Sponsor

Novartis

Generic Drug Name

RAD001/Everolimus

Trial Indication(s)

Renal function and efficacy in de novo heart transplant recipients

Protocol Number

CRAD001A2411

Protocol Title

A 12-month, multicenter, randomized, open-label non-inferiority study of renal function and efficacy comparing concentration-controlled Certican® (1.5 mg/day starting dose) with reduced Neoral® dose versus MMF with standard Neoral® dose in de novo heart transplant recipients

Clinical Trial Phase

Phase IIIB

Study Start/End Dates

15-Dec-2004 to 30-May-2007

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This is a 12-month, multicenter, randomized, open-label, parallel group (1:1) study of renal function and efficacy in adult de novo heart transplant recipients. After obtaining informed consent, eligibility evaluation of the patient and randomization (within 72 h post transplantation) were performed during the baseline period. Patients who met the inclusion/exclusion criteria were randomized into one of the two treatment groups (1:1): everolimus or MMF in combination with Neoral and corticosteroids. The treatment period started with first dose of study medication.

In the everolimus group, therapeutic drug monitoring (TDM) was mandatory throughout the study; targeting an everolimus trough level of 3-8 ng/mL. Neoral dose was adjusted according to the C0 value: In the everolimus group-Month 1: 200-350 ng/mL, Month 2: 150-250 ng/mL, Month 3,4: 100-200 ng/mL, Month 5,6: 75-150 ng/mL, Months 7 to 12: 50-100 ng/mL. In the MMF group, Neoral C0 value: Month 1-2: 200-350 ng/mL, Month 3,4: 200-300 ng/mL, Month 5,6: 150-250 ng/mL, Months 7 to 12 : 100-250 ng/mL.

Recruitment period was 18 months and treatment period was 12 months. No follow-up period was planned. Serious adverse events (SAEs) were recorded for a 4 week period after end of the treatment period.

Centers

29 centers in 8 countries: France (9), Italy (7), Spain (4), Germany (3), Belgium (2), Israel (2), Brazil (1) and South Africa (1)

Objectives:

Primary objective(s)

Primary Objective: To demonstrate that comparable (non-inferior) renal function (calculated creatinine clearance according to Cockroft-Gault) is achieved in cohorts of de novo heart recipients treated with Certican/reduced dose Neoral/steroids versus MMF/standard dose Neoral/steroids at 6 months post transplantation.

Secondary objective(s) (KEY secondary objectives, not all)

• To assess if comparable rates of biopsy-proven acute rejection of ISHLT grade ≥3A are achieved in the everolimus treatment arm compared to the MMF treatment arm at 6 and 12 months post transplantation.

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

Everolimus was provided as 0.25mg tablets, 0.5mg tables and 0.75mg tablet

Statistical Methods

Efficacy was analyzed in the intent-to-treat (ITT) and safety populations, while safety, in addition to creatinine clearance, was analyzed only in the safety population. Both creatinine clearance and BPAR were also analyzed on the Per-protocol population. The non-inferiority of everolimus with respect to creatinine clearance was measured by whether the lower limit of the 95% confidence interval for the difference in mean creatinine clearance was greater than -6 mL/min. The non-inferiority of everolimus with respect to BPAR rate was assessed by whether the upper limit of the 95% confidence interval for the difference in BPAR rate was less than 10% using a 0.025 significance level, 1-sided. All other tests were two sided at a 0.05 significance level. All summary statistics are presented by treatment group.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
Male or female cardiac recipients 18-65 years of age undergoing primary heart transplantation. The graft must be functional at the time of randomization.
Calculated creatinine clearance (Cockroft-Gault) ≥ 50 mL/min at screening.
Patients who have given written informed consent to participate in the study.

Exclusion Criteria:
Patients who are recipients of multiple solid organ transplants or have previously received organ transplants.
Patients who received any investigational drug or who have been treated with an immunosuppressive drug or treatment within 1 month prior to randomization Patients receiving induction therapy which is not standard per local practice Patients with donor greater than 60 years and/or with known donor coronary or heart disease at the time of transplant.
Donor heart cold ischemic time >6 hours. Patients with Panel Reactive Antibodies >20%. Patients who are recipients of ABO incompatible transplants Patients with platelet count <50,000/mm3 at the evaluation before randomization.
Presence of severe hypercholesterolemia (≥350 mg/dL; ≥9 mmol/L) or hypertriglyceridemia (≥750 mg/dL; ≥8.5 mmol/L)
Patients with an absolute neutrophil count of ≤1,500/mm3 or white blood cell count of ≤4000/mm3 at baseline before surgery Patients with a history of significant coagulopathy or medical condition requiring long term anti-coagulation after

