Sponsor

Novartis

Generic Drug Name

Everolimus

Therapeutic Area of Trial

Immunosuppressant in human renal allotransplantation

Approved Indication

- Indicated for the use as an immunosuppressant in adult renal transplantation combined with reduced-dose cyclosporine A (CsA, Neoral®)
- Everolimus is approved for the prevention of acute rejection (Renal and Heart) in over 80 countries

Study Number

CRAD001A2309

Title

A 24 month, multicenter, randomized, open-label non-inferiority study of efficacy and safety comparing concentration-controlled everolimus in two doses (1.5 and 3.0 mg/day starting doses) with reduced cyclosporine versus 1.44 g mycophenolic acid with standard dose cyclosporine in de novo renal transplant recipients

Phase of Development

Phase III

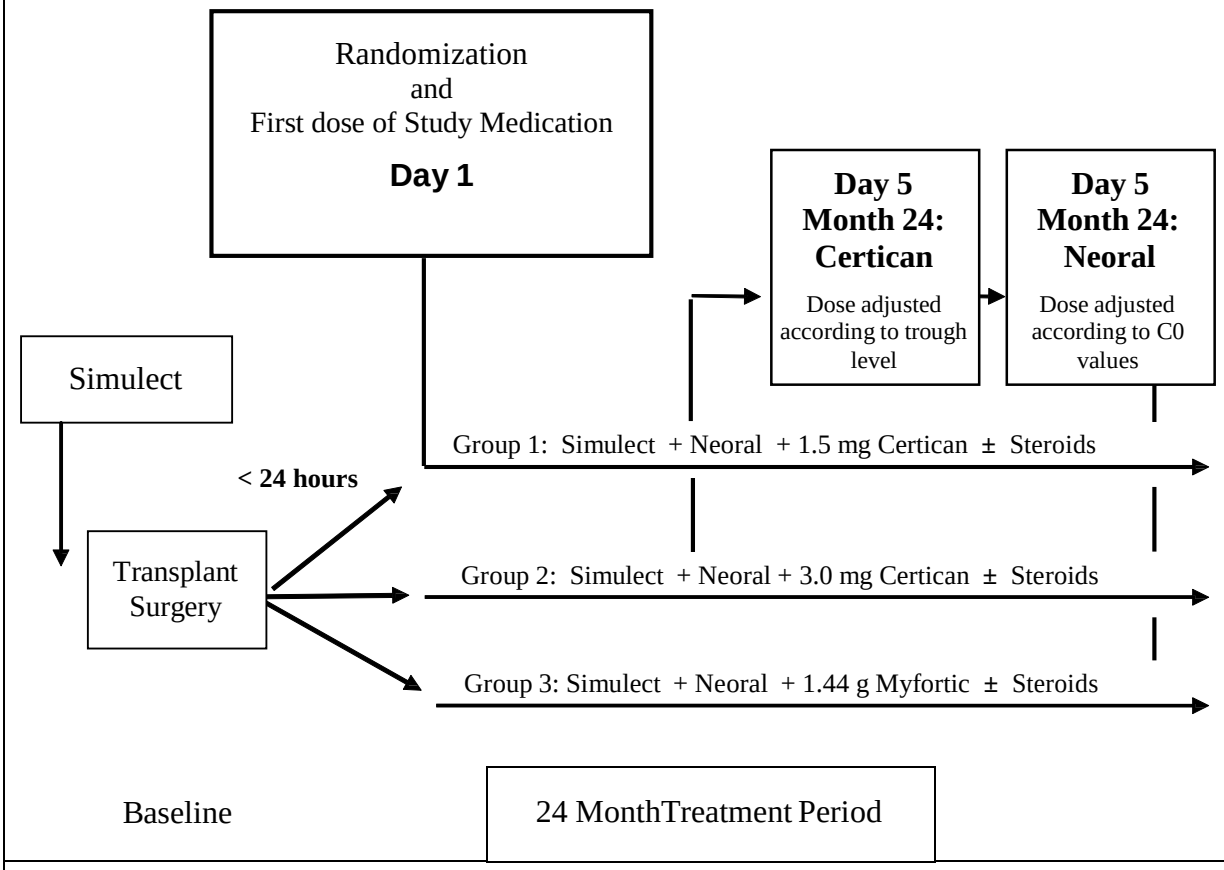
Study Start/End Dates

05-Oct-2005 to 18-Aug-2009

Study Design/Methodology

Multicenter, multinational, randomized, open-labeled, non-inferiority study of efficacy and safety study comparing concentration-controlled everolimus in two starting doses (1.5 and 3.0 mg) with reduced cyclosporine versus 1.44g mycophenolic acid with standard dose cyclosporine in de novo renal transplant recipients. All patients received antibody induction therapy using basilixi-mab. Corticosteroids were administered according to local therapy, and were consistent for all patients within each study center. Eligible patients were randomized to receive their first dose of study drug within 24 hours after transplantation. From day 5 onwards doses of everolimus and CsA could be adjusted in order to maintain trough levels within the target window to attain a C0 value within assigned ranges during the course of the study.

The figure below displays the study design:



Centres

Sixteen countries with a total of 79 centers participated in this study:(Argentina: 3 centers, Australia: 8 centers, Brazil: 4 centers, Canada: 1 center, Hong Kong: 1 center, Italy: 4 centers, New Zealand: 1 center, Singapore: 1 center, Slovakia: 2 centers, South Africa: 1 center, South Korea: 6 centers, Sweden: 1 center, Taiwan: 1 center, Turkey: 3 centers, United Kingdom: 3 centers, and United States: 39 centers).

Publication

H Tedesco-Silva Jr. et al. Everolimus Plus Reduced-Exposure CsA versus Mycophenolic Acid Plus Standard-Exposure CsA in Renal-Transplant Recipients: American Journal of Transplantation. 2010, 10, (6): 1401-1413

Objectives

Primary objective(s)

The primary objective of the study was to demonstrate that at least one of the everolimus treatment regimens was not inferior to the mycophenolic acid treatment regimen within 12 months of the initial dose of study medication with respect to primary efficacy failure, namely, the composite efficacy endpoint of treated BPAR episodes, graft loss, death, or loss to follow-up.

