Sponsor

Novartis

Generic Drug Name

Everolimus

Trial Indication(s)

renal transplant

Protocol Number

CRAD001AIT02

Protocol Title

Multicenter, randomized, open-label trial to evaluate the safety, tolerability and efficacy of two regimens of everolimus plus Neoral®, given according different blood target levels, in de novo renal transplant recipients (EVEREST: the upper target EVErolimus RandomizEd STudy)

Clinical Trial Phase

IIIB

Study Start/End Dates

31-May-2005 to 24-Jul-2007

Reason for Termination

Not applicable.

Study Design/Methodology

Prospective, multicenter, randomized, parallel group open-label efficacy and safety study of 6- month duration of everolimus administered according higher blood levels in combination with cyclosporine at very low exposure, in comparison with everolimus

administered according standard blood levels in combination with cyclosporine at low exposure, for prevention of acute rejection. Study planned to enroll at least 200 eligible patients to be randomized to receive their first dose of everolimus and cyclosporine within 24 hours of graft reperfusion. All patients also received basiliximab 20 mg iv. on day 0 and on day 4 after transplantation. Methylprednisolone will be administered iv. at a dose of 500 mg on day 0 and as a 40 mg dose on day 1.

Centers

The study was conducted in 20 kidney transplant centers in Italy.

Objectives:

Primary objective(s)

- To assess if the optimized new regimen with upper target everolimus trough blood levels (BTL) and very-low dose Neoral allowed to improve the 6-month creatinine clearance, in comparison with the standard everolimus regimen with low-dose Neoral, in de novo renal transplant recipients given basiliximab and steroids.
- To assess if the optimized new regimen was equally effective in preventing acute rejection, in comparison with the standard one, in de novo renal transplant recipients given basiliximab and steroids.

Secondary objective(s)

• To assess the incidence of biopsy-proven acute rejection episodes, graft loss, death or lost to follow-up (whichever occur first) in the two treatment arms

• To assess the incidence of the following efficacy parameters in the two treatment arms: biopsy-proven acute rejection, antibody-treated acute rejection and clinically-confirmed acute rejection

• To evaluate the percentage of patients with a stable (mean of 2 consecutive measurements) serum creatinine increase of more than 30% from the previous nadir (i.e. the lowest mean of any two consecutive post-transplant measures) after transplantation

• To assess the incidence of graft loss or death

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

The initial everolimus dose was 1.5 mg/day.

• Group 1: Upper target everolimus BTL: the dose was adjusted to reach a C0 level of 3-8 ng/mL within day 5 after reperfusion, and then increased to reach and maintain a target trough level of 10 (8-12) ng/ml until end of month 6.

• Group 2: Standard everolimus BTL: the dose was adjusted to reach a C0 level of 3- 8 ng/mL within day 5 after reperfusion; the target of 6 (3-8) ng/mL was maintained until end of month 6.

Statistical Methods

The primary efficacy evaluation was performed on the intention-to-treat (ITT) patients population of all randomized and treated patients who had at least one post-baseline creatinine assessment or either died or lose their graft before of it. All secondary evaluations were performed on the ITT patients as well. The results of the primary variable only were confirmed in the per-protocol (PP) population of all patients randomized and treated who did not have done any major protocol violation or deviation, nor discontinued prematurely the study for reasons other than death or graft loss.

Major protocol violations or deviations were defined with the analysis plan before of database lock.

All other analyses were performed on all randomized patients who received at least one dose of trial medication (safety population).

The study aimed at demonstrating a better 6-month renal function in Group 1 (optimized new regimen) with respect to Group 2 (standard regimen).
The null hypothesis is:
H0: $\mu_a = \mu_b$ where μ_a is the mean 6-month creatinine clearance in Group 1 and μ_b is the same in Group 2.
The alternative hypothesis is:
Ha: $\mu_a \neq \mu_b$.

The null hypothesis was verified by means of Wilcoxon-Mann-Whitney test, two tailed. The primary analysis was run in the ITT population. All tests were run at the 5% level of significance. Summary statistics (including medians) of creatinine clearance at all visits have been produced.

The primary results were also investigated by a non-parametric analysis of covariance according to the method proposed by Koch (11), using baselines as covariates.

The study also aimed at demonstrating non-inferiority of Group 1 vs. Group 2 in preventing BPAR. The number and percentage of patients with BPAR in each group was reported: the 97.5% confidence interval of the Group 1 – Group 2 difference in proportions of patients with BPAR was calculated. Non-inferiority was claimed if the upper limit of the interval did not exceed the non-inferiority limit of 15%.

A Kaplan-Meier analysis of time to first BPAR was also performed, comparing the two groups by means of logrank test.

The same analyses were performed as supportive analyses in the PP population.

All secondary efficacy analyses were run on the ITT population only.

