:

All subjects aged less than 10 years and undergone renal transplantation were administered with initial doses of everolimus at 0.8 mg/ m^2 BSA bid, 12 hours apart, in combination with cyclosporine and corticosteroids followed by administration of everolimus by therapeutic drug monitoring, targeting a blood trough level of > 3 nanogram (ng)/milliliter (mL). Cyclosporine was administered bid by therapeutic drug monitoring targeting reduced cyclosporine trough levels.

Reporting group title	Everolimus (concentration-controlled), subjects 10 to 16 years

Reporting group description:

All subjects aged between 10 to 16 years and undergone renal transplantation were administered with initial doses of everolimus at 0.8 mg/m^2 BSA bid, 12 hours apart, in combination with cyclosporine and corticosteroids followed by administration of everolimus by therapeutic drug monitoring, targeting a blood trough level of > 3ng/mL. Cyclosporine was administered targeting reduced cyclosporine trough levels.

Primary: Number of subjects with Adverse Events (AEs) including infections, Serious Adverse Events (SAEs), AE leading to discontinuation and who died

End point title	Number of subjects with Adverse Events (AEs) including infections, Serious Adverse Events (SAEs), AE leading to discontinuation and who died[1]

End point description:

AEs are defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events are any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgment of investigators represent significant hazards. The analysis was performed on the intent-to-treat (ITT) population defined as all subjects who entered the study, were transplanted, and received at least one dose of study medication.

End point type	Primary

End point timeframe:

From Day 1 to Day 450 for on-treatment events (AEs/infection with onset up to 7 days after the premature discontinuation)

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: Only descriptive analysis was planned to be reported for safety end point.

End point values	Everolimus (fixed dose), subjects <10 years	Everolimus (fixed dose), subjects 10 to 16 years	Everolimus (concentration-controlled), subjects <10 years	Everolimus (concentration-controlled), subjects 10 to 16 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	6	12
Units: Subjects				
AEs/Infections	10	8	6	11
SAEs	0	0	5	5
Deaths	0	0	0	0
AEs leading to discontinuation	1	0	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with hematologic abnormalities based on notable criteria

End point title	Number of subjects with hematologic abnormalities based on notable criteria[2]

End point description:

Subjects with hematologic abnormalities based on notable criteria values outside the defined normal range were graded as laboratory abnormalities. Hematologic parameters for cohort I were: hemoglobin low (< 8.0 gram (g)/deciliter (dL)), platelets low (<=75 *10^9/L), leukocytes low (<= 2.8 *10^9/L), leukocytes high (>=16 *10^9/L) and absolute neutrophils low (<= 1.5 *10^9/L). Hematologic parameters for cohort II were: hemoglobin low (< 5.0 g/dL), platelets high (>=700 *10^9/L), leukocytes low (<= 2.8 *10^9/L), leukocytes high (>= 16 *10^9/L) and absolute neutrophils low (<= 1.5 *10^9/L). The analysis was performed on ITT population.

End point type	Primary

End point timeframe:

From Day 1 to Day 450 for on-treatment events (AEs/infection with onset up to 7 days after the premature discontinuation)

Notes:

[2] - 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: Only descriptive analysis was planned to be reported for safety end point.

End point values	Everolimus (fixed dose), subjects <10 years	Everolimus (fixed dose), subjects 10 to 16 years	Everolimus (concentration-controlled), subjects <10 years	Everolimus (concentration-controlled), subjects 10 to 16 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	6	12
Units: Subjects				
Hemoglobin low	4	1	1	0
Platelets low	1	0	0	0
Platelets high	0	0	1	0
Leukocytes low	1	0	0	1
Leukocytes high	4	1	3	2
Absolute neutrophils low	4	1	2	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with biochemistry abnormalities based on notable criteria for fixed-dose everolimus

End point title	Number of subjects with biochemistry abnormalities based on notable criteria for fixed-dose everolimus[3]

End point description:

