Sponsor

Novartis

Generic Drug Name

Everolimus

Therapeutic Area of Trial

Liver transplantation

Approved Indication

Certican is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. In kidney and heart transplantation, Certican should be used in combination with ciclosporin for microemulsion and corticosteroids.

Certican is indicated for the prophylaxis of organ rejection in patients receiving a hepatic transplant. In liver transplantation, Certican should be used in combination with tacrolimus and corticosteroids.

Everolimus is approved in over 85 countries, including all of Europe apart from UK and Ireland under the brand name Certican® for use in renal, cardiac and liver transplantation. In USA, it is approved as Zortress® for use in renal and liver transplantation.

Study Number

CRAD001H2304

Title

A 24 month, multi-center, open-label, randomized, controlled study to evaluate the efficacy and safety of concentration-controlled everolimus to eliminate or to reduce tacrolimus compared to tacrolimus in de novo liver transplant recipients

Phase of Development

Phase III

Study Start/End Dates

28-Jan-2008 to12-Apr-2012

Study Design/Methodology

This study was a 24-month, multicenter, open-label, randomized, controlled study that consisted of a screening period, a baseline period (3 to 7 days post-transplantation) followed by a run-in period that ended on the day of randomization at 30 days (± 5 days) post-transplantation. Patients were consented and screened for eligibility prior to liver transplantation. Consented patients who had undergone successful liver transplantation were initiated on a tacrolimus-based regimen that included corticosteroids, with or without MMF according to local practice, and entered the base-line period (between 3 and 7 days post-transplantation). Patients who were administered MMF according to local practice had their MMF discontinued by the time of randomization. At 30 (± 5) days post-transplantation, patients that met the additional randomization inclusion/exclusion criteria were randomized into the study. At least 690 patients were planned to be randomized. Randomization stratification was based upon HCV status and the stratum of renal function (assessed by abbreviated MDRD equation). Randomization was to one of three treatment arms in a 1:1:1 ratio as follows: (1) tacrolimus (TAC) Elimination arm; (2) Everolimus (EVR) +Reduced TAC arm; or to (3) TAC Control arm. In April 2010, an independent Data Monitoring Committee (DMC) recommended stopping enrollment into the TAC Elimination arm (Group 1) of this study due to a higher rate of acute rejection and discontinuations in this group when approximately 690 patients had been randomized and a number of patients were in the screening/run in phase. The remaining patients were randomized into the two remaining treatment arms: Group 2: EVR+Reduced TAC arm; or Group 3: TAC Control. The patients in the TAC Elimination arm (who had not reached Day 180 post-randomization) were discontinued from the assigned study treatment and switched to local standard treatment, while patients who were beyond Day 180 post-randomization, were allowed to continue their study treatment or converted to local standard approved treatment. In all study arms, local results of tacrolimus levels were used to make ad-justments in tacrolimus dosing, and central everolimus measurements were recommended to guide dose adjustments for patients randomized to an everolimus study arm.

Centres

Participating countries and number of centers in each country (n) were; Australia (4), Argentina (5), Belgium (3), Brazil (4), Canada (4), Colombia (3), Czech Republic (1), France (7), Germany (7), Hungary (1), Ireland (1), Israel (2), Italy (5), Netherlands (1), Russia (2), Spain (9), Sweden (1), UK (2), USA (29).

Publication

De Simone P, Nevens F, De Carlis L, et al. Everolimus With Reduced Tacrolimus Improves Renal Function in *De Novo* Liver Transplant Recipients: A Randomized Controlled Trial. Am J Transplant. 2012;12: 3008-3020.

Saliba F, De Simone P, Nevens F, et al. : Renal function at two years in liver transplant patients receiving everolimus: Results of a randomized, multicenter study. Am J Transplant. accepted

Objectives

Primary objective

- Incidence Rate of Composite Efficacy Failure of treated biopsy proven acute rejection (tBPAR), graft loss (GL) or death (D) from randomization to Month 12

Secondary objectives

- Change in Renal Function from randomization to Months 12 and 24
- Incidence Rate of Composite Efficacy Failure of treated biopsy proven acute rejection, graft loss or death from randomization to Month 24
- Incidence Rate of Treated Biopsy Proven Acute Rejection (tBPAR) and BPAR at Months 12 and 24

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

Everolimus (labeled as RAD001) was provided as 1.0 mg tablets. Additionally, 0.5 and 0.75 mg tablets were supplied for dose adjustments.

