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Sponsor

Novartis Pharmaceuticals Corporation

Generic Drug Name

Everolimus

Therapeutic Area of Trial

Renal transplantation

Approved Indication

Indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. It is administered in combination with basiliximab induction and concurrently with reduced doses of cyclosporine and with corticosteroids.

Protocol Number

CRAD001AUS92

Title

A 12 month, multi-center, randomized, open-label non-inferiority study comparing the safety and efficacy of concentration-controlled everolimus with low dose tacrolimus to mycophenolate mofetil with standard dose tacrolimus in *de novo* renal transplant recipients

Study Phase

Phase IIIb

Study Start/End Dates

23 Jan 2010 to 06 Mar 2013

Study Design/Methodology

12 month, multi-center, randomized, open-label non-inferiority study comparing the safety and efficacy of concentration-controlled everolimus (EVR) with low dose tacrolimus (Low TAC) to

mycophenolate mofetil (MMF) with standard dose tacrolimus (Std TAC) in *de novo* renal transplant recipients. Approximately 590 patients who met the inclusion criteria were planned to be randomized.

After obtaining informed consent patients were screened for eligibility and randomized, stratified by induction therapy, within 24 hours post-transplantation to receive either everolimus or MMF (1:1) in combination with tacrolimus and corticosteroids for 12 months. Baseline evaluations occurred 24 hours prior to surgery, until randomization.

Antibody induction therapy was based on the panel-reactive (T cell) antibody (PRA) level. PRA levels within 6 months were acceptable. For patients with < 20% PRA levels, basiliximab 20 mg was to be administered within 2 hours prior to transplant and 20 mg at Day 4, or following local practice. For patients with ≥ 20% PRA levels or who were considered high risk (i.e., recipients of extended criteria donor organs or deceased donor organs after cardiac death), anti-thymocyte globulin (rabbit) was to be administered according to local practice.

Everolimus and tacrolimus were initiated within 24 hours after reperfusion of the graft. If the patient experienced delayed graft function (DGF), tacrolimus could be held for up to 14 days. Everolimus and MMF must have been started within 24 hours post-transplant.

Everolimus treatment arm: Therapeutic drug monitoring of everolimus and tacrolimus was mandatory throughout the study. From Day 5 onwards, the everolimus 0.75 mg b.i.d. dose was increased if the trough level was < 3 ng/mL, or reduced if the trough level was > 8 ng/mL. Tacrolimus was initiated according to local practice. In this treatment arm, the tacrolimus dose was adjusted from Day 3 onwards, to a target whole blood trough concentration of 4 ng/mL to 7 ng/mL. From Month 2 until Month 6, the target tacrolimus trough level was 3 ng/mL to 6 ng/mL. After Month 6, the tacrolimus dose was adjusted in order to achieve a target trough level of 2 ng/mL to 5 ng/mL.

MMF treatment arm: The MMF dose was initiated at 1 g b.i.d. (2 g/day). Adjustments were to be made for adverse events including, but not limited to, gastrointestinal intolerance and a decrease in WBC. MMF trough or AUC was not used to adjust dosing. In this group, tacrolimus was initiated according to local practice. The tacrolimus dose was adjusted from Day 3 on to achieve a target whole blood trough concentration of 8 ng/mL to 12 ng/mL. From Month 2 until Month 6, the target tacrolimus trough level was reduced to 7 - 10 ng/mL. After Month 6, the target level of tacrolimus was reduced to 5 - 8 ng/mL.

In both groups, steroids were administered according to local practice.

The recruitment period was planned for 24 months. The treatment period was 12 months. A biopsy was required at pre-implantation and at Month 6. No follow-up period was planned. Discontinued patients were followed for renal function and the incidence of efficacy failure at 3, 6, 9, and 12 months post-transplant.

Centers

52 centers in 2 countries: United States (50), Canada (2)

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

0.25mg, 0.50 mg and 0.75 mg oral tablets of everolimus dosing twice a day

Statistical Methods

Data from all centers that participated in this study were pooled, so that an adequate number of patients were available for analysis. Analyses were performed using SAS version 9.1.3 or higher.

All confidence intervals will be two-sided at 95% confidence level. All categorical data were summarized by frequencies and percentages. Continuous data were summarized by mean, median, standard deviation, minimum and maximum and the number of non-missing data points.

Statistical summaries are provided for each treatment group and for the two treatment groups combined. Selected summaries are provided by induction therapy (basiliximab or thymoglobulin) and treatment group.