The time to the first biopsy-proven, antibody-treated and clinically confirmed acute rejection episode were analyzed by means of the product limit method. The two survival curves were compared by means of logrank test. The same analysis was done for graft survival, patient survival and combined patient and graft survival, both including and excluding lost to followup patients as events.

The proportion of patients with stable serum creatinine increase of more than 30% (mean of any two consecutive measures) from the previous nadir (i.e. the lowest mean of any two consecutive post-transplant measures) was compared between groups by means of chi square test. A logistic regression analysis was also performed taking into account covariates other than treatment such as background variables (age, sex) as well as transplant-related variables (HLA, type of donor, etc.).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Recipients of deceased, living unrelated, or non-human leukocyte antigen (HLA) identical living related donor renal transplant who actually have a viable kidney transplant at the time of randomization (within 24 hours of graft reperfusion)
- The renal cold ischemic time must be < 36 hours.
- The age of the donor must be between 15 and 65 years.

Exclusion Criteria:

- Patients who are recipients of multiple organ transplants, including more than one kidney
- Patients who have previously received an organ transplant which failed within one year
- Patients with current panel reactive T-cell antibody titers of 50% or more
- Patients who are recipients of A-B-O incompatible transplants or T-cell crossmatch positive transplant

Participant Flow Table

Patient disposition – n (%) of patients (Safety population)

	Upper	Standard
Number (%) of patients		
Enrolled	142	143
Completed the study	129 (90.8%)	123 (86.0%)
Completed the study on treatment	116 (81.7%)	114 (79.7%)
Discontinued the study	13 (9.2%)	20 (14.0%)
Main reason for discontinuations - n(%)		
Adverse event(s)	6 (4.2%)	3 (2.1%)
Abnormal laboratory value(s)	0 (0.0%)	0 (0.0%)
Abnormal test procedure result(s)	0 (0.0%)	0 (0.0%)
Subject withdrew consent	0 (0.0%)	0 (0.0%)
Lost to follow-up	1 (0.7%)	2 (1.4%)
Administrative problems	1 (0.7%)	1 (0.7%)
Death	2 (1.4%)	2 (1.4%)
Graft loss	3 (2.1%)	12 (8.4%)
Pregnancy	0 (0.0%)	0 (0.0%)

Baseline Characteristics

Demographic summary by treatment group (Safety population)

	Upper (N=142)	Standard (N=143)
Age (years)		
Mean ± SD	45.4 ± 11.7	45.8 ± 10.6
Median (min-max)	48.0 (19-65)	46.0 (22-66)
Age group (yrs) - N(%)		
18 - 44 yrs	65 (45.8%)	70 (49.0%)
45 - 65 yrs	77 (54.2%)	72 (50.3%)
>65 yrs	0 (0.0%)	1 (0.7%)
Sex - n(%)		
Male	89 (62.7%)	94 (65.7%)
Female	53 (37.3%)	49 (34.3%)
Race - n(%)		
Caucasian	136 (95.8%)	141 (98.6%)
Black	3 (2.1%)	1 (0.7%)
Oriental	3 (2.1%)	1 (0.7%)
Other	0 (0.0%)	0 (0.0%)
Weight (kg)		
Mean ± SD	68.5 ± 13.1	70.2 ± 12.7
Median (min-max)	67.8 (40-108)	69.0 (39-107)
Height (cm)		
Mean ± SD	168.1 ± 8.9	167.7 ± 8.9
Median (min-max)	170.0 (140-190)	168.5 (146-190)

Summary of Efficacy

Primary Outcome Result(s)

Summary statistics of creatinine clearance, serum creatinine and glomerular filtration rate (GFR) at 6 month (ITT population)

	Upper (N=142)	Standard (N=143)
Creatinine Clearance (mL/min) at 6 months (Cockroft-Gault) - LOCF approach		
N	142	143
Mean ± SD	55.47 ± 22.0	53.23 ± 26.2
Median (min-max)	54.86 (0.0-111.8)	52.82 (0.0-130.6)
Wilcoxon test - p-value:	0.7997	
Creatinine Clearance (mL/min) at 6 months (Cockcroft-Gault)		
N	135	123
Mean ± SD	58.00 ± 19.2	60.20 ± 18.5
Median (min-max)	55.74 (17.4-111.8)	58.63 (24.9-130.6)
Creatinine (mg/dL) at 6 months		
N	135	123
Mean ± SD	1.62 ± 0.6	1.55 ± 0.5
Median (min-max)	1.50 (0.7- 4.7)	1.50 (0.6- 3.9)
GFR (mL/min) at 6 months (Nankivell)		
N	132	120
Mean ± SD	60.33 ± 16.5	62.39 ± 15.5
Median (min-max)	61.15 (19.0-104.8)	61.91 (25.6-116.6)

Note: in the computation of creatinine clearance LOCF, missing value are imputed as zero for patient died or lost their graft before 6 month. In the other cases LOCF approach was used.