Control drug, tacrolimus was provided as 0.5, 1.0 mg and 5.0 mg capsules. Tacrolimus was purchased locally if all dosage strengths were commercially available in the country.

Investigational or control drug was administered in combination with corticosteroids. MMF was provided as 500 mg film coated tablet and was supplied centrally by Novartis.

At Day 30 post transplantation, Patients were randomized to one of the following treatment groups in a ratio of 1:1:1:

- Group 1: Tacrolimus (TAC) Elimination arm (low dose tacrolimus until Month 4, then tacrolimus eliminated) + everolimus + corticosteroids.
- Group 2: Everolimus (EVR) + Reduced TAC arm (low dose tacrolimus) + everolimus + corticosteroids.
- Group 3: TAC Control arm (Control dose tacrolimus) + corticosteroids

Randomization of new patients into the TAC Elimination arm (Group 1) of this study was prematurely stopped (see before).

Regular monitoring of blood everolimus and tacrolimus were undertaken with dose adjustment seeking to achieve concentration within the predefined range.

Target trough (C0) ranges for everolimus were 3-8 ng/mL until Month 4 and 6-10 ng/mL afterwards (Group 1) or 3-8 ng/mL for the duration of the study (Group 2).

In the TAC Elimination arm, tacrolimus dose was tapered from 3-8 ng/mL to 3-5 ng/mL once everolimus trough level was in the range of 3-8 ng/mL and tacrolimus was eliminated when everolimus trough level of 6-10 ng/mL was achieved. In the EVR + Reduced TAC arm, target trough level for tacrolimus was 3-8 ng/mL and was tapered to achieve a trough concentration of 3-5 ng/mL when everolimus trough concentration was within the range. In TAC control arm, tacrolimus trough concentration was to be maintained in the range 8-12 ng/mL until Month 4, after which the target range was 6-10 ng/mL until study end.

Criteria for Evaluation

Primary variables

- Incidence Rate of Composite Efficacy Failure of treated biopsy proven acute rejection (tBPAR), graft loss (GL) or death (D) from randomization to Month 12

Secondary variables

- Change in Renal Function from randomization to Months 12 and 24
- Incidence Rate of Composite Efficacy Failure of treated biopsy proven acute rejection, graft loss or death from randomization to Month 24
- Incidence Rate of Treated Biopsy Proven Acute Rejection (tBPAR) and BPAR at Months 12 and 24

Safety and tolerability

- Adverse events/infections and SAEs

Statistical Methods

Due to the early discontinuation of TAC Elimination arm, only one between group comparison (EVR+Reduced TAC vs. TAC control) was performed. Data collected for the TAC Elimination group was summarized in a similar fashion to the other two groups to provide descriptive statistics as a separate group.

The primary efficacy endpoint was the composite efficacy failure of treated biopsy proven acute rejection (tBPAR), graft loss, or death (tBPAR/GL/D) at 12 months post-transplantation. This primary endpoint was analyzed based on a non-inferiority test at Month 12.

In the 24-month analysis, the incidence rates of composite efficacy failure as well as its components at Month 24 were compared between EVR + Reduced TAC and TAC control groups. The event rates were estimated using Kaplan-Meier product-limit formula based on the ITT population. Greenwood's formula was used to estimate variances of Kaplan-Meier event rates and to derive the two-sided 97.5% normal distribution approximation based (Z-test based) confidence interval (CI) for differences in Kaplan-Meier event rates between the two groups. In addition, time to the occurrence of a particular event was analyzed using Kaplan-Meier (KM) survival analysis.

The key secondary endpoint was renal function assessed by eGFR (using MDRD-4) at 12-months post-transplantation. This endpoint was analyzed at Month 12 based on an analysis-of-covariance (ANCOVA) model. At Month 24, a similar analysis with ANCOVA model was performed with the change in eGFR from randomization to 24 months as the response variable, treatment, pre-transplant HCV status and eGFR at randomization as covariates. This analysis was based on the ITT population.