All p-values were adjusted by the baseline stratification by induction therapy. P-values for continuous variables were computed from the Type II sum of squares for an ANOVA model with treatment and stratum as explanatory factors. P-values for categorical variables were computed from the Cochran-Mantel-Haenszel (CMH) general association test stratified by induction therapy. P-values for rank tests were computed by Van Elteren's test, stratifying by induction therapy.

Four populations were established for this study:

- Randomized Set: consisted of all patients randomized into the study.
- Full Analysis Set (FAS): consisted of all patients randomized after transplantation. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization.
- Safety Set (SS): consisted of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.
- Per Protocol Set (PPS): consisted of all FAS patients without a major protocol violation. The PPS was identified prior to database lock.

To test the non-inferiority of the everolimus with reduced dose tacrolimus treatment group with the MMF with standard dose tacrolimus treatment group, the following null hypothesis was tested: treatment effect of the everolimus with reduced dose tacrolimus treatment group, with respect to the composite efficacy failure rate, is at least 10% greater than the MMF with standard dose tacrolimus treatment group. The alternative hypothesis was that the treatment effect of the everolimus with reduced dose tacrolimus treatment group was not greater than that of MMF with standard dose tacrolimus treatment group by 10% or more:

(a) Ho: $\pi_E \geq \pi_M + 0.10$ versus Ha: $\pi_E < \pi_M + 0.10$

where π_E and π_M are the composite efficacy failure rates for the everolimus with reduced dose tacrolimus treatment group and the MMF with standard dose tacrolimus treatment group, respectively. The test of the everolimus with reduced dose tacrolimus treatment group versus the MMF with standard dose tacrolimus treatment group is a one-sided test at the 2.5% significance level.

The everolimus with reduced dose tacrolimus treatment group was considered to be statistically non-inferior to the MMF with standard dose tacrolimus treatment group with respect to the composite efficacy failure rate if the null hypothesis is rejected, i.e., if the one-sided confidence interval for $\pi_E - \pi_M$ corresponding to the comparability test in (a) was entirely below 0.10. This analysis was performed for the FAS, and for the PPS as a supportive analysis.

All information pertaining to AEs/infections, notable events (e.g., death, non-fatal serious AEs/infections, AEs/infections leading to premature discontinuation of the study drug), selected AEs of interest, wound complication and effusion events, CMV events, vital sign data and laboratory data were summarized.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Male or female renal recipients 18-70 years of age undergoing kidney transplantation, either primary or re-transplant
- Recipient of a cadaveric, deceased donor (including expanded criteria donor organs and deceased donor organs after cardiac death), living unrelated or non-HLA identical living related donor kidney
- Graft must be functional (producing greater than or equal to 100 ml of urine within 24 hours after transplantation) at time of randomization

Exclusion criteria

- Donor organ with a cold ischemic time > 30 hours
- Patients who produce less than 100 ml of urine in the first 24 hours post-transplantation
- Patients who are recipients of ABO incompatible transplants, or T cell, or B cell crossmatch positive transplant
- Patients with severe total hypercholesterolemia (> 350 mg/dL; > 9 mmol/L) or total hypertriglyceridemia (> 500 mg/dL; > 5.6 mmol/L). Patients on lipid lowering treatment with controlled hyperlipidemia are acceptable.
- Patients who have any surgical or medical condition, such as severe diarrhea, active peptic ulcer disease, or uncontrolled diabetes mellitus, which in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism and/or excretion of study medication

Participant Flow

	EVR+Low TAC n (%)	MMF+ Std TAC n (%)	Total n (%)
Total no. of patients	309 (100)	304 (100)	613 (100)
Completed study medication	204 (66.0)	232 (76.3)	436 (71.1)
Completed study phase	293 (94.8)	282 (92.8)	575 (93.8)
Discontinued study medication	105 (34.0)	72 (23.7)	177 (28.9)
Adverse events	66 (21.4)	39 (12.8)	105 (17.1)
Protocol deviation	9 (2.9)	8 (2.6)	17 (2.8)