Secondary objective(s)

The main secondary efficacy (composite) objective was to compare the incidence of graft loss, death, or loss to follow-up between everolimus and mycophenolic acid treatment arms at 12 months post-transplantation.

The main safety objective was to demonstrate that non-inferior renal function was achieved in the everolimus treatment arms compared to the mycophenolic acid treatment arm at 12 months post-transplantation. Renal function was measured with calculated glomerular filtration rate (GFR) using the MDRD formula

Other secondary variables included the assessment of the composite endpoint at 6 and 24 months, and assessment of the individual components at 6, 12 and 24m

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

Oral tablet of everolimus 0.75mg bid or 2 tablets of everolimus 0.75mg administered bid in combination with reduced exposure to Neoral. Everolimus 0.25-mg and 0.5-mg tablets were supplied for dose adjustments.

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

2 oral capsules of mycophenolic acid 360mg administered bid in combination with standard exposure to Neoral

Criteria for Evaluation

Primary variables

Composite efficacy endpoint of treated BPAR episodes, graft loss, death, or loss to follow-up at 12 months

Secondary variables

Renal function assessed by Calculated glomerular filtration rate (GFR) using the MDRD (Modification of Diet in Renal Disease) formula.

Secondary variables included the assessment of the composite endpoint at 6 and 24 months, and assessment of the individual components at 6, 12 and 24 months

Safety and tolerability

Safety assessments consisted of collecting all AEs, SAEs, with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry, and urine and regular assessments of vital signs, physical condition, and body weight. Infections, unusually severe rejection episodes, major adverse cardiac events (MACE) and wound healing events (reported in the 12 month CSR only) were also studied.

Pharmacology

NA

Other

Bioanalytics: Regular monitoring of blood everolimus and cyclosporine levels was undertaken with dose adjustments seeking to achieve concentrations within the predefined range. Target trough (C0) ranges for everolimus were 3-8 ng/mL and 6-12 ng/mL in the everolimus 1.5 mg and 3.0 mg treatment groups, respectively.

Among patients receiving everolimus, the cyclosporine dose was similarly adjusted seeking to obtain trough (C0) concentrations within the pre-specified target ranges: 100-200 ng/mL starting at the day 5 visit; 75–100 ng/mL starting at the month 2 visit; 50–100 ng/mL starting at the month 4 visit; and 25-50 ng/mL from the month 6 visit onward.