Other safety parameters including AEs/infections, laboratory tests, vital signs and other safety data were also analyzed

Study Population: Inclusion/Exclusion Criteria and Demographics

Ages Eligible for Study: 18 Years to 70 Years
Genders Eligible for Study: Both

Inclusion Criteria:

- Ability and willingness to provide written informed consent and adhere to study regimen.
- Recipients who are 18-70 years of age of a primary liver transplant from a deceased donor.
- Recipients who have been initiated on an immunosuppressive regimen that contains corticosteroids and tacrolimus, 3-7 days post-transplantation.
- Confirmed recipient hepatitis C virus (HCV) status at Screening (either by antibody or by PCR (polymerase chain reaction).
- Allograft is functioning at an acceptable level by the time of randomization as defined by protocol specific laboratory values.
- Abbreviated Modification of Diet in Renal Disease estimated glomerular filtration rate (MDRD eGFR) $\geq$ 30 mL/min/1.73m^2. Results obtained within 5 days prior to randomization are acceptable, however, no sooner than Day 25 post-transplantation.
- Verification of at least 1 tacrolimus trough level of $\geq$ 8 ng/mL in the week prior to randomization. Investigators should make adjustments in tacrolimus dosing to continue to target trough levels above 8 ng/mL prior to randomization.

Exclusion Criteria

- Patients who are recipients of multiple solid organ or islet cell tissue transplants, or have previously received an organ or tissue transplant. Patients who have a combined liver-kidney transplant.
- Recipients of a liver from a living donor, or of a split liver.
- History of malignancy of any organ system within the past 5 years whether or not there is evidence of local recurrence or metastases, other than non-metastatic basal or squamous cell carcinoma of the skin, or HCC (hepatocellular carcinoma) (see next criteria).
- Hepatocellular carcinoma that does not fulfill Milan criteria (1 nodule ≤ 5 cm, 2-3 nodules all < 3 cm) at the time of transplantation as per explant histology of the recipient liver.
- Any use of antibody induction therapy.
- Patients with a known hypersensitivity to the drugs used on study or their class, or to any of the excipients.
- Patients who are recipients of ABO incompatible transplant grafts.
- Recipients of organs from donors who test positive for Hepatitis B surface antigen or HIV are excluded.
- Patients who have any surgical or medical condition, which in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism and excretion of study drug.
- Women of child-bearing potential (WOCBP) unless they meet the protocol-defined exceptions.
- Patients with any history of coagulopathy or medical condition requiring long-term anticoagulation which would preclude liver biopsy after transplantation. (Low dose aspirin treatment or interruption of chronic anticoagulant is allowed).
- The presence of thrombosis via Doppler ultrasound of the major hepatic arteries, major hepatic veins, portal vein and inferior vena cava.

Other protocol-defined inclusion/exclusion criteria may apply.

Number of Subjects

A total of 719 patients were randomized into the study, with slightly fewer patients in the TAC Elimination group than in the two other groups reflecting the DMC recommendation to stop further enrollment to this arm. The three treatment groups were balanced with respect to demographic and background characteristics.

Patient disposition (ITT population – 24 month analysis)

	EVR+Reduced TAC	TAC Elimination	TAC Control
Planned N	230	230	230
Randomised N	245	231	243
Intent-to-treat population (ITT) N (%)	245 (100)	231 (100)	243 (100)
Completed study, n (%)	202 (82.4)	174 (75.3)	204 (84.0)
Discontinued study medication, n (%)	104 (42.4)	166 (71.9)	79 (32.5

