Sponsor

Novartis

Generic Drug Name

Everolimus

Therapeutic Area of Trial

Heart transplantation

Approved Indication

Everolimus is approved for the prophylaxis of acute rejection in renal and/or cardiac transplant patients in many countries. This product is not approved in the Unites States, Canada, United Kingdom and Ireland.

Study Number

CRAD001A2403

Title

A six-month, multicenter, randomized, open-label study of the safety, tolerability and efficacy of two cyclosporine doses in addition to everolimus (RAD001) and steroids in *de novo* heart transplant recipients.

Phase of Development

Phase IV

Study Start/End Dates

09-Aug-2004 to 08-Jan-2007

Study Design/Methodology

This was a six-month, multicenter, prospective, randomized, open-label study comparing the renal function at six months post-transplant in *de novo* heart transplant recipients treated with everolimus in combination with corticosteroids and a standard dose (SD) cyclosporine or a reduced dose (RD) cyclosporine. The patient's eligibility to participate in the study was determined using the baseline assessments which needed to be made within 72 hours post-transplantation and prior to the administration of the first dose of study medication. Eligible patients received their first dose of everolimus no later than 72 hours after transplantation with a starting dose of 1.5 mg/day. Following the baseline assessments, the patients were to be randomized (1:1) within 72 hours post-transplant to a SD cyclosporine dose or RD cyclosporine dose. Cyclosporine was to be started as soon as possible within 72 hours post-transplantation. Cyclosporine could be started

prior to the first everolimus dose. After randomization, everolimus was always to be given at the same time as cyclosporine. In order to ensure that everolimus trough levels ≥ 3 ng/mL whole blood trough levels were measured starting at Day 6 and thereafter, at pre-specified timepoints, the dose was adjusted as necessary. Everolimus through levels were intended to be maintained below 8 ng/mL throughout the study.

In both treatment groups, the cyclosporine dose was adjusted for achieving and maintaining the whole blood cyclosporine C-2h levels within the pre-specified target range, throughout the study, as listed in the table below:

Target cyclosporine C-2h levels (ng/mL)

	Day 1-59	**Day 60-89**	**Day 90-149**	**Day 150-180**
Group 1 (SD) cyclosporine	1000-1400	800-1200	800-1200	600-1000
Group 2 (RD) cyclosporine	1000-1400	600-800	400-600	300-500

During the first two months of the trial, investigators were blinded to the treatment group allocation. All the patients were targeting the same cyclosporine level.

In the centers that did not use induction therapy, none of the patients should have received induction therapy. In the centers that used induction therapy, all patients should have received the same induction therapy. All patients were to receive steroids for the six months of study participation.

The patients were seen at Days 1, 3, 5, 8, 15, 22, 30, 60, 90, 120, 150 and 180. Day 1 was the day of randomization and the day of first dose of everolimus administration.

Centres

26 centers in 10 countries: Australia (2), Austria(2), Brazil(2), Canada (2), Germany (2), Italy (2), Poland (2), Spain (3), Taiwan (1), United States (8).

Objectives

Primary objective(s)

The primary objective was to determine whether cyclosporine dose optimization can improve renal function in *de novo* heart transplant recipients receiving cyclosporine in addition to everolimus. This objective was assessed by comparing renal function at six months post-transplant between two groups of patients, one receiving standard dose (SD) cyclosporine and one receiving reduced dose (RD) cyclosporine.

Secondary objective(s)

The secondary objectives were to assess the efficacy and safety of the administration of reduced and standard cyclosporine dose together with therapeutic drug monitoring of everolimus. This was assessed at six months by comparing RD cyclosporine and SD cyclosporine groups with respect to:

- The incidence of efficacy failure defined as biopsy proven acute rejection ≥3A, acute rejection associated with hemodynamic compromise, graft loss, death or loss to follow up.
- The incidence of biopsy proven acute rejection ≥3A.
- The incidence of acute rejection associated with hemodynamic compromise (HDC).
- The incidence of graft loss.
- The incidence of death.
- The incidence of premature patient withdrawal and study treatment discontinuation.
- The incidence of serious adverse events (SAEs).
- The incidence of adverse events (AEs).