First biopsy proven acute rejection episode (ITT population)

	Upper N = 142	Standard N = 143
Event Rate - n(%)	16 (11.3%)	20 (14.0%)
Probability of BPAR	11.94%	14.67%
LogRank test - p-value	0.4744	
Difference between proportions		
Upper-Standard	-2.72%	
97.5%Upper C.L. of difference	4.99%	

Secondary Outcome Result(s)

Number (%) of patients with acute rejection, chronic rejection, graft loss, delayed graft function and death after 6 months of treatment (ITT population)

	Upper (N=142)			Standard (N=143)		
	n	%	95% C.I.	n	%	95% C.I.
Acute rejection	23	(16.2%)	22.3	30	(21.0%)	27.7
Biopsy proven acute rejection	16	(11.3%)	16.5	20	(14.0%)	19.7
Chronic rejection	0	(0.0%)	.	2	(1.4%)	3.3
Subclinical rejection	0	(0.0%)	.	1	(0.7%)	2.1
Treated rejection	23	(16.2%)	22.3	29	(20.3%)	26.9
Acute rejection (AR) steroid resistant	3	(2.1%)	4.5	9	(6.3%)	10.3
Graft Loss	3	(2.1%)	4.5	14	(9.8%)	14.7
Delayed graft function (DGF)	33	(23.2%)	30.2	44	(30.8%)	38.3
Death	2	(1.4%)	3.3	2	(1.4%)	3.3
BPAR/patient/graft loss	21	(14.8%)	20.6	29	(20.3%)	26.9

NOTES: 95% Confidence Limits are computed 1-tailed.
AR is defined as BPAR, AR without biopsy, acute and chronic rejection.
BPAR is defined as BPAR and acute and chronic rejection.
Chronic rejection is defined as acute and chronic rejection.
Subclinical rejection is defined as histological evidence of rejection without clinical diagnosis.
Treated rejection is defined as acute rejection treated.
AR steroid resistant is defined as acute rejection treated with globuline including rituximab.
DGF is defined as a need of dialysis in the first 7 days post tx or as a serum creatinine >4mg/dL for two weeks or more post tx.

Proportion of patients with stable serum creatinine increase more than 30% of the previous nadir (ITT population)

	Upper (N=142)	Standard (N=143)
Number (%) of pts with		
Serum creatinine increase >30%	11 (7.7%)	9 (6.3%)
Chi-Square test - p-value:	0.6312	

Notes: A patients is considered with stable serum creatinine increase of more than 30% if the mean of 2 consecutive assessments -and all the following means- is >30% of the lowest mean of any two consecutive post-tx measures.

Summary of Safety

Safety Results

Adverse events overall and frequently affected system organ classes - n (%) of patients (all patients / > 10% in any group) (Safety population)

	Upper N= 142	Standard N= 143
Number of patients with any AEs/infections	142 (100.0%)	142 (99.30%)
Number of patients with any AEs	142 (100.0%)	142 (99.30%)
Number of patients with any Infections	77 (54.23%)	87 (60.84%)
Preferred Term		
Anaemia	72 (50.70%)	68 (47.55%)
Dyslipidaemia	62 (43.66%)	47 (32.87%)
Urinary tract infection	58 (40.85%)	72 (50.35%)
Hypocalcaemia	33 (23.24%)	19 (13.29%)
Pyrexia	30 (21.13%)	37 (25.87%)
Lymphocele	29 (20.42%)	22 (15.38%)
Oedema peripheral	28 (19.72%)	25 (17.48%)
Hypertension	26 (18.31%)	25 (17.48%)
Complications of transplanted kidney	23 (16.20%)	36 (25.17%)
Hyperlipidaemia	23 (16.20%)	22 (15.38%)
Hypokalaemia	21 (14.79%)	28 (19.58%)
Hyperuricaemia	21 (14.79%)	23 (16.08%)
Hypercholesterolaemia	20 (14.08%)	20 (13.99%)
Blood creatinine increased	20 (14.08%)	15 (10.49%)
Hypertriglyceridaemia	19 (13.38%)	15 (10.49%)
Constipation	17 (11.97%)	11 (7.69%)
Hyperglycaemia	15 (10.56%)	8 (5.59%)
Kidney transplant rejection	9 (6.34%)	16 (11.19%)
Cytomegalovirus infection	7 (4.93%)	15 (10.49%)

Patients are only counted once in each term regardless of the number of AEs experienced in that preferred terms. Arranged in descending order of frequency.

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

	Upper (N=142)	Standard (N=143)
Patients with AE(s)	142 (100%)	142 (99.3%)
Serious or other significant AEs		
SAE(s)	59 (41.5%)	72 (50.3%)
Death	2 (1.4%)	2 (1.4%)
Clinically significant AEs	42 (29.6%)	45 (31.5%)
Discontinued due to SAE(s)	4 (2.8%)	2 (1.4%)
Discontinued due to clin.sign. AE(s)	6 (4.2%)	3 (2.1%)

Date of Clinical Trial Report

16-Jul-2010