Adverse events, n (%)	70 (28.6)	64 (27.7)	44 (18.1)
Abnormal laboratory value(s), n (%)	4 (1.6)	1 (0.4)	2 (0.8)
Abnormal test procedure result(s), n (%)	0	1 (0.4)	0
Unsatisfactory therapeutic effect, n (%)	3 (1.2)	21 (9.1)	7 (2.9)
Subject withdrew consent, n (%)	4 (1.6)	8 (3.5)	5 (2.1)
Lost to follow-up, n (%)	1 (0.4)	1 (0.4)	0
Administrative problems, n (%)	6 (2.4)	56 (24.2)	5 (2.1)
Death, n (%)	5 (2.0)	3 (1.3)	7 (2.9)
Graft loss, n (%)	3 (1.2)	1 (0.4)	2 (0.8)
Protocol deviation, n (%)	7 (2.9)	9 (3.9)	7 (2.9)
Missing, n (%)	1 (0.4)	1 (0.4)	0
Discontinued study, n (%)	43 (17.6)	57 (24.7)	39 (16.0)
Subject withdrew consent, n (%)	13 (5.3)	17 (7.4)	11 (4.5)
Administrative problems, n (%)	11 (4.5)	17 (7.4)	13 (5.3)
Death, n (%)	12 (4.9)	15 (6.5)	10 (4.1)
Lost to follow-up, n (%)	2 (0.8)	4 (1.7)	2 (0.8)
Graft loss, n (%)	5 (2.0)	3 (1.3)	2 (0.8)
Missing, n (%)	0	1 (0.4)	1 (0.4)

Patient demographic summary by treatment group (ITT population – 24 month analysis)

	Novartis product		**Comparator**
	EVR+Reduced TAC	**TAC Elimination**	**TAC Control**
N (ITT)	245	231	243
Females : males	65 : 180	67 : 164	64 : 179
Mean age, years (SD)	53.6 ± 9.2	53.2 ± 10.8	54.5 ± 8.7
BMI (kg/m^2) (SD)	25.2 ± 4.2	25.3 ± 4.3	24.5 ± 4.2
Race			
White n (%)	211 (86.1)	196 (84.8)	195 (80.2)
Black n (%)	4 (1.6)	6 (2.6)	9 (3.7)
Asian n (%)	4 (1.6)	8 (3.5)	5 (2.1)
Native American	1 (0.4)	0	2 (0.8)
Other n (%)	20 (8.2)	17 (7.4)	27 (11.1)
Missing (%)	5 (2.0)	4 (1.7)	6 (2.5)
HCV status – n (%) positive	79 (32.2)	72 (31.2)	76 (3.1.3)
eGFR(MDRD4) (mL/min/1.73m^2), mean (SD)	81.3 ± 33.3	82.9 ± 37.2	78.9 ± 27.7

Primary Objective Result(s)

Comparison between treatment groups for Kaplan-Meier incidence rates of primary efficacy endpoint (ITT population – 12 month analysis)

Statistics	EVR+Reduced TAC N=245	TAC Elimination N=231	TAC Control N=243
Number of composite efficacy failure (tBPAR, graft loss or death) from randomization till Month 12	16	45	23
KM estimate of incidence rate of composite efficacy failure (tBPAR, graft loss or death) at Month 12	6.7%	24.2%	9.7%
Difference in KM estimates (vs. Control)	-3.0%	14.5%	
97.5% CI for difference	(-8.7%, 2.6%)		
P-value of Z-test for (Reduced TAC - Control = 0) (No Difference Test)	0.230		
P-value* of Z-test for (Reduced TAC - Control ≥ 0.12) (Non-inferiority Test)	<0.001		

1. tBPAR = treated biopsy proven acute rejection. Local laboratory biopsy results are used to define tBPAR.
2. *Z-test p-value for non-inferiority test (non-inferiority margin = 12%) is for one-sided test and was compared to 0.0125 significance level.
3. In Kaplan-Meier estimate, the censoring day for patients without event is the last contact day.

In the ITT population, the primary efficacy endpoint of tBPAR, graft loss or death at month 12 occurred in 45/231 patients (19.5%) in the TAC elimination arm, 16/245 (6.5%) EVR+Reduced TAC patients and 23/243 (9.5%) TAC controls. The Kaplan-Meyer incidence rate of the primary efficacy endpoint was statistically non-inferior for EVR+Reduced TAC compared to TAC control: 6.7% versus 9.7%, respectively, with a difference of -3.0% (97.5% CI -8.7%, 2.6%).