Furthermore, the 1.5mg/day everolimus arm of the pivotal study RAD B253 was to be compared with each treatment arm of this trial for the following safety and efficacy variables at 6 months:

- The incidence of efficacy failure defined as acute rejection ≥3A, acute rejection associated with hemodynamic compromise, graft loss, death or loss to follow up.
- The incidence of biopsy proven acute rejection ≥ 3A.
- Mean serum creatinine at Month 6.

Test Product (s), Dose(s), and Mode(s) of Administration

Patients were randomized within 72 hours post-transplant into one of two treatment groups:

Group 1: Standard cyclosporine dose + Everolimus 1.5 mg/day + Steroids

Group 2: Reduced cyclosporine dose + Everolimus 1.5 mg/day + Steroids

Everolimus was administrated twice daily by mouth (per os), within 72 hours post-transplant, simultaneously with cyclosporine, on a consistent schedule with regards to time of day and relation to meals. The starting dose was two tablets of 0.75 mg tablets (1.5 mg/day) for all patients. Additional medication for dose titration was provided in 0.50 mg tablets strength.

Cyclosporine was to be introduced to patients at ATG or anti-IL-2-RA centers per local practice.

At non-ATG or anti-IL-2-RA centers cyclosporine administration began at doses up to 12 mg/kg/day and adjusted as necessary to maintain a C-2h level within the specified target range. cyclosporine capsules were used throughout the study unless cyclosporine oral solution or intravenous administration of cyclosporine could not be avoided.

Anti-IL-2-RA (basiliximab or daclizumab):

All patients will receive the labeled full dose of IL-2 RA administered per the manufacturer's instructions.

Oral prednisone (or methylprednisolone equivalent) was initiated once oral medication was tolerated at 0.5-1.0 mg/kg/day. Oral prednisolone was to be tapered in order to achieve a dose of 0.3-0.5 mg/kg/day by Day 21 and no less than 0.1 mg/kg per day by Month 6.

Reference Product(s), Dose(s), and Mode(s) of Administration

None.

Criteria for Evaluation

Primary variables

The primary efficacy variable for this study was to determine whether cyclosporine dose optimization can improve renal function in *de novo* heart transplant recipients receiving cyclosporine in addition to everolimus. This objective was assessed by measuring and comparing mean serum creatinine concentrations at six months post-transplant between two groups of patients, one receiving SD cyclosporine and one receiving RD cyclosporine.

Secondary variables

The secondary efficacy variables were the proportion of patients experiencing a composite endpoint (biopsy-proven acute rejection of grade ≥ 3A, acute rejection associated with hemodynamic compromise, death, graft loss, or loss to follow up) at six months; the proportion of patients with biopsy-proven acute rejection of grade ≥ 3A at six months; the proportion of patients with acute rejection associated with hemodynamic compromise; the proportion of patients with graft loss at six months; the proportion of deaths at 6 months.

Safety and tolerability

The safety assessments consisted of recording all AEs and infections, including SAEs with their severity and relationship to study medication, deaths and adverse dropouts up to Day 225. They also included the regular monitoring of hematology, blood chemistry, and urine performed by a central laboratory, and regular assessments of vital signs, physical condition and body weight. All information regarding pregnancies was collected.

Pharmacology

Not Applicable.

Other

Not Applicable.

Statistical Methods

Unless otherwise specified, all statistical tests were conducted against a two-sided alternative hypothesis, employing a significance level of 0.05. The efficacy analyses were performed on the intent-to-treat (ITT) population and the safety analysis in the safety population.

The ITT population consisted of all patients that received at least one dose of study drug and had at least one post-baseline assessment. All efficacy analyses were based on ITT population. The primary endpoint, serum creatinine level at six months was analyzed for all ITT patients that had 6-month serum creatinine values.