Subjects with biochemistry abnormalities based on notable criteria values outside the defined normal range were graded as laboratory abnormalities by the sponsor. Biochemistry parameters included, liver function: serum glutamic oxaloacetic transaminase aspartate transaminase (SGOT(AST)) high (>= 3 * upper limit of normal (ULN)), serum glutamic pyruvic transaminase alanine transaminase (SGPT(ALT)) high (>= 3 *ULN); renal function: creatinine high (30% increase from previous visit or >= 354 micromole(µmol)/L Day 8 to Week 4 or >= 265 µmol/L after week 4, uric acid high (>= 0.714 millimole(mmol)/L [males] and >= 0.535 mmol/L [females]); lipids:total cholesterol high (>=9.1 mmol/L), triglycerides high (>= 5.6 mmol/L); metabolites and electrolytes: potassium low (<= 3 mmol/L), potassium high (>= 6 mmol/L); enzymes: amylase (>= 2 x ULN), lipase (>= 2 x ULN). The analysis was performed on ITT population.

End point type	Primary

End point timeframe:

From Day 1 to Day 450 for on-treatment events (AEs/infection with onset up to 7 days after the premature discontinuation)

Notes:

[3] - 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: Only descriptive analysis was planned to be reported for safety end point.

End point values	Everolimus (fixed dose), subjects <10 years	Everolimus (fixed dose), subjects 10 to 16 years	Everolimus (concentration-controlled), subjects <10 years	Everolimus (concentration-controlled), subjects 10 to 16 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	6	12
Units: Subjects				
Liver function: SGOT (AST) high	1	0	1	1
Liver function: SGPT (ALT) high	2	3	3	2
Renal function: Creatinine high	4	3	5	3
Renal function: Uric acid high	1	1	0	0
Lipids: Total cholesterol high	2	3	0	2
Lipids: Triglycerides high	1	2	0	1
Metabolites and electrolytes: Potassium low	1	0	2	1
Metabolites and electrolytes: Potassium high	0	1	0	0
Metabolites and electrolytes: Magnesium high	0	0	1	0
Metabolites and electrolytes: Uric acid high	0	0	1	0
Enzymes: Amylase	1	0	0	1

Enzymes: Lipase	5	2	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with urinalysis abnormalities

End point title	Number of subjects with urinalysis abnormalities[4]

End point description:

Subjects with urinalysis abnormalities such as positive urinary glucose and urinary protein post baseline were analyzed. Glucose and protein was determined using dipstick method. The analysis was performed on ITT population.

End point type	Primary

End point timeframe:

From Day 1 to Day 450 for on-treatment events (AEs/infection with onset up to 7 days after the premature discontinuation)

Notes:

[4] - 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: Only descriptive analysis was planned to be reported for safety end point.

End point values	Everolimus (fixed dose), subjects <10 years	Everolimus (fixed dose), subjects 10 to 16 years	Everolimus (concentration-controlled), subjects <10 years	Everolimus (concentration-controlled), subjects 10 to 16 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	6	12
Units: Subjects				
Positive urinary glucose	0	0	0	1
Positive urinary protein	2	4	1	1

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with clinically significant changes in vital signs and electrocardiogram (ECG)

End point title	Number of subjects with clinically significant changes in vital signs and electrocardiogram (ECG)[5]

End point description:

Subjects were evaluated for abnormal vital signs and ECG parameters. Vital signs like blood pressure (BP): systolic blood pressure (SBP) (>=140 millimeter of mercury (mmHg) and diastolic blood pressure (DBP) (>=90 mmHg) outside baseline range were graded as clinically significant vital signs. The analysis was performed on ITT population.

End point type	Primary

End point timeframe:

From Day 1 to Day 450 for on-treatment events (AEs/infection with onset up to 7 days after the premature discontinuation)

Notes:

[5] - 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: Only descriptive analysis was planned to be reported for safety end point.

End point values	Everolimus (fixed dose), subjects <10 years	Everolimus (fixed dose), subjects 10 to 16 years	Everolimus (concentration-controlled), subjects <10 years	Everolimus (concentration-controlled), subjects 10 to 16 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	6	12
Units: Subjects				
SBP	5	7	3	9
DBP	7	5	4	6
ECG	0	0	1	4

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with biopsy-proven acute rejection/graft loss/death/lost to follow-up within 12 months of the study

End point title	Number of subjects with biopsy-proven acute rejection/graft loss/death/lost to follow-up within 12 months of the study

End point description:

Efficacy failure was determined as biopsy-proven acute rejection/graft loss/death/lost to follow-up. Graft loss was defined as graft failure, including death due to graft failure. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Day 1 to Day 381