	EVR+Low TAC n (%)	MMF+ Std TAC n (%)	Total n (%)
Subject withdrew consent	8 (2.6)	9 (3.0)	17 (2.8)
Administrative problems	7 (2.3)	5 (1.6)	12 (2.0)
Unsatisfactory therapeutic effect	7 (2.3)	0	7 (1.1)
Abnormal test procedure	4 (1.3)	0	4 (0.7)
Graft loss	2 (0.6)	5 (1.6)	7 (1.1)
Death	2 (0.6)	2 (0.7)	4 (0.7)
Abnormal lab values	0	2 (0.7)	2 (0.3)
Subjects condition no longer required study drug	0	1 (0.3)	1 (0.2)
Lost to follow-up	0	1 (0.3)	1 (0.2)
Discontinued study	16 (5.2)	22 (7.2)	38 (6.2)
Subject withdrew consent	8 (2.6)	16 (5.3)	24 (3.9)
Death	6 (1.9)	5 (1.6)	11 (1.8)
Missing	2 (0.6)	0	2 (0.3)
Lost to follow-up	0	1 (0.3)	1 (0.2)

In total, 738 patients were screened, and 613 were randomized to treatment (n=309 to EVR+Low TAC and n=304 to MMF+Std TAC).
EVR = Everolimus and low dose tacrolimus; MMF = Mycophenolate mofetil and standard dose tacrolimus

Baseline Characteristics

		EVR + Low TAC (N=306)	MMF + Std TAC (N=304)
Age (years)	Mean ± SD	50.0 ± 13.34	48.4 ± 12.91
Gender - n (%)	Male	205 (67.0)	202 (66.4)
	Female	101 (33.0)	102 (33.6)
Race – n (%)	Caucasian	196 (64.1)	201 (66.1)
	Black	70 (22.9)	74 (24.3)
	Asian	17 (5.6)	11 (3.6)
	Native American	3 (1.0)	1 (0.3)
	Pacific Islander	3 (1.0)	1 (0.3)
	Other	17 (5.6)	16 (5.3)
BMI (kg/m^2) at randomization	n	305	303
	Mean ± SD	27.7 (5.55)	28.3 (5.13)
Diabetic status at randomization - n (%)	Yes	111 (36.3)	95 (31.3)
	No	195 (63.7)	209 (68.8)

Outcome Measures

Primary Outcome Result(s)

Incidence Rates of Efficacy Endpoints by treatment group (Full analysis set)

Efficacy Endpoints	EVR + Low TAC N=309 n (%)	MMF + Std TAC N=304 n (%)
Composite endpoint*	76 (24.6)	62 (20.4)
- Treated Biopsy-Proven Acute Rejection (BPAR)	59 (19.1)	34 (11.2)
- Graft loss	4 (1.3)	12 (3.9)
- Death	6 (1.9)	5 (1.6)
- Loss to follow-up	9 (2.9)	17 (5.6)

Efficacy failure rate used the composite endpoint of: (1) treated biopsy-proven acute rejection (BPAR)*, (2) graft loss**, (3) participant death or(4) loss to follow-up.
*A treated BPAR was defined as a biopsy graded IA, IB, IIA, IIB, or III and which was treated with anti-rejection therapy.
**Graft loss is defined as when the allograft was presumed lost on the day the participant started dialysis and was not able to subsequently be removed from dialysis.

Secondary Outcome Result(s)

Summary statistics of renal function at Month 12: Calculated GFR (MDRD) [mL/min/1.73m^2] (Full Analysis Set)

Visit	Treatment Group	n	Mean (SD)
Month 12	Evr + Low TAC	253	63.14 (22.042)
	MMF + Std TAC	248	63.06 (19.512)

Renal function was assessed by estimated Glomerular Filtration Rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula.
MDRD formula: GFR [mL/min/1.73m^2] = 186.3*(C^-1.154)*(A^-0.203)*G*R.
DEFINITIONS: C = serum concentration of creatinine [mg/dL]; A = age [years]; G = 0.742 when gender is female, otherwise G = 1; R = 1.21 when race is black, otherwise R = 1

Incidence rates of CMV syndrome, laboratory evidence of CMV and CMV disease (Safety Set)

Characteristic Category	Evr + Low TAC (N=306)	MMF + Std TAC (N=304)	Total (N=610)
CMV Syndrome Event			
Yes	9 (2.9)	13 (4.3)	22 (3.6)
Lab evidence of CMV Viremia			
Yes	7 (2.3)	10 (3.3)	17 (2.8)
CMV Disease			
Yes	2 (0.7)	8 (2.6)	10 (1.6)

Participants with incidence of CMV (viremia, syndrome and disease). CMV is cytomegalovirus.