Patients receiving mycophenolic acid were targeted for cyclosporine dose adjustments to achieve CsA trough (C0) values between 200–300 ng/mL starting at the day 5 visit; and 100–250 ng/mL from the month 2 visit onward.

Statistical Methods

Data from all centers participating in the study were pooled so that an adequate number of pa-

tients were available for analysis. All categorical data were summarized by frequencies and percentages. Continuous data was summarized by mean, median, standard deviation, minimum and maximum and the number of non-missing data points. The Intent-To-Treat (ITT) population consists 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. The Safety population consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Patients were analyzed according to treatment received. The Per-protocol (PP) population consists of all randomized patients who took study treatment according to the protocol without any major deviations from the protocol procedures.

Demographic and background information was summarized in the ITT population using frequency distribution for categorical variables and descriptive statistics of mean, median, maximum, minimum and standard deviation for continuous variables. Demographic information was also summarized for the PP population.

The primary objective of the study was tested for each of the 2 treatment comparisons of everolimus to mycophenolic acid, with regard to the following null hypothesis:

H_0: the proportion of patients experiencing efficacy failure at 12 months on the everolimus arm is higher than that of the mycophenolic acid arm by 10% or more, where 10% represents the non-inferiority margin chosen.

The non-inferiority tests were based on confidence intervals (CI) constructed using the Z-test statistic, performed on the ITT population.

The trial was to be claimed as successful if the incidence rate of the primary composite efficacy failure from either of the two everolimus arms was non-inferior to the mycophenolic acid arm. Hence, to control for multiple comparisons (i.e., everolimus 1.5 mg vs. mycophenolic acid and everolimus 3.0 mg vs. mycophenolic acid) the Hochberg procedure was used to maintain the overall Type I error rate at 0.05. Following the Hochberg procedure, two-sided 95% and 97.5% CIs for the difference in primary efficacy failure rates at 12 months between the everolimus and mycophenolic acid arms were computed. An everolimus group was claimed to have non-inferior efficacy failure rate at 12 months to mycophenolic acid if the upper limit of the appropriate CI was less than 10%.

As a supportive analysis and robustness check, the primary analysis was repeated using the PP population.

Safety variables included discontinuation from study, discontinuation from treatment, renal function, AE/infection, SAE, notable events, laboratory tests, and vital signs.

The main safety objective of the trial was to demonstrate that non-inferior renal function (calculated GFR using the MDRD formula) was achieved between an everolimus treatment arm and the myfortic treatment arm at 12 months post-transplantation. The main safety endpoint was calculated GFR using the MDRD formula. Central laboratory serum creatinine values were used for all renal function data analysis. If the serum creatinine value from central laboratory was missing within a visit window, the serum creatinine value from local laboratory was used for that visit window. Again the multiple comparison method outlined for the primary endpoint was applied. T-test based, two-sided 95% and 97.5% confidence intervals (CI) for the difference in mean GFR at 12 months between the everolimus and mycophenolic acid arms were computed. An everolimus arm was claimed to have non-inferior renal function at 12 months to the mycophenolic acid

arm if the lower limit of the appropriate CI was greater than -8.

All other safety parameters were analyzed using the safety population and all post-treatment follow-up safety information was analyzed and attributed to the randomized study medication for each patient.

Infection data was coded with SNOMED for micro-organism and type of infection (viral, bacterial, fungal and others). In addition to being analyzed similarly as AEs and SAEs, as described above, the incidence rate of infection by type and micro-organism was tabulated for each treatment arm.

Notable events included death, non-fatal SAEs (including infections), AEs (including infections) leading to discontinuation of study drug, and adverse drop out. These events were summarized by treatment group. Contrary to adverse events and infections, tabular summaries of incidence rates of notable events did not exclude events with onset 8 or more days after the discontinuation of randomized study medication (unless the event occurred after the analysis cut-off date).

Vital signs variables included measurements of systolic and diastolic blood pressures, pulse, and body weight. Vital signs were examined for abnormal values and change from Baseline according to pre-specified clinically notable criteria. Descriptive statistics of change from Baseline of all vital signs variables was presented by visit.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Male or female renal recipients
- 18-70 years of age undergoing primary kidney transplantation
- Females with a negative pregnancy test

Exclusion criteria

- No evidence of graft function within 24 hours of transplantation
- Receipt of kidneys from HLA-identical living related donors
- Donor organ with a cold ischemia time > 40 hours
- Received kidney from a non-heart beating donor
- Donor age > 65 years
- Platelet count < 100,000/mm^3 at the evaluation before randomization
- Absolute neutrophil count (ANC) < 1,500/mm^3 at baseline before surgery or white blood cell (WBC) count < 4,500/mm^3
- Receipt of dual kidney transplants
- Recipients of multiple solid organ or tissue transplants or recipients of a previous organ or tissue transplant
- Severe hypercholesterolemia (> 350 mg/dL; > 9 mmol/L) or Hypertriglyceridaemia (> 500 mg/dL; > 8.5 mmol/L); controlled hyperlipidemia was acceptable
- Abnormal liver profile such as alanine aminotransferase (ALT), Aspartate aminotransferase (AST), alkaline phosphatase, or total bilirubin > 3 times the upper limit of normal (ULN)
- Most recent anti-HLA Class I panel reactive antibodies > 20% by a Complement Dependent

Cytotoxicity (CDC)-based assay or > 50% by a flow cytometry or Enzyme Linked Immuno-sorbent Assay (ELISA)-based assay

- Receipt of ABO incompatible transplants or T-cell crossmatch positive transplant

Number of Subjects

	Novartis product		Comparator
	1.5 mg EVR	**3.0mg EVR**	**Myfortic**
Planned N	275	275	275
Randomised n	277	279	277
Intent-to-treat population (ITT) n (%)	277(100%)	279(100%)	277 (100%)
Completed n (%)	232 (84%)	238(85%)	246 (89%)
Withdrawn n (%)	110 (40%)	118(42%)	92 (33%)
Withdrawn due to adverse events n (%)	68 (25%)	71(25%)	40 (15%)
Withdrawn due to lack of efficacy n (%)	12 (4%)	14(5%)	19 (7%)
Withdrawn for other reasons n (%)	30 (11%)	33(12%)	33 (11%)

Demographic and Background Characteristics

	Novartis product		Comparator
	1.5mg EVR	**3.0mg EVR**	**Myfortic**
N (ITT)	277	279	277
Females : males	100:177	88:191	88:189
Mean age, years (SD)	45.7(12.72)	45.3(13.36)	47.2 (12.74)
Mean weight, kg (SD)	75.06 (18.28)	75.35(19.04)	75.68 (16.57)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 193 (70%) 35 (13%) 32 (12%) 17 (6%)	 180 (65%) 40 (14%) 38 (14%) 21 (8%)	 190 (69%) 39 (14%) 36 (13%) 12 (4%)
Primary disease leading to transplantation Hypertension/nephrosclerosis Glomerulonephritis/glomerular disease Polycystic disease Diabetes mellitus	 50 (18.1%) 44 (15.9) 36 (13%) 39 (14.1%)	 56 (20.1) 55(18.7%) 29(10.4%) 29(10.4%)	 45 (16.2) 40 (14.4) 33 (11.9%) 45 (16.2%)

Primary Objective Result(s)

The primary objective of the study was to demonstrate that at least one of the everolimus treatment regimens was not inferior to the Myfortic treatment regimen with respect to the composite efficacy endpoint in the 12 month analysis. The non-inferiority analysis is shown in the table below.

Non-inferiority analysis for composite efficacy failure rates (ITT population - 12

month analysis)

Month Treatment	N	n (rate %)	Everolimus - Myfortic Difference in rates (%)	95% CI of difference	p-value (no diff)†	p-value (non-inf)‡
Month 12						
Everolimus 1.5 mg	277	75 (27.1)	1.8	-5.5, 9.1	0.628	0.014
Everolimus 3.0 mg	279	60 (21.5)	-3.8	-10.8, 3.3	0.293	<0.001
Myfortic 1.44 g	277	70 (25.3)				

Everolimus is non-inferior to Myfortic if the upper limit of the confidence interval for the difference in composite efficacy failure rates is <10%.

† P-value of Z-test for Everolimus - Myfortic = 0 (no difference test)

‡ P-value of Z-test for Everolimus - Myfortic ≥0.1 (non-inferiority test), one-sided test at the 0.025 significance level for each comparison of Everolimus versus Myfortic.

Note: In the definition of composite efficacy failure, loss to follow-up includes patients who did not experience treated BPAR, graft loss or death on or after day 1 and whose last day of contact was prior to day 316, the start day of the 12 month visit window.