The safety population consisted of all patients that received at least one dose of study medication

and had at least one post-baseline safety assessment. All safety analysis were based on the safety population.

Demographic and background information for the ITT population were summarized using frequency distribution (for categorical variables) and descriptive statistics of mean, standard deviation, median, minimum, maximum (for continuous variables). Background information included medication taken before study entry, past/current medical conditions and transplant history.

Duration (days) of study medication (everolimus) administration were summarized by treatment groups for the ITT population. In calculation of duration, periods of temporary interruption of study medication for safety reasons were included. Frequency of dose reduction (including temporary dose interruption) by reasons were presented for each treatment group.
Average daily doses by visit window and treatment group were also calculated. In calculating average daily doses, zero doses were used for periods of temporary interruption of study medication, regardless of whether this was due to safety reasons or non-compliance.

The daily dose of study medication (everolimus) and cyclosporine were summarized by timepoint and by treatment group. The everolimus and cyclosporine C-0h and C-2h levels were summarized by timepoint as well.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Male or female cardiac patients 18-65 years old undergoing primary heart transplantation.
- Females of potential childbearing age must have had a negative serum pregnancy test within 7 days prior to enrollment. Patients must have agreed to use effective contraception during the trial and for 6 weeks following discontinuation of the study medication, even where there had been a history of infertility.
- Patients who were willing and able to participate in the full course of the study and from whom written informed consent had been obtained.

Exclusion criteria

- Patients with donor hearts greater than 60 years of age and/or with a cold ischemia time of more than 6 hours and/or donor hearts which have obvious coronary disease or are known to have heart disease at time of transplant.
- Patients who were recipients of multiple solid organ transplants, or who were previously received transplanted organs.
- Patients who had received any investigational drug or who have been treated with an immunosuppressive drug treatment within 4 weeks prior to study entry.
- Patients with serum creatinine level > 250 µmol/L.
- Patients with platelet count ≤ 50,000/mm^3 or with a white blood cell count of ≤

2,500/mm^3.

- Patients with active systemic infection, according to the investigator judgment, requiring continued therapy.
- Patients with a known hypersensitivity to mTOR inhibitors.
- Patients with Panel Reactive Antibodies ≥ 25%.
- Presence of severe hypercholesterolemia (≥ 350mg/dL;≥9 mmol/L) or hypertriglyceridemia (≥ 750 mg/dL; ≥ 8.5 mmol/L).
- Presence of any severe allergy requiring acute (within 4 weeks of baseline) or chronic treatment, or hypersensitivity to drugs similar to everolimus (e.g., macrolides).
- Symptoms of a significant mental illness, which in the opinion of the investigator might interfere with the patients ability to comply with the protocol. History of drug or alcohol abuse within 1 year of baseline.
- Patients with any past (within the last 5 years) or present malignancy other than excised squamous or basal cell carcinoma.
- Patients with any history of significant coagulopathy or medical condition requiring long-term anticoagulation after transplantation (low dose of aspirin treatment is allowed).
- Abnormal physical or laboratory findings of clinical significance within 2 weeks prior to study entry which would interfere with the objectives of the study.
- Inability to cooperate or communicate with the investigator.
- Female of childbearing potential who were planning to become pregnant, who were pregnant and/or lactating or who were unwilling to use effective means of contraception.
- Breast feeding women.
- Patients who were recipients of A-B-O incompatible transplants.
- Patients who were known to have chronic active Hepatitis C (PCR+ only), who are HIV or Hepatitis B surface antigen positive. Laboratory results obtained within 6 months prior to randomization were acceptable.
- Recipients of organs from donors who test positive for Hepatitis B surface antigen or Hepatitis C (PCR+ only) are excluded.