Incidence rates of BKV viremia, viruria and nephropathy (Safety Set)

Characteristic Category	Evr + Low TAC Overall (N=306)	MMF + Std TAC Overall (N=304)	Total (N=610)
Lab evidence of BKV Viremia			

Characteristic Category	Evr + Low TAC Overall (N=306)	MMF + Std TAC Overall (N=304)	Total (N=610)
Yes	19 (6.2)	27 (8.9)	46 (7.5)
Lab evidence of BKV Viruria			
Yes	19 (6.2)	15 (4.6)	34 (5.6)
BKV Disease (Nephropathy)			
Yes	5 (1.6%)	5 (1.6%)	10 (1.6%)

Participants with incidence of BKV (viremia, viruria or nephropathy). BKV is Polyomavirus type BK.

Incidence of patients with new onset diabetes mellitus

New Onset Diabetes	Evr + Low TAC (N=306)	MMF + Std TAC (N=304)
Any New Onset Diabetes	25/306 (8.2%)	22/304 (7.2%)
Glucose (random) ≥ 200 mg/dL with two fasting glucose ≥ 126 mg/dL	15/306 (4.9%)	12/304 (3.9%)
Concomitant medication for Diabetes for 30 days or more	13/306 (4.2%)	14/304 (4.6%)

Incidence of new onset diabetes mellitus defined as non-diabetic patients before transplantation, who are receiving glucose lowering treatment for more than 30 days post-transplant, or with a random plasma glucose ≥200 mg dL (11.1 mmol/L) with 2 fasting plasma glucose values ≥126 mg/dL (7 mmol/L).

Summary of proteinuria events (Safety Set)

Visit: Window Category (mg/g)	Evr + Low TAC Overall (N=306)	MMF + Std TAC Overall (N=304)
Baseline		
Proteinuria (>=300 mg/g)	243/304 (79.9%)	250/304 (82.2%)
Month 12: Day 316-450		
Proteinuria (>=300 mg/g)	36/203 (17.7%)	35/232 (15.1%)

Number of participants with incidence of proteinuria events indicating chronic kidney disease

Safety Results

Incidence rates of adverse events by primary system organ class (Safety set)

System Organ Class	Evr + Low TAC Overall (N=306) n (%)	MMF + Std TAC Overall (N=304) n (%)

Any system organ class	303 (99.0)	302 (99.3)
Metabolism and nutrition disorders	266 (86.9)	263 (86.5)
Gastrointestinal disorders	233 (76.1)	247 (81.3)
Injury, poisoning and procedural complications	223 (72.9)	202 (66.4)
General disorders and administration site conditions	199 (65.0)	177 (58.2)
Infections and infestations	184 (60.1)	196 (64.5)
Investigations	150 (49.0)	143 (47.0)
Renal and urinary disorders	141 (46.1)	160 (52.6)
Vascular disorders	131 (42.8)	121 (39.8)
Blood and lymphatic system disorders	130 (42.5)	163 (53.6)
Nervous system disorders	125 (40.8)	150 (49.3)
Respiratory, thoracic and mediastinal disorders	122 (39.9)	134 (44.1)
Musculoskeletal and connective tissue disorders	110 (35.9)	114 (37.5)
Skin and subcutaneous tissue disorders	109 (35.6)	108 (35.5)
Psychiatric disorders	96 (31.4)	106 (34.9)
Reproductive system and breast disorders	56 (18.3)	40 (13.2)
Cardiac disorders	51 (16.7)	47 (15.5)
Eye disorders	26 (8.5)	36 (11.8)
Immune system disorders	13 (4.2)	11 (3.6)
Endocrine disorders	12 (3.9)	8 (2.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (3.3)	15 (4.9)
Ear and labyrinth disorders	7 (2.3)	11 (3.6)
Hepatobiliary disorders	6 (2.0)	3 (1.0)
Surgical and medical procedures	2 (0.7)	0
Congenital, familial and genetic disorders	0	6 (2.0)
Social circumstances	0	1 (0.3)

Primary system organ classes are presented in descending order for column 2
AE/infections with onset date eight or more days after the discontinuation of randomized study medication are not included in this analysis.
A patient with multiple occurrences of an AE or infection is counted only once for each system organ class, or for any system organ class.