As the upper limits of the 95% confidence intervals for the differences between either everolimus group and Myfortic were less then 10%, the predefined non-inferiority margin, both everolimus 1.5 mg and everolimus 3.0 mg were statistically non-inferior to Myfortic under the Hochberg's procedure. There was no statistically significant difference between both everolimus group and Myfortic group with regard to the incidence rates of the composite efficacy endpoint in the 12 month analysis.

Secondary Objective Result(s)

The main secondary efficacy endpoint was the 12 month analysis of rates of combined graft loss, death or loss to follow-up. Loss to follow-up patients for this endpoint were those who did not experience graft loss or death and whose last day of contact was prior to day 316, the start day of the 12 month visit Non-inferiority of the main secondary efficacy endpoint was assessed similarly to the primary variable, as shown below.

Non-inferiority analysis for rates of combined graft loss, death, or loss to follow-up (ITT population - 12 month analyses)

			Everolimus - Myfortic			
Month Treatment	**N**	**n (rate %)**	**Difference in rates (%)**	**95% CI of difference**	**p-value (no diff)†**	**p-value (non-inf)‡**
Month 12*						
Everolimus 1.5 mg	277	32 (11.6)	2.2	-2.9, 7.3	0.404	0.001
Everolimus 3.0 mg	279	27 (9.7)	0.3	-4.6, 5.2	0.906	<0.001
Myfortic 1.44g	277	26 (9.4)				

Everolimus is non-inferior to Myfortic if the upper limit of the confidence interval for the difference in combined graft loss, death or loss to follow-up rates is <10%.

† P-value of Z-test for Everolimus - Myfortic = 0 (no difference test)

‡ P-value of Z-test for Everolimus - Myfortic ≥0.1 (non-inferiority test), one-sided test at the 0.025 significance level for each comparison of Everolimus versus Myfortic.

* In the 12 month analysis of combined graft loss, death or loss to follow-up: loss to follow-up includes patients who did not experience graft loss or death on or after day 1 and whose last day of contact was prior to day 316, i.e. the start day of the 12 month visit window.

There was no statistical difference between either everolimus group or the Myfortic group with regard to rates of combined graft loss, death or loss to follow-up in the 12 month analysis. Both the 1.5 mg and 3.0 mg doses of everolimus were statistically non-inferior to Myfortic at the non-inferiority margin of 10%, as the upper limits of the 95% confidence intervals for the differences between everolimus and Myfortic were less than 10% ($p \leq 0.001$). These results were supported by the per-protocol analysis of rates of combined graft loss, death or loss to follow-up

The main analysis of renal function to test for non-inferiority of everolimus 1.5 mg and 3.0 mg versus Myfortic in terms of calculated GFR (MDRD) is shown below.

Non-inferiority analysis of renal function: calculated GFR (MDRD) at months 12 and 24 (ITT population - 12 and 24 month analyses)

			Everolimus - Myfortic			
Month Treatment	**N**	**Mean GFR (ml/min/1.73 m^2)**	**Difference in mean GFR**	**95% CI of diff**	**p-value (no diff)†**	**p-value (non-inf)‡**
Month 12*						
Everolimus 1.5 mg	277	54.66	2.42	(-1.6, 6.5)	0.241	<0.001
Everolimus 3.0 mg	279	51.41	-0.83	(-4.9, 3.3)	0.692	<0.001
Myfortic 1.44 g	277	52.24				
Month 24**						
Everolimus 1.5 mg	277	52.20	1.69	(-2.1, 5.5)	0.385	<0.001
Everolimus 3.0 mg	279	49.44	-1.07	(-4.8, 2.7)	0.574	<0.001
Myfortic 1.44 g	277	50.51				

* 12 month GFR missing value imputation, Method 1: graft-loss = assign GFR value of 0; death or lost to follow up for renal function = LOCF1 (last-observation-carried-forward approach 1: : End of Treatment (up to Month 12).
** 24 month GFR missing value imputation, Method-Best: graft-loss = assign GFR value of 0; death or lost to follow up at Month 24 for renal function = last-observation-carried-forward (End of Study (up to Month 24).
Everolimus is non-inferior to Myfortic if the lower limits of the confidence intervals for the difference in mean GFR (MDRD) are greater than -8 ml/min/1.73m^2.
†P-value of t-test for Everolimus - Myfortic = 0 (no difference test)
‡ P-value of t-test for Everolimus - Myfortic ≤ -8 (non-inferiority test), one-sided test at the 0.025 significance level for each comparison of Everolimus versus Myfortic.

Both 1.5 mg and 3.0 mg doses of everolimus were non-inferior to Myfortic in the 12 month analyses of GFR (MDRD) as the lower limits of the 95% confidence intervals for the differences between everolimus and Myfortic were greater than the non-inferiority margin defined as -8 ml/min/1.73m^2, (t-test, $p<0.001$). The treatment comparisons of GFR (MDRD) demonstrating non-inferiority of everolimus to Myfortic at month 12 were independent of imputation method. In the 24 month analyses of GFR (MDRD), everolimus and Myfortic groups were comparable and treatment comparisons were independent of imputation method.

Safety Results

Adverse events/infections (n (%) of patients) by primary system organ class and treatment (Safety population - 24 month analysis)

Primary system organ class	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 g N=273 n (%)
Number (%) of patients with AE/infection in any primary system organ class	272 (99.3)	276 (99.3)	270 (98.9)
Metabolism and nutrition disorders	226 (82.5)	238 (85.6)	210 (76.9)
Gastrointestinal disorders	206 (75.2)	219 (78.8)	215 (78.8)
General disorders and administration site conditions	188 (68.6)	191 (68.7)	173 (63.4)
Infections and infestations	186 (67.9)	193 (69.4)	207 (75.8)
Injury, poisoning and procedural complications	176 (64.2)	184 (66.2)	170 (62.3)
Investigations	148 (54.0)	129 (46.4)	149 (54.6)
Musculoskeletal and connective tissue disorders	130 (47.4)	112 (40.3)	117 (42.9)
Vascular disorders	128 (46.7)	146 (52.5)	138 (50.5)
Renal and urinary disorders	121 (44.2)	153 (55.0)	137 (50.2)
Nervous system disorders	105 (38.3)	104 (37.4)	115 (42.1)
Skin and subcutaneous tissue disorders	103 (37.6)	112 (40.3)	115 (42.1)
Blood and lymphatic system disorders	101 (36.9)	120 (43.2)	113 (41.4)
Respiratory, thoracic and mediastinal disorders	101 (36.9)	120 (43.2)	101 (37.0)
Psychiatric disorders	93 (33.9)	84 (30.2)	79 (28.9)
Reproductive system and breast disorders	59 (21.5)	59 (21.2)	33 (12.1)
Cardiac disorders	46 (16.8)	49 (17.6)	47 (17.2)
Eye disorders	40 (14.6)	28 (10.1)	43 (15.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22 (8.0)	15 (5.4)	24 (8.8)
Ear and labyrinth disorders	19 (6.9)	6 (2.2)	15 (5.5)
Immune system disorders	18 (6.6)	10 (3.6)	16 (5.9)
Endocrine disorders	13 (4.7)	14 (5.0)	22 (8.1)
Hepatobiliary disorders	10 (3.6)	10 (3.6)	13 (4.8)
Congenital, familial and genetic disorders	8 (2.9)	4 (1.4)	3 (1.1)
Surgical and medical procedures	1 (0.4)	2 (0.7)	0
Social circumstances	1 (0.4)	1 (0.4)	1 (0.4)
Pregnancy, puerperium and perinatal conditions	1 (0.4)	0	0

AE/Infections with onset date ≥8 days after discontinuation of study drug are not included in this analysis.
Primary system organ classes are sorted in descending order of frequency in the everolimus 1.5 mg group.

Most frequent adverse events/infections (>=10% of patients in any group) by preferred term (grouped by SOC) and treatment (Safety population - 12 month analysis)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 g N=273 n (%)
Number (%) of patients with any AEs/infections	271 (98.9)	276 (99.3)	270 (98.9)
Blood and lymphatic system disorders			
Anemia	72 (26.3)	85 (30.6)	67 (24.5)
Leucopenia	8 (2.9)	6 (2.2)	33 (12.1)
Gastrointestinal disorders			
Constipation	106 (38.7)	126 (45.3)	116 (42.5)
Nausea	84 (30.7)	80 (28.8)	88 (32.2)
Diarrhea	56 (20.4)	56 (20.1)	59 (21.6)
Vomiting	43 (15.7)	49 (17.6)	62 (22.7)
Abdominal pain	39 (14.2)	25 (9.0)	43 (15.8)
Dyspepsia	15 (5.5)	23 (8.3)	36 (13.2)
Abdominal pain upper	11 (4.0)	15 (5.4)	32 (11.7)
General disorders and administration site conditions			
Edema peripheral	125 (45.6)	121 (43.5)	110 (40.3)
Pyrexia	54 (19.7)	57 (20.5)	43 (15.8)
Fatigue	25 (9.1)	21 (7.6)	28 (10.3)
Infections and infestations			
Urinary tract infection	61 (22.3)	61 (21.9)	65 (23.8)
Upper respiratory tract infection	46 (16.8)	44 (15.8)	54 (19.8)
Injury, poisoning and procedural complications			
Incision site pain	45 (16.4)	55 (19.8)	45 (16.5)
Procedural pain	43 (15.7)	35 (12.6)	43 (15.8)
Complications of transplanted kidney	25 (9.1)	31 (11.2)	24 (8.8)
Investigations			
Blood creatinine increased	52 (19.0)	54 (19.4)	62 (22.7)
Weight increased	20 (7.3)	22 (7.9)	29 (10.6)
Metabolism and nutrition disorders			
Hyperlipidemia	56 (20.4)	61 (21.9)	42 (15.4)
Hyperkalemia	52 (19.0)	59 (21.2)	47 (17.2)
Hypercholesterolemia	49 (17.9)	50 (18.0)	35 (12.8)
Dyslipidemia	39 (14.2)	36 (12.9)	24 (8.8)
Hypomagnesemia	38 (13.9)	39 (14.0)	41 (15.0)
Hyperglycemia	37 (13.5)	44 (15.8)	38 (13.9)
Hypophosphatemia	37 (13.5)	44 (15.8)	35 (12.8)
Hypokalemia	34 (12.4)	44 (15.8)	32 (11.7)
Hypocalcemia	28 (10.2)	30 (10.8)	21 (7.7)
Musculoskeletal and connective tissue disorders			
Back pain	34 (12.4)	20 (7.2)	30 (11.0)
Pain in extremity	33 (12.0)	25 (9.0)	29 (10.6)

Arthralgia	26 (9.5)	34 (12.2)	27 (9.9)
Nervous system disorders			
Headache	52 (19.0)	44 (15.8)	41 (15.0)
Tremor	23 (8.4)	22 (7.9)	38 (13.9)
Psychiatric disorders			
Insomnia	49 (17.9)	50 (18.0)	44 (16.1)
Renal and urinary disorders			
Haematuria	34 (12.4)	26 (9.4)	34 (12.5)
Dysuria	29 (10.6)	26 (9.4)	29 (10.6)
Proteinuria	27 (9.9)	37 (13.3)	21 (7.7)
Respiratory, thoracic and mediastinal disorders			
Cough	23 (8.4)	27 (9.7)	32 (11.7)
Dyspnoea	20 (7.3)	27 (9.7)	28 (10.3)
Skin and subcutaneous tissue disorders			
Acne	27 (9.9)	42 (15.1)	24 (8.8)
Vascular disorders			
Hypertension	82 (29.9)	79 (28.4)	82 (30.0)
Lymphocele	22 (8.0)	32 (11.5)	16 (5.9)

Includes AE/Infections with onset date from day 1 to day 450.
AE/Infections with onset date ≥8 days after discontinuation of study drug are not included in this analysis.
Preferred terms grouped by primary system organ class are sorted in descending order of frequency in the everolimus 1.5 mg group.

Notable events (n (%) of patients, non-mutually exclusive presentation) by treatment (Safety population - 24 month analysis)

Notable Events	Everolimus 1.5mg N=274 n (%)	Everolimus 3.0mg N=278 n (%)	Myfortic 1.44g N=273 n (%)
Number (%) of patients with any notable events (1)	187 (68.2)	209 (75.2)	179 (65.6)
Death	9 (3.3)	10 (3.6)	8 (2.9)
Non-fatal Serious AE	174 (63.5)	192 (69.1)	166 (60.8)
AE leading to study drug discontinuation (DAE)	78 (28.5)	85 (30.6)	56 (20.5)
Adverse Dropout	70 (25.5)	76 (27.3)	45 (16.5)
Adverse events	68 (24.8)	70 (25.2)	40 (14.7)
Abnormal laboratory values	1 (0.4)	5 (1.8)	3 (1.1)
Abnormal test procedure results	1 (0.4)	1 (0.4)	2 (0.7)

(1) Notable events include Death, Non-fatal SAE (including infections), AEs (including infections) leading to study drug discontinuation (DAE), and Adverse Dropout (recorded on Treatment and Study Completion CRF with Reason for premature discontinuation of study medication as either Adverse Events or Abnormal laboratory values or Abnormal test results.

Other Relevant Findings

Most frequent serious infections (>=1.5% of patients in any group) by type of organism, specific micro-organism and treatment (Safety population - 24 month analysis)

Type of organism Micro-organism preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 g N=273 n (%)
Number (%) of patients with any serious infection	78 (28.5)	96 (34.5)	91 (33.3)
Bacterial - Total (all serious bacterial infections)	48 (17.5)	52 (18.7)	39 (14.3)
Enterococcus, nos	3 (1.1)	5 (1.8)	2 (0.7)
Escherichia coli	17 (6.2)	15 (5.4)	12 (4.4)
Gram-positive coccus	4 (1.5)	2 (0.7)	0
Klebsiella pneumoniae	2 (0.7)	1 (0.4)	6 (2.2)
Pseudomonas aeruginosa	5 (1.8)	3 (1.1)	2 (0.7)
Staphylococcus aureus	7 (2.6)	8 (2.9)	3 (1.1)
Staphylococcus epidermidis	1 (0.4)	8 (2.9)	3 (1.1)
Fungal - Total (all serious fungal infections)	1 (0.4)	6 (2.2)	3 (1.1)
Viral - Total (all serious viral infections)	8 (2.9)	8 (2.9)	21 (7.7)
Cytomegalovirus, nos	2 (0.7)	1 (0.4)	11 (4.0)
Other - Total (all serious other infections)	39 (14.2)	49 (17.6)	49 (17.9)
No living organism identified	15 (5.5)	27 (9.7)	21 (7.7)
Not coded	15 (5.5)	17 (6.1)	19 (7.0)
Unknown living organism	12 (4.4)	12 (4.3)	6 (2.2)

Number (%) of patients with wound events, including lymphoceles (>=1% per treatment group), by preferred term (Safety population – 12 month analysis)

Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 g N=273 n (%)
Any wound event	**95 (34.7)**	**107 (38.5)**	**71 (26.0)**
Lymphocele	19 (6.9)	30 (10.8)	14 (5.1)
Perinephric collection	18 (6.6)	10 (3.6)	5 (1.8)
Post procedural discharge	8 (2.9)	4 (1.4)	12 (4.4)
Wound secretion	7 (2.6)	5 (1.8)	4 (1.5)
Impaired healing	5 (1.8)	12 (4.3)	4 (1.5)
Incisional hernia	5 (1.8)	6 (2.2)	4 (1.5)
Seroma	5 (1.8)	5 (1.8)	0
Post procedural urine leak	5 (1.8)	3 (1.1)	2 (0.7)
Wound dehiscence	4 (1.5)	9 (3.2)	4 (1.5)
Wound infection	4 (1.5)	6 (2.2)	4 (1.5)
Incision site complication	4 (1.5)	1 (0.4)	2 (0.7)
Incision site hematoma	3 (1.1)	4 (1.4)	2 (0.7)

Hematoma	3 (1.1)	3 (1.1)	0
Perirenal hematoma	3 (1.1)	1 (0.4)	5 (1.8)
Incision site infection	2 (0.7)	4 (1.4)	4 (1.5)
Abdominal hernia	2 (0.7)	3 (1.1)	0
Incision site hemorrhage	1 (0.4)	4 (1.4)	2 (0.7)
Post procedural hematoma	1 (0.4)	3 (1.1)	0
Postoperative wound infection	1 (0.4)	2 (0.7)	6 (2.2)
Localised intraabdominal fluid collection	1 (0.4)	1 (0.4)	5 (1.8)
Intra-abdominal hematoma	1 (0.4)	0	3 (1.1)
Abdominal wound dehiscence	0	5 (1.8)	2 (0.7)
Renal lymphocele	0	3 (1.1)	2 (0.7)

Date of Clinical Trial Report

26-Jul-2010

Date Inclusion on Novartis Clinical Trial Results Database

13 Sept 2010

Date of Latest Update