transplantation (low dose aspirin treatment is allowed) Patients who are HIV-positive or Hepatitis C (PCR+ only) or B surface antigen positive. Laboratory results obtained within 6 months prior to study entry are acceptable.
Recipients of organs from donors who test positive for Hepatitis B surface antigen or Hepatitis C (PCR+ only) are excluded Patients with a known hypersensitivity to similar drugs and to the components of the formulations Patients being treated with terfenadine, astemizole, or cisapride. Patients who are treated with drugs strong inducers or inhibitors of cytochrome P450 3A4.
Patients with any past (within the past 5 years) or present malignancy (other than excised basal cell carcinoma) Patients with clinically significant systemic infection Patients who are unable to take oral medication Existence of any surgical or medical condition, which in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism and excretion of study medication, and/or the presence of severe diarrhea or active peptic ulcer Abnormal physical or laboratory findings of clinical significance within 2 weeks of randomization which would interfere with the objectives of the study Females of childbearing potential who are planning to become pregnant, who are pregnant and/or lactating, who are unwilling to use effective means of contraception

Participant Flow Table

Patient disposition – n (%) of patients by treatment group (ITT population – 12 month analysis)

Disposition Reason	RAD N=92 n (%)	MMF N=84 n(%)
Completed study medication up to Month 12	72 (78.3)	66 (78.6)
Completed study up to Month 12	81 (88.0)	74 (88.1)
Randomized but did not commence study medication	1 (1.1)	1 (1.2)
Discontinued study medication prior to Month 12		
- Total	19 (20.7)	17 (20.2)
Adverse Event(s)	14 (15.2)	13 (15.5)
Death	4 (4.3)	2 (2.4)

Unsatisfactory therapeutic effect	0	2 (2.4)
Subject withdrew consent	1 (1.1)	0
Abnormal laboratory value(s)	0	0
Abnormal test procedure result(s)	0	0
Administrative problems	0	0
Graft loss	0	0
Lost to follow-up	0	0
Protocol violation	0	0
Discontinued study prior to Month 12		
- Total	11 (12.0)	10 (11.9)
Death	10 (10.9)	10 (11.9)
Subject withdrew consent	1 (1.1)	0
Lost to follow-up	0	0

Primary discontinuation reasons summarized here are those listed on the 'Treatment and study completion' CRF.
Percentages are based on the number of patients in the ITT population.

Baseline Characteristics

Recipient demographic summary by treatment group (ITT population – 12 Month analysis)

Demographic Variable	RAD N=92	MMF N=84
Baseline age subgroup (years) - n (%)		
< 50	34 (37.0)	24 (28.6)
>=50	58 (63.0)	60 (71.4)
Baseline age (years)		
N	92	84
Mean	50.6	51.9
Median	52.5	56.0
SD	10.64	11.36
Minimum	20	20
Maximum	65	66
Sex - n (%)		
Female	21 (22.8)	13 (15.5)
Male	71 (77.2)	71 (84.5)
Race - n (%)		
Black	0	1 (1.2)
Caucasian	90 (97.8)	81 (96.4)
Oriental	0	1 (1.2)
Other	2 (2.2)	1 (1.2)
Baseline height (cm)		
N	90	83
Mean (SD)	170.1 (8.81)	172.0 (8.32)
Median	171.5	172.0
Minimum –Maximum	145-196	152-198
Baseline weight (kg)		
N	89	83
Mean (SD)	73.70 (12.1)	74.46 (14.9)
Median	75.00	73.00
Minimum-Maximum	45.0-97.0	47.8-116.0

Summary of Efficacy

Primary Outcome Result(s)

Mean renal function (measured by Cockroft-Gault calculated creatinine clearance (mL/min)), by visit window and treatment group (All data analysis) (Safety population – 12 Month analysis)

Visit window	Statistic	RAD N=91	MMF N=83	Difference in means RAD - MMF
Baseline	N	91	82	-4.31
	Mean (SD)	72.51 (27.879)	76.82 (32.080)	
	Median	69.94	71.46	
Month 1	N	87	79	-10.73
	Mean (SD)	68.49 (31.531)	79.22 (35.761)	
	Median	59.08	71.07	
Month 3	N	80	75	-6.81
	Mean (SD)	67.58 (25.131)	74.39 (26.516)	
	Median	63.27	72.57	
Month 6	n	83	73	-6.85
	Mean (SD)	65.37 (24.688)	72.22 (26.231)	
	Median	62.43	69.26	
Month 9	n	83	73	-4.86
	Mean (SD)	68.45 (27.289)	73.31 (27.785)	
	Median	64.16	71.37	
Month 12	n	82	72	-3.10
	Mean (SD)	68.69 (27.706)	71.79 (29.805)	
	Median	62.98	67.11	