Secondary Objective Result(s)

Comparison between treatment groups for Kaplan-Meier incidence rate of primary efficacy endpoint (ITT population – 24 month analysis)

Statistics	EVR+Reduced TAC N=245	TAC Elimination N=231	TAC Control N=243
Number of composite efficacy failure (tBPAR, graft loss or death) from randomization to Month 24	24	55	29
KM estimate of incidence rate of composite efficacy failure (tBPAR, graft loss or death) at Month 24	10.3%	26.0%	12.5%
Difference in KM estimates (vs. Control)	-2.2%	13.5%	
97.5% CI for difference	(-8.8%, 4.4%)		
P-value of Z-test for (Reduced TAC - Control = 0) (No Difference Test)	0.452		
P-value of Z-test for (Reduced TAC - Control ≥ 0.12) (Non-inferiority Test)	<0.001		

tBPAR = treated biopsy proven acute rejection. Local laboratory biopsy results are used to define tBPAR.
One-sided Z-test p-value for non-inferiority test (non-inferiority margin = 12%) is presented.
In Kaplan-Meier estimate, the censoring day for patients without event is the last contact day.

The incidence of the primary efficacy failure endpoint was similar between the two groups EVR+Reduced TAC and TAC control during month 12 to 24. Comparability for the primary efficacy endpoint was maintained at month 24.

Comparison between treatment groups for Kaplan-Meier incidence rate of treated Biopsy Proven Acute Rejection (tBPAR) and BPAR (ITT population at Months 12 and 24)

Efficacy variable	EVR+Reduced TAC N=245 (n=KM %)	TAC Elimination N=231 (n=KM %)	TAC Control N=243 (n=KM %)	Difference Risk (KM%)	97.5% CI	p-value
tBPAR at Month 12	7 (2.9)	38 (16.5)	17 (7.0)	-4.1	(-8.0, -0.3)	0.0345
BPAR at Month 12	10 (4.1)	46 (19.9)	26 (10.7)	-6.6	(-11.2, -2.0)	0.0052
tBPAR at Month 24	11 (4.8)	42 (19.9)	18 (7.7)	-2.9	(-7.9, 2.2)	0.2031
BPAR at Month 24	14 (6.1)	52 (26.4)	30 (13.3)	-7.2	(-13.5, -0.9)	0.0100

P-value and 97.5% CI are obtained using Kaplan-Meier (KM) probability estimates of event rates and standard error derived based on Greenwood's formula. Risk difference for EVR+rTAC versus TAC Control.

The incidence of BPAR at month 12 and 24 was significantly lower in the EVR+Reduced TAC group versus the TAC control group (Kaplan-Meier incidence rate 4.1% versus 10.7%, p=0.0052 at month 12 and 6.1% versus13.3%, p=0.0100 at month 24).

Comparison between treatment groups for change in eGFR (MDRD4) from randomization to Month 24 (ITT population – 24 month analysis)

Treatment	N	LS Mean (SE) – vs	Difference vs control LS Mean (SE) – vs con-	97.5% CI	p-value(1)	p-value(2)

		Baseline	trol			
At Month 12						
EVR+Reduced TAC	244	-2.23 (1.54)	8.50 (2.12)	(3.74, 13.27)	<0.001	<0.001
TAC Elimination	231	-1.51 (1.58)	9.22 (2.15)	(4.39, 14.06)		
TAC Control	243	-10.73 (1.54)				
At Month 24						
EVR+Reduced TAC	245	-7.94 (1.53)	6.66 (2.12)	(1.90, 11.42)	<0.0001	<0.0018
TAC Elimination	231	-4.19 (1.58)	10.41 (2.15)	(5.58,15.25)		
TAC Control	243	-14.60 (1.54)				

Least squares means, 97.5% confidence intervals, and p-values are from an ANCOVA model containing treatment and HCV status as factors, and baseline eGFR as a covariate.
Missing Month 24 eGFR (MDRD4) values are imputed.
p-value(1): one-sided non-inferiority test with NI margin = -6 mL/min/1.73m^2.
p-value(2): two-sided superiority test.

Mean eGFR (MDRD4) was similar between the EVR+Reduced TAC and TAC Control group at the randomization. Estimated GFR in the EVR+Reduced TAC arm was statistically higher to the TAC Control arm at month 12 and month 24. At month 12, mean eGFR (SD) in the EVR+Reduced TAC and TAC Control groups was 80.6 (27.5) and 70.3 (23.1) mL/min/1.73m^2, respectively (p<0.001); at month 24, the corresponding values were 74.7 (26.1) and 67.8 (21.0) mL/min/1.73m^2 (p=0.007).

eGFR (MDRD4, mL/min/1.73m^2) according to treatment group (ITT population), values are shown as mean (SD)

Efficacy variable	EVR+Reduced TAC		TAC Elimination		TAC Control		p-value
	n	eGFR	n	eGFR	n	eGFR	
Week 4 (randomization)	233	81.1 (32.6)	218	82.6 (37.2)	227	78.0 (27.5)	0.553
Month 12	216	80.6 (27.5)	195	81.1 (32.9)	209	70.3 (23.1)	<0.001
Month 24	184	74.7 (26.1)	163	77.5 (26.2)	186	67.8 (21.0)	0.007

P-value comparing EVR+Reduced TAC versus TAC Control (Wilcoxon Rank sum test).

Safety Results

Incidence rates of Adverse Events/ infections by primary System Organ Class (Safety population – 24 month analysis)

	EVR+Reduced TAC	TAC Elimination	TAC Control
	N (%)	N (%)	N (%)
Patients studied			
Randomized patients	245	231	243
Patients with AE/infection	236 (96.3)	216 (94.3)	237 (97.9)
AEs/infections by primary system organ class			
Blood and lymphatic system disorders	79 (32.2)	67 (29.3)	58 (24.0)
Cardiac disorders	28 (11.4)	21 (9.2)	28 (11.6)
Congenital, familial and genetic disorders	2 (0.8)	5 (2.2)	1 (0.4)
Ear and labyrinth disorders	10 (4.1)	9 (3.9)	8 (3.3)
Endocrine disorders	12 (4.9)	6 (2.6)	8 (3.3)
Eye disorders	20 (8.2)	15 (6.6)	16 (6.6)
Gastrointestinal disorders	148 (60.4)	135 (59.0)	138 (57.0)
General disorders and administration site conditions	113 (46.1)	110 (48.0)	98 (40.5)
Hepatobiliary disorders	54 (22.0)	61 (26.6)	72 (29.8)
Immune system disorders	11 (4.5)	31 (13.5)	13 (5.4)
Infections and infestations	136 (55.5)	132 (57.6)	125 (51.7)
Injury, poisoning and procedural complications	86 (35.1)	68 (29.7)	77 (31.8)
Investigations	92 (37.6)	89 (38.9)	98 (40.5)
Metabolism and nutrition disorders	134 (54.7)	106 (46.3)	106 (43.8)
Musculoskeletal and connective tissue disorders	82 (33.5)	66 (28.8)	101 (41.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	24 (9.8)	17 (7.4)	27 (11.2)
Nervous system disorders	99 (40.4)	80 (34.9)	101 (41.7)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.4)
Psychiatric disorders	53 (21.6)	43 (18.8)	52 (21.5)
Renal and urinary disorders	67 (27.3)	54 (23.6)	73 (30.2)
Reproductive system and breast disorders	18 (7.3)	14 (6.1)	17 (7.0)
Respiratory, thoracic and mediastinal disorders	75 (30.6)	49 (21.4)	62 (25.6)

Skin and subcutaneous tissue disorders	68 (27.8)	66 (28.8)	78 (32.2)
Social circumstances	1 (0.4)	1 (0.4)	0
Surgical and medical procedures	0	1 (0.4)	0
Vascular disorders	72 (29.4)	50 (21.8)	68 (28.1)

Incidence rates of frequent (more than or equal to 10% in any treatment group) AEs/infections by primary SOC, preferred term and treatment (Safety population – 24 month analysis), n (%)