End point values	Everolimus (fixed dose), subjects <10 years	Everolimus (fixed dose), subjects 10 to 16 years	Everolimus (concentration-controlled), subjects <10 years	Everolimus (concentration-controlled), subjects 10 to 16 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	6	12
Units: Subjects				
Biopsy-proven acute rejection	0	3	0	0
Graft loss	0	0	0	0
Death	0	0	0	0
Loss to follow-up	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically confirmed acute rejection, antibody treated acute rejection, allograft nephropathy, chronic rejection, delayed graft function within 12 months of the study

End point title	Number of subjects with clinically confirmed acute rejection, antibody treated acute rejection, allograft nephropathy, chronic rejection, delayed graft function within 12 months of the study

End point description:

Efficacy of everolimus in the prevention of chronic allograft rejection (chronic graft dysfunction) was determined as clinically confirmed acute rejection/biopsy-proven acute rejection/antibody treated acute rejection/biopsy-proven chronic allograft nephropathy/clinically confirmed chronic rejection and delayed graft function. Delayed graft function was defined as need for dialysis within 7 days post-transplantation. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Day 1 to Day 381

End point values	Everolimus (fixed dose), subjects <10 years	Everolimus (fixed dose), subjects 10 to 16 years	Everolimus (concentration-controlled), subjects <10 years	Everolimus (concentration-controlled), subjects 10 to 16 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	6	12
Units: Subjects				
Clinically confirmed acute rejection	0	3	0	0
Antibody treated acute rejection	0	0	0	0
Biopsy-proven chronic allograft nephropathy	2	1	0	0
Clinically confirmed chronic rejection	1	1	0	0
Delayed graft function	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	0.0

Reporting groups

Reporting group title	Age Group <10 years

Reporting group description:

All subjects aged less than 10 years and undergone renal transplantation were administered with fixed-dose everolimus 0.8 mg/m ^2 BSA (maximum 1.5 mg) b.i.d, 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner. Cyclosporine was dosed according to trough blood levels based on a conventional down-titration of exposure.

Reporting group title	Age Group 10 to 16 years

Reporting group description:

All subjects aged 10 to 16 years and undergone renal transplantation were administered with 0.8 mg/m^2 BSA of everolimus (not to exceed 1.5 mg as a single dose independent of BSA) b.i.d, 12 hours apart after cyclosporine and corticosteroids administration and at least one hour prior to or after breakfast or dinner. Cyclosporine was dosed according to trough blood levels based on a conventional down-titration of exposure.

Serious adverse events	Age Group <10 years	Age Group 10 to 16 years	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	5 / 12 (41.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Cytomegalovirus test positive			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoproliferative disorder			

subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (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 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peritonitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder distension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Otitis media			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
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	Age Group <10 years	Age Group 10 to 16 years	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	10 / 12 (83.33%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	4 / 6 (66.67%)	4 / 12 (33.33%)	
occurrences (all)	4	4	
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Lymphocele			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	2 / 6 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	3 / 12 (25.00%)	
occurrences (all)	0	3	
Pain			

subjects affected / exposed	3 / 6 (50.00%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Pyrexia			
subjects affected / exposed	4 / 6 (66.67%)	4 / 12 (33.33%)	
occurrences (all)	5	3	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Genital erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Scrotal oedema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Scrotal swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 6 (50.00%)	3 / 12 (25.00%)	
occurrences (all)	6	5	
Epistaxis			
subjects affected / exposed	2 / 6 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Nasal congestion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Pharyngolaryngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	1	2	
Pulmonary oedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Rhinorrhoea			

subjects affected / exposed	4 / 6 (66.67%)	3 / 12 (25.00%)	
occurrences (all)	7	7	
Sinus congestion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Tachypnoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	3	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 12 (25.00%)	
occurrences (all)	0	4	
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 12 (25.00%)	
occurrences (all)	0	2	
Blood potassium decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Blood triglycerides increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Cytomegalovirus test positive			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Heart rate increased			

subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Immunosuppressant drug level increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Urine output decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Graft complication			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Incision site pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Incisional hernia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Lower limb fracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Post procedural discharge			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Skin laceration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Cardiomegaly			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Left ventricular hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Coordination abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	1 / 6 (16.67%)	4 / 12 (33.33%)	
occurrences (all)	1	5	
Lethargy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	5 / 12 (41.67%)	
occurrences (all)	0	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Eye disorders			