Incidence rates of adverse events / infections frequent (more than or equal to 10% in any treatment group) by preferred term (Safety Set)

	Evr + Low TAC	MMF + Std TAC
System Organ Class	**Overall (N=306) n (%)**	**Overall (N=304) n (%)**
Any system organ class	303 (99.0)	302 (99.3)
Constipation	119 (38.9)	121 (39.8)
Oedema peripheral	116 (37.9)	90 (29.6)
Nausea	114 (37.3)	136 (44.7)
Hypophosphataemia	108 (35.3)	94 (30.9)
Hypomagnesaemia	102 (33.3)	124 (40.8)
Hyperkalaemia	94 (30.7)	84 (27.6)
Procedural pain	93 (30.4)	95 (31.3)
Anaemia	85 (27.8)	69 (22.7)
Diarrhoea	76 (24.8)	127 (41.8)
Hyperglycaemia	76 (24.8)	84 (27.6)

Hyperlipidaemia	71 (23.2)	31 (10.2)
Insomnia	68 (22.2)	71 (23.4)
Hypertension	68 (22.2)	73 (24.0)
Urinary tract infection	64 (20.9)	81 (26.6)
Fatigue	59 (19.3)	52 (17.1)
Blood creatinine increased	58 (19.0)	51 (16.8)
Hypokalaemia	56 (18.3)	54 (17.8)
Tremor	51 (16.7)	87 (28.6)
Vomiting	51 (16.7)	70 (23.0)
Pyrexia	50 (16.3)	53 (17.4)
Incision site pain	46 (15.0)	54 (17.8)
Hypocalcaemia	46 (15.0)	40 (13.2)
Headache	45 (14.7)	54 (17.8)
Dyspnoea	43 (14.1)	52 (17.1)
Graft dysfunction	43 (14.1)	39 (12.8)
Metabolic acidosis	35 (11.4)	40 (13.2)
Oedema	34 (11.1)	28 (9.2)
BK virus infection	33 (10.8)	42 (13.8)
Diabetes mellitus	33 (10.8)	33 (10.9)
Pruritus	32 (10.5)	32 (10.5)
Proteinuria	32 (10.5)	19 (6.3)
Haematuria	31 (10.1)	36 (11.8)
Arthralgia	31 (10.1)	24 (7.9)
Abdominal pain	31 (10.1)	35 (11.5)
Upper respiratory tract infection	28 (9.2)	34 (11.2)
Cough	28 (9.2)	43 (14.1)
Leukopenia	27 (8.8)	66 (21.7)
Dizziness	26 (8.5)	36 (11.8)
Hypotension	25 (8.2)	31 (10.2)
Leukocytosis	23 (7.5)	32 (10.5)
Anxiety	17 (5.6)	34 (11.2)

Preferred terms are sorted in descending order for column 2.
AE/infections with onset date eight or more days after the discontinuation of randomized study medication are not included in this analysis.
A patient with multiple occurrences of an AE or infection is counted only once for each preferred term, each system organ class, or for any system organ class.

Incidence rates of notable events (presented in non-mutually exclusive way) (Safety Set)

Notable Events	Evr + Low TAC (N=306) n (%)	MMF + Std TAC (N=304) n (%)	Total (N=610) n (%)
Any notable event	173 (56.5)	162 (53.3)	335 (54.9)
Death	6 (2.0)	5 (1.6)	11 (1.8)
SAE	156 (51.0)	144 (47.4)	300 (49.2)
AE leading to discontinuation of study medication	68 (22.2)	44 (14.5)	112 (18.4)
Adverse dropout	70 (22.9)	41 (13.5)	111 (18.2)
Adverse event	66 (94.3)	39 (95.1)	105 (94.6)
Abnormal laboratory value	0	2 (4.9)	2 (1.8)
Abnormal test procedure results	4 (5.7)	0	4 (3.6)

Notable Events	Evr + Low TAC (N=306) n (%)	MMF + Std TAC (N=304) n (%)	Total (N=610) n (%)

Notable events include deaths, SAEs (including infections), AEs (includinginfections) leading to discontin uation of study medication, and Adverse Dropout (recorded on Treatment and Study Completion CRF = Reason for premature discontinuation of study medication: Adverse Events; Abnormal laboratory values; Abnormal test procedure results)
Note: Events with onset date >30 days after study completion are not included in this analysis

Other Relevant Findings

Date of Clinical Trial Report

24 February 2014

Date Inclusion on Novartis Clinical Trial Results Database

3 March 2014

Date of Latest Update