Number of Subjects

Patient Disposition for each treatment group

Disposition	Standard cyclosporine N=100	Reduced cyclosporine N=99
Number of patients		
Randomized **n(%)**	100 (100.0)	99 (100.0)
Intent-to-treat **n(%)**	100 (100.0)	99 (100.0)
Safety **n(%)**	100 (100.0)	99 (100.0)
Completed **n(%)**	94 (94.0)	90 (90.9)
Discontinued from study n(%)	6 (6.0)	9 (9.1)
Completed treatment n(%)	66 (66.0)	62 (62.6)
Discontinued study medication n(%)	34 (34.0)	37 (37.4)
Adverse Event(s)	21 (21.0)	25 (25.3)
Abnormal laboratory value(s)	2 (2.0)	1 (1.0)
Abnormal test procedure result(s)	0	0
Unsatisfactory therapeutic effect	2 (2.0)	1 (1.0)
Patient’s condition no longer re quires study medication	0	0
Protocol violation	1 (1.0)	1 (1.0)
Patient withdrew consent	1 (1.0)	0
Lost to follow-up	0	1 (1.0)
Administrative problems	6 (6.0%)	6 (6.1)
Death	1 (1.0%)	2 (2.0)
Graft loss	0	0

Demographic and Background Characteristics

Baseline Demographic Characteristics by treatment group - (ITT population – 6 month analysis)

Demographic variable	Standard cyclosporine	Reduced cyclosporine
	N=100	N=99
Sex, n (%)		
	n (%)	n (%)
Female	22 (22.0)	25 (25.3)
Male	78 (78.0)	74 (74.7)
Age group, n (%)		
<18	0	0
18-25	3 (3.0)	7 (7.1)
26-35	8 (8.0)	7 (7.1)
36-45	25 (25.0)	17 (17.2)
46-55	30 (30.0)	28 (28.3)
56-64	30 (30.0)	40 (40.4)
≥65	4 (4.0)	0
<50	44 (44.0)	35 (35.4)
≥50	56 (56.0)	64 (64.6)
Age (years)		
n	100	99
Mean ± SD	49.4 ± 10.44	49.8 ± 11.77
Median	51.0	53.0
Minimum-Maximum	21 - 66	18 - 64
Race, n (%)		
Black	4 (4.0)	4 (4.0)
Caucasian	77 (77.0)	79 (79.8)
Oriental	14 (14.0)	12 (12.1)
Other	5 (5.0)	4 (4.0)
Baseline weight (kg)		
N	92	94
Mean	74.07	75.59
SD	15.859	14.945
Median	72.50	75.70
Minimum	42.0	47.0
Maximum	121.0	106.7
Baseline height (cm)		
N	96	98
Mean	170.2	170.7
SD	9.60	9.70
Median	170.0	170.0
Minimum	147	148
Maximum	190	198
Baseline BMI (kg/m^2)		
N	92	94
Mean	25.5	25.8

SD	4.20	3.94
Median	24.9	26.0
Minimum	16	19
Maximum	38	34
Presence of diabetes at base-line, n (%)		
No	69 (69.0)	68 (68.7)
Yes	31 (31.0)	31 (31.3)

Primary Objective Result(s)

Comparison of mean serum creatinine [µmol/L] at 6 months between the SD and RD cyclosporine arms: observed cases (ITT population – 6 month analysis)

Standard cyclosporine (N=100)		Reduced cyclosporine (N=99)					
N	**Mean**	**n**	**Mean**	**Mean difference**	**p-value [1]**	**95% CI [2]**	**Df [3]**
89	141.02	80	130.08	10.95	0.093	(-5.30, 27.19)	164.7

[1] One-sided t-test is based on the null hypothesis: the mean serum creatinine value for the reduced dose cyclosporine arm is not lower than the mean serum creatinine value for the standard cyclosporine dose arm at 6 months, against the alternative hypothesis: the mean serum creatinine value for the reduced dose cyclosporine arm is lower than the mean serum creatinine value for the standard dose cyclosporine arm at 6 months.

[2] 95% confidence interval based on the two-sided t-test

3] DF: The t-test test statistics is computed under the assumptions that the two samples variances are unequal and the degrees of freedom is computed using the Satterthwaite's approximation method.

Secondary Objective Result(s)

Number (%) of patients with first efficacy failure (ITT Population – 6 month analysis)

	Standard cyclosporine (N=100)	Reduced cyclosporine (N=99)	S – N [1]	95% CI
	n (%)	n (%)		
Composite efficacy failure:				
Death, graft loss, biopsy proven acute rejection of grade ≥3A, acute rejection associated with HDC or lost to follow-up	25 (25.0)	26 (26.3)	-1.3%	(-13.4, 10.9)
Biopsy proven acute rejection of grade ≥3A	21 (21.0)	16 (16.2)	4.8%	(-5.9, 15.6)
Acute rejection associated with HDC	4 (4.0)	3 (3.0)	1.0%	(-4.1, 6.1)
Biopsy proven acute rejection of grade ≥3A or acute rejection associated with HDC	23 (23.0)	19 (19.2)	3.8%	(-7.5, 15.1)
Acute rejection treated with anti-body therapy	1 (1.0)	0	1.0%	(-1.0, 3.0)
Graft loss	1 (1.0)	1 (1.0)	0.0%	(-2.8, 2.8)
Death	3 (3.0)	6 (6.1)	-3.1%	(-8.8, 2.7)
Lost to follow-up	1 (1.0)	2 (2.0)	-1.0%	(-4.4, 2.4)

Notes:

1. Lost to follow-up are those patients who have not experienced biopsy-proven acute rejection of grade ≥3A, acute rejection associated with hemodynamic compromise, graft loss or death at or before the time of their last contact, which is before study day 165.
2. All events that occurred during the study up to day 195 are summarized

[1] (S-N) = Standard – Reduced cyclosporine

Safety Results

Adverse Events/Infections Overall by System Organ Class

Summary of Adverse Events or Infections (Safety Population – 6 month analysis)

	Standard cyclosporine (N=100)	Reduced cyclosporine (N=99)	S – N [1]	95% CI
	n (%)	n (%)		
At least one AE	100 (100.0)	99 (100.0)	0.0%	N/A
Any severe AEs	31 (31.0)	42 (42.4)	-11.4%	(-24.7, 1.9)
Any SAEs	57 (57.0)	59 (59.6)	-2.6%	(-16.3, 11.1)
Any drug related AEs	59 (59.0)	58 (58.6)	0.4%	(-13.3, 14.1)
Any infections	47 (47.0)	52 (52.5)	-5.5%	(-19.4, 8.3)
Any severe infections	3 (3.0)	17 (17.2)	-14.2%	N/A
Any serious infections	15 (15.0)	25 (25.3)	-10.3%	(-21.3, 0.8)

Notes:

1. AEs include infections.
2. an asterix (*) indicates a 95% confidence interval that does not include zero.
3. a 95% confidence interval is calculated if there are at least 5 patients experiencing the event in each group

[1] (S-N) = Standard – Reduced cyclosporine

Adverse Events by System Organ Class

System Organ Classification Preferred Term	Standard cyclosporine (N=100)	Reduced cyclosporine (N=99)
	n (%)	n (%)
Any frequent AE/Infection	97 (97.0)	94 (94.9)
Blood and lymphatic system disorders	22 (22.0)	30 (30.3)
Cardiac disorders	25 (25.0)	11 (11.1)
Gastrointestinal disorders	50 (50.0)	50 (50.5)
General disorders and administration site conditions	35 (35.0)	32 (32.3)
Injury, poisoning and procedural complications	19 (19.0)	23 (23.2)
Investigations	13 (13.0)	6 (6.1)
Metabolism and nutrition disorders	58 (58.0)	49 (49.5)
Nervous system disorders	24 (24.0)	21 (21.2)
Psychiatric disorders	37 (37.0)	30 (30.3)
Renal and urinary disorders	16 (16.0)	14 (14.1)
Respiratory, thoracic and mediastinal disorders	26 (26.0)	27 (27.3)
Vascular disorders	42 (42.0)	46 (46.5)