Eye swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Ocular hyperaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	3 / 6 (50.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	4 / 6 (66.67%)	2 / 12 (16.67%)	
occurrences (all)	4	3	
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	3 / 12 (25.00%)	
occurrences (all)	4	2	
Epigastric discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gingival hyperplasia			
subjects affected / exposed	3 / 6 (50.00%)	6 / 12 (50.00%)	
occurrences (all)	3	8	
Ileus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Inguinal hernia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Melaena			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	3 / 12 (25.00%)	
occurrences (all)	2	3	
Vomiting			
subjects affected / exposed	3 / 6 (50.00%)	3 / 12 (25.00%)	
occurrences (all)	5	5	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 6 (0.00%)	4 / 12 (33.33%)	
occurrences (all)	0	7	
Dermatitis diaper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hirsutism			
subjects affected / exposed	5 / 6 (83.33%)	7 / 12 (58.33%)	
occurrences (all)	6	10	
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	2 / 12 (16.67%)	
occurrences (all)	1	3	
Rash			
subjects affected / exposed	2 / 6 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Rash papular			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Rash pruritic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Skin odour abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Enuresis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	3 / 6 (50.00%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Hydronephrosis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Renal hydrocele			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Urethral disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Urethral pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Vesicoureteric reflux			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	4 / 6 (66.67%)	8 / 12 (66.67%)	
occurrences (all)	4	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	4 / 12 (33.33%)	
occurrences (all)	0	4	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infections and infestations			
BK virus infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Fungal infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Oral candidiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	2 / 6 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			

subjects affected / exposed	3 / 6 (50.00%)	5 / 12 (41.67%)	
occurrences (all)	7	9	
Urinary tract infection			
subjects affected / exposed	4 / 6 (66.67%)	2 / 12 (16.67%)	
occurrences (all)	8	2	
Varicella			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	4 / 6 (66.67%)	1 / 12 (8.33%)	
occurrences (all)	4	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Fluid overload			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Fluid retention			
subjects affected / exposed	1 / 6 (16.67%)	2 / 12 (16.67%)	
occurrences (all)	1	3	
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Hyperlipidaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	

Hypokalaemia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1	
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 12 (8.33%) 2	
Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 12 (8.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2000	• Dosing guidelines were amended so that study drug could be taken with or without food, with the exception of visit days with PK profile blood sample collection. • No restrictions on the kind of food or fluid taken after administration of study medication or for meals were required, except that grapefruit or grapefruit juice was not allowed. This amendment was issued prior to the recruitment of the first subject to Cohort II, therefore the actual Cohort II protocol incorporated these amendments.
30 April 2001	Based on findings of possible cyclosporine-related nephrotoxicity in related studies, cyclosporine target levels were reduced, everolimus drug level targeting was introduced (in place of fixed dosing per BSA) and renal function were more closely monitored as follows: • Cyclosporine levels were progressively lowered to 50-100 ng/mL by Month 3. • Everolimus trough levels were maintained at ≥ 3 ng/mL. • Blood samples for serum creatinine, blood urea nitrogen, everolimus and cyclosporine trough levels were collected regularly. This amendment was issued prior to the recruitment of the first subject to Cohort II, therefore the actual Cohort II protocol incorporated these amendments.
09 July 2001	This amendment applied only to Cohort I subjects: • Blood samples were to be obtained every 6 months for the determination of endocrine parameters (follicle stimulating hormone, luteinizing hormone, testosterone [boys and girls]) and safety or drug effects, and included retrospective analysis of stored blood samples taken since the start of the study. • Sexual maturity was to be assessed at each scheduled visit using Tanner staging, if possible. In boys, testicular volume was also to be assessed every 6 months.
04 February 2004	This amendment applied only to Cohort II subjects: • An additional blood sample was added to each study visit for the determination of the endocrine parameters (follicle stimulating hormone and luteinizing hormone in males and females; testosterone in males only). • Sexual maturity was to be assessed at each visit using Tanner staging in males and females. In males, testicular volume was also to be assessed every 6 months. This amendment was issued prior to the recruitment of the first subject to Cohort II, therefore the actual Cohort II protocol incorporated these amendments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported