Sponsor

Novartis

Generic Drug Name

Everolimus

Trial Indication(s)

Renal transplant

Protocol Number

CRAD001B351/ CRAD001AB351

Protocol Title

Multicenter, open-label, single-arm, safety, tolerability, efficacy, and pharmacokinetic study of RAD001 in pediatric *de novo* renal transplant patients

Clinical Trial Phase

Phase III

Study Start/End Dates

18-Aug-2004 to 21-Mar-2007

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

Multicenter, open-label trial, pediatric de novo kidney transplant recipients began treatment with 0.8 mg/m2 (maximum 1.5 mg) everolimus twice-daily in addition to corticosteroids and cyclosporine with the optional addition of a CD25 monoclonal

antibody. Cohort 1 was previously reported. This report covers cohort 2 in which everolimus and cyclosporine doses were individualized by therapeutic monitoring of trough blood levels targeting everolimus ≥3 ng/ml and a rapid cyclosporine down-titration targeting 50-100 ng/ml by month 3 and thereafter. Pharmacokinetic assessments consisted of everolimus and cyclosporine trough levels obtained before the morning dose on days 3, 5, 6, 7, 14 and months 1, 2, 3, 6, 9, 12 as well as steady-state AUC-profiles of both analytes on day 7 and month 3.

Centers

3 centers in 1 country: United States (3)

Objectives:

Primary objective(s)

Primary Objective: To evaluate the safety and tolerability of concentration-controlled everolimus administered twice daily (bid) in combination with reduced Neoral® and corticosteroids in pediatric de novo renal transplant recipients..

Secondary objective(s)

(1) To evaluate the efficacy of concentration-controlled everolimus administered bid in combination with reduced Neoral and corticosteroids as measured by the incidence of biopsy-proven acute allograft rejection episodes, graft loss or death at 6 and 12 months after initial dose of study medication.

(2) To evaluate the efficacy of concentration-controlled everolimus administered bid in combination with reduced Neoral and corticosteroids in the prevention of chronic allograft rejection (chronic graft dysfunction) at 12 months post-transplantation.

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

Everolimus was supplied as 0.1 and 0.25 mg dispersible tablets.

Statistical Methods

All data were analyzed by age group and combined for the 2 age groups using the intent-to-treat (ITT) population. Efficacy variables were analyzed descriptively by generating frequency tables (number and percentage of patients with each event). Safety variables were evaluated by descriptive statistics.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Male or female pediatric patients ≤ 16 years of age who had undergone primary cadaveric or non-human leukocyte antigen identical living donor (related or unrelated) renal transplantation.

Exclusion criteria

- Cold ischemia time > 40 hours or panel reactive antibodies ≥ 50% at the last assessment prior to transplantation.
- Recipients of multiple solid organ transplants or who had previously received transplanted organs. Patients who were recipients of donor-specific transfusions.
- Patients unable to undergo renal biopsies post-transplantation. Patients with any history of significant coagulopathy or medical conditions requiring long-term systemic anticoagulation post-transplantation that would have interfered with obtaining biopsies. However, low-dose aspirin was allowed.
- Patients who received induction therapy with anti-lymphocyte globulin (ALG), anti-thymocyte globulin (ATG) or orthoclonal T3 (OKT3), antifungal azoles (i.e., ketoconazole, itraconazole or fluconazole), rifampin, carbamazepine, phenobarbital or phenytoin at study entry. Patients who had received an investigational immunosuppressant or any investigational drug within 4 months and 4 weeks, respectively, prior to administration of the initial dose of study medication.
- Patients with any surgical or medical condition that might have significantly altered the absorption, distribution, metabolism or excretion of any drug. Patients with evidence of liver injury (aspartate transaminase [AST] or alanine transaminase [ALT] ≥ 3 x upper limit of normal or total bilirubin ≥ 2 mg/dL).
- Patients with non-diarrhea associated hemolytic uremic syndrome, uncontrolled hypercholesterolemia ≥ 350 mg/dL or≥ 9 .1 mmol/L) or hypertriglyceridemia (≥ 500 mg/dL or ≥ 5.6 mmol/L), severe systemic infections, any past or present malignancy (other than excised basal cell carcinoma), splenectomy, white blood cell (WBC) count ≤4500 cells/mm3 or platelet count ≤ 100,000 cells/mm3

Participant Flow Table

Patient Disposition - Premature Discontinuation of Study Medication (Cohort 2 ITT population - 12 month analysis)

	Age Group <10 years (N=6)	Age Group 10-16 years (N=12)
Still on Study medication (3)	6 (100.0%)	10 (83.3%)
Discontinued study medication-	0 (0.0%)	2 (16.7%)
Adverse Event(s)	0 (0.0%)	1 (8.3%)
Abnormal laboratory value(s)	0 (0.0%)	1 (8.3%)

Notes: 1. Primary discontinuation reasons summarized here are those listed on the 'Premature Discontinuation of study medication' CRF
2. Percentages are based on the number of patients in the ITT population
3. Patients discontinuing study mendication after day 450 are considered 'still on study medication'

Baseline Characteristics

Characteristic	Cohort 1	Cohort 2
Number of patients	19	18
Age (years)	9.9 ± 4.4	10.9 ± 4.7
Age categories (N)		
Infants	1	1
Children	10	7
Adolescents	8	10
Weight (kg)	32.7 ± 19.7	39.4 ± 27.3
Body surface area (m^2)	1.06 ± 0.43	1.17 ± 0.50
Sex ratio (male:female)	9 : 10	13 : 5

Values are mean ± sd (range).

Summary of Efficacy

Primary Outcome Result(s)

Number (%) of patients with efficacy failure within 12 months of the initial dose of study medication (Cohort 2 ITT population - 12 month Analysis)

Endpoint	Age Group <10 years (N=6)	Age Group 10-16 years (N=12)	All (N=18)
Efficacy Failure: Biopsy-proven acute rejection, Graft loss, Death or Loss to follow-up	0	0	0
Biopsy-proven acute rejection	0	0	0
Graft loss / Death	0	0	0
Graft Loss	0	0	0
Death	0	0	0
Loss to follow-up	0	0	0

Notes: 1. Components of efficacy failure are generally not mutually exclusive
2. Graft Loss is defined as graft failure, including death due to graft failure
3. Loss to follow up for primary efficacy failure does not include patients who experienced biopsy proven acute rejection, graft loss or death (graft loss or death) at or before the time of their last contact, i.e. 329 days after the start of study medication

Number (%) of patients with efficacy related events within 12 months of the initial dose of study medication (Cohort 2 ITT population - 12 month Analysis)

Endpoint	Age Group <10 years (N=6)	Age Group 10-16 years (N=12)	All (N=18)
Clinically confirmed acute rejection including biopsy-proven acute rejection	0	0	0
Antibody treated acute rejection	0	0	0
Biopsy-proven chronic allograft nephropathy	0	0	0
Clinically confirmed chronic rejection	0	0	0
Delayed graft function	0	0	0

Notes: 1. Above endpoints are generally not mutually exclusive
2. Delayed graft function is defined as need for dialysis within 7 days post-transplantation

Secondary Outcome Result(s) (Only Key Secondary outcome measures not all)

Not applicable

Summary of Safety

Safety Results

Non-Fatal Serious Adverse Events (Including Infections) (Cohort 2 ITT Population - 12 Month Analysis)

Age Group <10 years	Age Group 10-16 years
Preferred term / Reported term	Preferred term / Reported term
S Otitis media / OTITIS MEDIA	S Pancreatitis / PANCREATITIS
S Gastrointestinal haemorrhage / GASTROINTESTINAL BLEED	S Viral upper respiratory tract infection / VIRAL UPPER RESPIRATORY INFECTION
S Abdominal pain / ABDOMINAL PAIN	S Lymphoproliferative disorder / POST TRANSPLANT LYMPHOPROLIFERATIVE DISEASE
S Bladder distension / OVERDISTENDED BLADDER	S Pyrexia / FEBRILE ILLNESS
S Abdominal distension / INCREASED ABDOMINAL DISTENSION	S Pyelonephritis / PYELONEPHRITIS
S Ascites / ASCITES	S Blood creatinine increased / INCREASED CREATININE
S Hypertension / HYPERTENSION	S Peritonitis / PERITONITIS
S Adenovirus infection / ADENOVIRUS	S Peritonitis / PERITONITIS
S Cytomegalovirus test positive / CMV	S Peritonitis / PERITONITIS
S Urinary tract infection / UTI	S Pyrexia / FEVER
S Pyrexia / FEVER	S Diarrhoea / DIARRHEA
S Pyelonephritis / PYELONEPHRITIS	S Gastroenteritis / GASTROENTERITIS

Number (%) of patients reporting common adverse events, including infections (≥ 20% in either group) (ITT population)

MedDRA system organ class Preferred term	Group I < 10 yrs (N=6) n (%)	Group II 10-16 yrs (N=12) n (%)
Any AE/Infection	6 (100)	11 (91.7)
Cardiac disorders	0	3 (25.0)
Endocrine disorders	4 (66.7)	8 (66.7)
Cushingoid	4 (66.7)	8 (66.7)
Gastrointestinal disorders	6 (100.0)	9 (75.0)
Abdominal pain	3 (50.0)	0

Constipation	4 (66.7)	2(16.7)
Diarrhea	1 (16.7)	3 (25.0)
Gingival hyperplasia	3 (50.0)	6 (50.0)
Nausea	2 (33.3)	3 (25.0)
Vomiting	3 (50.0)	3 (25.0)
General disorders & administration site conds.	6 (100.0)	6 (50.0)
Generalised Edema	2 (33.3)	0
Edema peripheral	0	3 (25.0)
Pain	3 (50.0)	0
Pyrexia	4 (66.7)	4 (33.3)
Infections & infestations	6 (100.0)	10 (83.3)
Otitis media	2 (33.3)	0
Upper respiratory tract infection	3 (50.0)	5 (41.7)
Urinary tract infection	4 (66.7)	2 (16.7)
Viral infection	4 (66.7)	1 (8.3)
Injury, poisoning & procedural complications	2 (33.3)	4 (33.3)
Investigations	4 (66.7)	7 (58.3)
Blood cholesterol increased	0	3 (25.0)
Blood creatinine increased	0	3 (25.0)
Metabolism & nutrition disorders	3 (50.0)	4 (33.3)
Musculoskeletal & connective tissue disorders	0	4 (33.3)
Arthralgia	0	4 (33.3)
Nervous system disorders	1 (16.7)	8 (66.7)
Headache	1 (16.7)	4 (33.3)
Tremor	0	5 (41.7)
Renal & urinary disorders	5 (83.3)	3 (25.0)
Hematuria	3 (50.0)	1 (8.3)
Reproductive system and breast disorders	2 (33.3)	0
Respiratory, thoracic & mediastinal disorders	6 (100.0)	6 (50.0)
Cough	3 (50.0)	3 (25.0)
Epistaxis	2 (33.3)	0
Rhinorrhea	4 (66.7)	3 (25.0)
Skin & subcutaneous tissue disorders	6 (100.0)	10 (83.3)
Acne	0	4 (33.3)
Hirsutism	5 (83.3)	7 (58.3)
Rash	2 (33.3)	0
Vascular disorders	4 (66.7)	7 (58.3)
Hypertension	4 (66.7)	4 (33.3)

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

31-Aug-2007 and 08-Oct-2007