10 Most frequently Reported AEs Overall by Preferred Term n(%)

	Standard cyclosporine (N=100)	Reduced cyclosporine (N=99)
	n (%)	n (%)
Anemia	16 (16.0)	21 (21.2)
Pericardial effusion	25 (25.0)	11 (11.1)
Constipation	31 (31.0)	27 (27.3)
Nausea	19 (19.0)	25 (25.3)
Edema peripheral	22 (22.0)	22(22.2)
Hypercholesterolemia	12 (12.0)	14 (14.1)
Headache	16 (16.0)	17 (17.2)
Insomnia	30 (30.0)	27 (27.3)
Pleural effusion	13 (13.0)	15 (15.2)
Hypertension	40 (40.0)	39 (39.4)

Serious Adverse Events and Deaths

	Standard cyclosporine (N=100)	Reduced cyclosporine (N=99)
No. (%) of subjects studied	100	99
No. (%) of subjects with at least one AE (s)	100 (100.0)	99 (100.0)
Number (%) of subjects with serious or other significant events	**n (%)**	**n (%)**
Deaths	3 (3.0)	6 (6.1)
Any SAEs	57 (57.0)	60 (60.6)
Discontinued due to SAE(s) from study	6 (6.0)	9 (9.1)
Any AE(s) causing premature discontinuation of study drug	**27 (27.0)**	**26 (26.3)**
Adverse dropouts:		
AE	**21 (21.0)**	**25 (25.3)**
Abnormal laboratory values	**2 (2.0)**	**1 (1.0)**
Abnormal test procedure	**0**	**0**

SAEs: 2 anemia, 2 pancytopenia, 2 leucopenia, 20 pericardial effusion, 10 cardiac tamponade, 2 atrial fibrillation, 1 bradycardia, 2 cardiac arrest, 1 tachycardia, 2 pericardial haemorrhage, 5 diarrhea, 2 abdominal pain, 3 gastritis, 1 megacolon, 3 nausea, 3 multi-organ failure, 3 oedema peripheral, 4 pyrexia, 1 impaired healing, 2 choletithiasis, 2 heart transplant rejection, 6 transplant rejection, 7 postoperative wound infection, 6 pneumonia, 4 sepsis, 2 Herpes zoster, 2 pulmonary tuberculosis, 5 postoperative thoracic procedure complication, 3 wound complication, 2 wound dehiscence, 3 infections, 1 pylonephritis, 1 respiratory tract infection, 11 renal failure acute, 10 renal failure, 1 renal failure chronic, 1 encephalitis, 1 cerebral haemorrhage, 3 dyspnoea, 3 pleural effusion and 2 lymphocele.

Other Relevant Findings

The primary study objective to demonstrate that Neoral® dose optimization can improve renal function (defined by serum creatinine) at six months in *de novo* heart transplant recipients was not achieved. However a numerical and statistical trend was observed towards lower serum creatinine at six months with reduced Neoral®. The serum creatinine values between groups were statistically not significantly different, possibly due inadequate adherence to target Neoral® C-2h levels.

The protocol pre-specified supportive analyses comparing serum creatinine at Month 6 with imputation of missing values showed significant differences between the two treatment groups. The small distinctiveness in the separation of achieved exposure to cyclosporine between the two groups was the factor that likely contributed to the renal function not being more separated between the two groups. However, the results from this present study can be better appreciated when they are considered in the context of the data from *de novo* cardiac transplant recipients who were exposed to fixed doses of everolimus while targeting levels of cyclosporine that exceeded those studied in this investigation.

Date of Clinical Trial Report

15-June-2007

Date Inclusion on Novartis Clinical Trial Results Database

December 18,2007

Date of Latest Update

18 December 2007