All data analysis: includes data obtained after patient discontinued study medication

Comparison of mean renal function (measured by Cockroft-Gault calculated creatinine clearance (mL/min)) between treatment groups at Months 6 and 12 (All data analysis- Safety population – 12 Month analysis)

Visit window	Statistic	RAD N=91	MMF N=83	Difference in means RAD - MMF	95% CI of the difference in means	p-value
Month 6	N	83	73	-6.85	(-14.91, 1.21)	0.4182
	Mean	65.37	72.22			
	Median	62.43	69.26			
	SD	24.688	26.231			
	Minimum	18.0	27.3			
	Maximum	127.9	142.1			
Month 12	N	82	72	-3.10	(-12.26, 6.06)	0.2671
	Mean	68.69	71.79			
	Median	62.98	67.11			
	SD	27.706	29.805			
	Minimum	7.3	24.5			
	Maximum	131.6	197.9			

The p-value is based on the one-sided 0.025 level t-test of non-inferiority where the non-inferiority margin for the Certican-MMF difference is -6 mL/min. Two-sided 95% confidence interval based on the t-statistic. All data analysis includes data obtained after patient discontinued study medication.

Secondary Outcome Result(s)

Efficacy event rates by treatment group (All data analysis) (ITT population – 12 Month analysis)

Efficacy endpoint	RAD N=92 n (%)	MMF N=84 n (%)	Difference in event rates RAD – MMF (95% CI)	p-value
Main secondary variable:				
Biopsy-proven acute rejection of grade >=3A	21 (22.8)	25 (29.8)	-6.9 (-19.9, 6.1)	0.0054
Other efficacy variables:				
Composite efficacy failure	30 (32.6)	35 (41.7)	-9.1 (-23.3, 5.2)	0.2737
Acute rejection associated with hemodynamic compromise	2 (2.2)	1 (1.2)	1.0 (-2.8, 4.8)	1.0000
Death or Graft loss/retransplant	10 (10.9)	10 (11.9)	-1.0 (-10.4, 8.4)	1.0000
Acute rejection treated with antibody	5 (5.4)	2 (2.4)	3.1 (-2.6, 8.7)	0.4471

n is the number of patients with an event. % is the event rate. For the main secondary variable the two-sided 95% CI is based on the z-statistic and the p-value is based on the one-sided 0.025 level z-test of non-inferiority. For the other efficacy variables Fisher's exact p-value for testing no difference is shown. All data analysis: includes data obtained after patient discontinued study medication.

BPAR >=3A by everolimus exposure- Safety population- 12 month analysis

Everolimus exposure *	BPAR Incidence % (n/group)
<3 ng/mL	36.4% (4/11)
3-8 ng/mL	21.3% (16/75)
≥ 8 ng/mL	20.0% (1/5)
Total **	22.8% (21/92)
MMF	29.8% (25/84)

* Everolimus exposure: time normalized mean trough till event or censoring at day 450

** Total including patients without everolimus measurements before BPAR or censoring

Summary of Safety

Safety Results

Serious adverse events, excluding deaths, regardless of study drug relationship, by primary system organ class, preferred term and treatment Safety population - 12 Month analysis

Primary system organ class Preferred term	RAD N=91 n (%)	MMF N=83 n (%)
-Any primary system organ class		
-Total	60 (65.9)	39 (47.0)
Blood and lymphatic system disorders		
-Total	5 (5.5)	3 (3.6)
Anaemia	1 (1.1)	0
Coagulopathy	1 (1.1)	0
Disseminated intravascular coagulation	0	1 (1.2)
Leukopenia	2 (2.2)	1 (1.2)
Neutropenia	1 (1.1)	2 (2.4)
Pancytopenia	1 (1.1)	0
Thrombocytopenia	1 (1.1)	0
Cardiac disorders		
-Total	12 (13.2)	14 (16.9)
Atrial fibrillation	0	2 (2.4)
Atrial flutter	0	1 (1.2)
Atrioventricular block	1 (1.1)	1 (1.2)
Cardiac arrest	0	1 (1.2)
Cardiac failure	1 (1.1)	1 (1.2)
Cardiac failure congestive	0	1 (1.2)

Cardiac tamponade	4 (4.4)	1 (1.2)
Coronary artery stenosis	0	1 (1.2)
Coronary artery thrombosis	0	1 (1.2)
Pericardial effusion	7 (7.7)	3 (3.6)
Pericardial haemorrhage	0	1 (1.2)
Supraventricular tachycardia	0	1 (1.2)
Ventricular tachycardia	0	1 (1.2)
Eye disorders		
-Total	1 (1.1)	1 (1.2)
Blindness	0	1 (1.2)
Endophthalmitis	1 (1.1)	0
Optic ischaemic neuropathy	0	1 (1.2)
Gastrointestinal disorders		
-Total	7 (7.7)	10 (12.0)
Abdominal hernia	1 (1.1)	0
Ascites	0	1 (1.2)
Diarrhoea	3 (3.3)	3 (3.6)
Diverticulum intestinal haemorrhagic	1 (1.1)	0
Gastrointestinal haemorrhage	0	1 (1.2)

Haematemesis	0	1 (1.2)
Haemorrhoids	0	1 (1.2)
Ileus	0	1 (1.2)
Inguinal hernia	1 (1.1)	1 (1.2)
Intestinal infarction	0	1 (1.2)
Intestinal ischaemia	0	1 (1.2)
Malabsorption	1 (1.1)	0
Peritonitis	0	1 (1.2)
Vomiting	0	2 (2.4)
General disorders and administration site conditions		
-Total	13 (14.3)	7 (8.4)
Discomfort	1 (1.1)	0
Disease progression	0	1 (1.2)
Hyperpyrexia	1 (1.1)	0
Hyperthermia	1 (1.1)	0
Implant site pain	0	1 (1.2)
Loss of control of legs	1 (1.1)	0
Multi-organ failure	1 (1.1)	3 (3.6)
Oedema peripheral	1 (1.1)	0

Pyrexia	7 (7.7)	2 (2.4)
Sudden death	1 (1.1)	1 (1.2)
Hepatobiliary disorders		
-Total	2 (2.2)	1 (1.2)
Cholelithiasis	1 (1.1)	0
Hepatic failure	0	1 (1.2)
Hepatitis cholestatic	1 (1.1)	0
Immune system disorders		
-Total	4 (4.4)	1 (1.2)
Heart transplant rejection	0	1 (1.2)
Transplant rejection	4 (4.4)	0
Infections and infestations		
-Total	25 (27.5)	18 (21.7)
Acinetobacter bacteraemia	0	1 (1.2)
Aspergillosis	0	1 (1.2)
Bacteraemia	0	1 (1.2)
Bronchopneumonia	1 (1.1)	0
Bronchopulmonary aspergillosis	1 (1.1)	0

Candidiasis	0	1 (1.2)
Cardiac infection	0	1 (1.2)
Catheter related infection	0	1 (1.2)
Cytomegalovirus infection	2 (2.2)	4 (4.8)
Empyema	0	1 (1.2)
Fungal infection	1 (1.1)	0
Gastroenteritis	1 (1.1)	0
Gingival abscess	1 (1.1)	0
Groin abscess	1 (1.1)	0
Herpes zoster	1 (1.1)	0
Infection	0	1 (1.2)
Lung infection	1 (1.1)	1 (1.2)
Nocardiosis	1 (1.1)	1 (1.2)
Orchitis	1 (1.1)	1 (1.2)
Osteomyelitis	0	1 (1.2)
Pneumonia	7 (7.7)	4 (4.8)
Pneumonia escherichia	1 (1.1)	0
Postoperative wound infection	0	1 (1.2)
Pulmonary sepsis	1 (1.1)	1 (1.2)
Pyopneumothorax	0	1 (1.2)
Respiratory tract infection	1 (1.1)	0

Retroperitoneal abscess	1 (1.1)	0
Sepsis	3 (3.3)	1 (1.2)
Septic shock	3 (3.3)	3 (3.6)
Sinusitis	1 (1.1)	0
Staphylococcal infection	0	1 (1.2)
Upper respiratory tract infection	1 (1.1)	0
Urinary tract infection	1 (1.1)	1 (1.2)
Varicella	0	1 (1.2)
Viral diarrhoea	0	1 (1.2)
Viral infection	1 (1.1)	0
Injury, poisoning and procedural complications		
-Total	7 (7.7)	4 (4.8)
Ankle fracture	1 (1.1)	0
Complications of transplant surgery	0	1 (1.2)
Complications of transplanted heart	1 (1.1)	0
Dislocation of sternum	1 (1.1)	0
Graft dysfunction	0	1 (1.2)
Lumbar vertebral fracture	1 (1.1)	0
Meniscus lesion	0	1 (1.2)

Post procedural stroke	0	1 (1.2)
Postoperative thoracic procedure complication	3 (3.3)	0
Investigations		
-Total	4 (4.4)	6 (7.2)
Blood creatinine increased	1 (1.1)	1 (1.2)
Blood urea increased	0	1 (1.2)
C-reactive protein increased	1 (1.1)	0
Central venous pressure increased	0	1 (1.2)
Cytomegalovirus antigen positive	1 (1.1)	2 (2.4)
Cytomegalovirus test positive	0	2 (2.4)
Immunosuppressant drug level increased	1 (1.1)	0
International normalised ratio increased	1 (1.1)	0
Platelet count decreased	1 (1.1)	0
Prothrombin time prolonged	1 (1.1)	0
Metabolism and nutrition disorders		
-Total	5 (5.5)	3 (3.6)
Cachexia	1 (1.1)	0

Dehydration	0	1 (1.2)
Diabetes mellitus	2 (2.2)	1 (1.2)
Hyperglycaemia	1 (1.1)	1 (1.2)
Hyperkalaemia	1 (1.1)	0
Musculoskeletal and connective tissue disorders		
-Total	5 (5.5)	0
Back pain	2 (2.2)	0
Bone disorder	1 (1.1)	0
Muscle haemorrhage	1 (1.1)	0
Muscular weakness	1 (1.1)	0
Rhabdomyolysis	1 (1.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
-Total	4 (4.4)	3 (3.6)
Kaposi's sarcoma	0	1 (1.2)
Lymphoma	1 (1.1)	0
Ovarian neoplasm	1 (1.1)	0
Pancreatic neoplasm	0	1 (1.2)
Prostate cancer	1 (1.1)	0
Rectal adenoma	0	1 (1.2)
Squamous cell carcinoma	1 (1.1)	0
Nervous system disorders		
-Total	2 (2.2)	2 (2.4)
Cerebral infarction	0	1 (1.2)
Cerebrovascular accident	0	1 (1.2)
Hypokinesia	1 (1.1)	0
Neuropathy peripheral	1 (1.1)	0
Paraplegia	1 (1.1)	0
Psychiatric disorders		
-Total	1 (1.1)	1 (1.2)
Depression	0	1 (1.2)
Major depression	1 (1.1)	0
Renal and urinary disorders		
-Total	13 (14.3)	4 (4.8)
Leukocyturia	1 (1.1)	0
Oliguria	1 (1.1)	0

Renal failure	6 (6.6)	2 (2.4)
Renal failure acute	5 (5.5)	1 (1.2)
Renal impairment	2 (2.2)	2 (2.4)
Reproductive system and breast disorders		
-Total	1 (1.1)	1 (1.2)
Prostatitis	0	1 (1.2)
Testicular swelling	1 (1.1)	0
Respiratory, thoracic and mediastinal disorders		
-Total	7 (7.7)	5 (6.0)
Cough	0	1 (1.2)
Dyspnoea	1 (1.1)	0
Dyspnoea exertional	1 (1.1)	0
Hypoxia	0	1 (1.2)
Lung disorder	0	1 (1.2)
Pleural effusion	2 (2.2)	1 (1.2)
Pleural haemorrhage	1 (1.1)	0
Pneumothorax	0	1 (1.2)
Productive cough	0	1 (1.2)
Pulmonary fibrosis	1 (1.1)	0
Pulmonary hypertension	1 (1.1)	0
Respiratory distress	1 (1.1)	0
Respiratory failure	1 (1.1)	0
Thoracic haemorrhage	1 (1.1)	0
Social circumstances		
-Total	1 (1.1)	0
Cardiac assistance device user	1 (1.1)	0
Vascular disorders		
-Total	3 (3.3)	1 (1.2)
Haematoma	1 (1.1)	0
Haemodynamic instability	1 (1.1)	0
Hypertension	0	1 (1.2)
Shock haemorrhagic	1 (1.1)	0

Adverse events and infections overall and most frequent events - n (%) of patients (> = 5% for any group) (Safety population – 12 Month analysis)

	RAD N=91 n (%)	MMF N=83 n (%)
Total no. of patients with AEs or Infections	91 (100.0)	83 (100.0)
Adverse events		
Hypertension	44 (48.4)	35 (42.2)
Oedema peripheral	36 (39.6)	29 (34.9)
Anemia	28 (30.8)	26 (31.3)

Pericardial effusion	33 (36.3)	21 (25.3)
Leukopenia	15 (16.5)	25 (30.1)
Pyrexia	22 (24.2)	14 (16.9)
Diarrhea	15 (16.5)	20 (24.1)
Nausea	14 (15.4)	20 (24.1)
Pleural effusion	22 (24.2)	11 (13.3)
Headache	16 (17.6)	12 (14.5)
Hypokalemia	15 (16.5)	12 (14.5)
Hyperuricemia	10 (11.0)	15 (18.1)
Insomnia	10 (11.0)	13 (15.7)
Urinary tract infection	7 (7.7)	15 (18.1)
Vomiting	8 (8.8)	13 (15.7)
Cough	13 (14.3)	7 (8.4)
Renal failure	12 (13.2)	8 (9.6)
Back pain	11 (12.1)	8 (9.6)
Blood creatinine increased	8 (8.8)	9 (10.8)
Dyspnea	9 (9.9)	7 (8.4)
Pneumonia	8 (8.8)	8 (9.6)
Hypercholesterolemia	9 (9.9)	5 (6.0)
Hyperglycemia	6 (6.6)	8 (9.6)
Tremor	5 (5.5)	9 (10.8)
Dyslipidemia	9 (9.9)	4 (4.8)
Pain in extremity	6 (6.6)	7 (8.4)
Cytomegalovirus infection	3 (3.3)	9 (10.8)
Pain	7 (7.7)	5 (6.0)
Procedural pain	8 (8.8)	4 (4.8)
Renal failure acute	8 (8.8)	4 (4.8)
Renal impairment	9 (9.9)	3 (3.6)
Anxiety	5 (5.5)	6 (7.2)
Arthralgia	6 (6.6)	5 (6.0)
Atrial fibrillation	1 (1.1)	10 (12.0)
Constipation	5 (5.5)	6 (7.2)
Depression	1 (1.1)	10 (12.0)
Oral herpes	6 (6.6)	5 (6.0)
Muscle spasms	7 (7.7)	3 (3.6)
Respiratory tract infection	8 (8.8)	2 (2.4)
Tachycardia	4 (4.4)	6 (7.2)
Thrombocytopenia	4 (4.4)	6 (7.2)
Cardiac tamponade	5 (5.5)	4 (4.8)
Hyperkalemia	6 (6.6)	3 (3.6)
Hypertriglyceridemia	7 (7.7)	2 (2.4)

Myalgia	3 (3.3)	6 (7.2)
Nasopharyngitis	3 (3.3)	6 (7.2)
Oral candidiasis	3 (3.3)	6 (7.2)
Productive cough	4 (4.4)	5 (6.0)
Abdominal pain	1 (1.1)	7 (8.4)
Abdominal pain upper	2 (2.2)	6 (7.2)
Fluid retention	3 (3.3)	5 (6.0)
Hypotension	2 (2.2)	6 (7.2)
Oliguria	7 (7.7)	1 (1.2)
Osteoporosis	3 (3.3)	5 (6.0)
Sinus tachycardia	3 (3.3)	5 (6.0)
Asthenia	2 (2.2)	5 (6.0)
Blood creatine phosphokinase increased	6 (6.6)	1 (1.2)
Bronchitis	6 (6.6)	1 (1.2)
Cardiac disorder	5 (5.5)	2 (2.4)
Hyperlipidemia	6 (6.6)	1 (1.2)
Hyperthyroidism	6 (6.6)	1 (1.2)
Sleep disorder	5 (5.5)	2 (2.4)
Hypertensive crisis	0	5 (6.0)
Paresthesia	0	5 (6.0)

AEs are listed by descending frequency overall. A patient may be counted in more than one category.

Deaths, other serious or clinically significant adverse events or related discontinuations – n (%) of patients (Safety population – 12 Month analysis)

	RAD N=91 n(%)	MMF N=83 n (%)
Total no. of patients with AEs or Infections	91 (100.0)	83 (100.0)
Serious or significant events		
Death	9 (9.9)	9 (10.8)
Serious AEs or Infections	60 (65.9)	39 (47.0)
Discontinued due to event	18 (19.8)	15 (18.1)
Event causing dose adjustment/interruption	31 (34.1)	45 (54.2)

A patient may be counted in more than one category.

Date of Clinical Trial Report

04-Oct-2007