	EVR+Reduced TAC	TAC Elimination	TAC Control
Blood and lymphatic system disorders	79 (32.2)	67 (29.3)	58 (24.0)
Leukopenia	31 (12.7)	23 (10.0)	12 (5.0)
Anemia	24 (9.8)	29 (12.7)	24 (9.9)
Gastrointestinal disorders	148 (60.4)	135 (59.0)	138 (57.0)
Diarrhea	59 (24.1)	62 (27.1)	61 (25.2)
Abdominal pain	37 (15.1)	33 (14.4)	31 (12.8)
Nausea	36 (14.7)	26 (11.4)	33 (13.6)
Vomiting	21 (8.6)	23 (10.0)	21 (8.7)
General disorders and administration site conditions	113 (46.1)	110 (48.0)	98 (40.5)
Edema peripheral	49 (20.0)	43 (18.8)	31 (12.8)
Pyrexia	43 (17.6)	51 (22.3)	28 (11.6)
Fatigue	27 (11.0)	22 (9.6)	28 (11.6)
Immune system disorders	11 (4.5)	31 (13.5)	13 (5.4)
Liver transplant rejection	5 (2.0)	27 (11.8)	9 (3.7)
Infections and infestations	136 (55.5)	132 (57.6)	125 (51.7)
Hepatitis C	33 (13.5)	24 (10.5)	24 (9.9)
Nasopharyngitis	24 (9.8)	24 (10.5)	26 (10.7)
Investigations	92 (37.6)	89 (38.9)	98 (40.5)
Liver function test abnorma	19 (7.8)	27 (11.8)	25 (10.3)
Hepatic enzyme increased	15 (6.1)	23 (10.0)	18 (7.4)
Metabolism and nutrition disorders	134 (54.7)	106 (46.3)	106 (43.8)
Hypercholesterolemia	27 (11.0)	21 (9.2)	9 (3.7)
Hyperlipidemia	21 (8.6)	24 (10.5)	5 (2.1)
Musculoskeletal and connective tissue disorder	82 (33.5)	66 (28.8)	101 (41.7)
Back pain	20 (8.2)	14 (6.1)	29 (12.0)
Nervous system disorders	99 (40.4)	80 (34.9)	101 (41.7)
Headache	53 (21.6)	40 (17.5)	54 (22.3)
Tremor	25 (10.2)	17 (7.4)	37 (15.3)
Renal and urinary disorders	67 (27.3)	54 (23.6)	73 (30.2)

Renal failure	24 (9.8)	15 (6.6)	27 (11.2)
Vascular disorders	72 (29.4)	50 (21.8)	68 (28.1)
Hypertension	52 (21.2)	35 (15.3)	44 (18.2)

Serious Adverse Events and Deaths

	EVR+Reduced TAC	TAC Elimination	TAC Control
No. (%) of subjects studied	245 (100)	231 (100)	243 (100)
No. (%) of subjects with AE(s)	236 (96.3)	216 (94.3)	237 (97.9)
Number (%) of subjects with serious or other significant events	**n (%)**	**n (%)**	**n (%)**
Death	12 (4.9)	15 (6.6)	10 (4.1)
Graft loss	9 (3.9)	6 (2.8)	7 (3.2)
SAE(s)	138 (56.3)	152 (66.4)	131 (54.1)

Overall death at 24 months occurred for 12 patients (4.9%) in the EVR+Reduced TAC group, 15 patients (6.6%) in the TAC Elimination group and 10 patients (4.1%) in the TAC control group. Of note, 2 of the patients who died in the EVR+Red TAC group never took everolimus. Multiorgan failure was reported as the cause of death for seven patients, with no other term being recorded for more than one patient in a treatment group, with the exception of metastatic hepatic cancer (two patients in the TAC Elimination group).

Most deaths were not suspected to be study drug related by the investigator. An independent Adjudication Committee review of death cases considered 11/12 deaths in the EVR+Reduced TAC group, 13/15 deaths in the TAC Elimination group and 8/10 deaths in the TAC Control to be not related to study medication.

Graft losses were recorded for 9 (3.9%) EVR+Reduced TAC, 6 (2.8%) TAC Elimination and 7 (3.2%) TAC Control patients.

None of the cases of graft loss in the EVR+Reduced TAC group were considered to be related to study medication *vs.* 1 graft loss in the TAC Elimination group (probable) and 2 in the TAC Control group (possible).

A higher proportion of TAC Elimination patients had SAEs, which included serious infections (hepatitis C, pneumonia), gastrointestinal disorders (diarrhea, abdominal hernia) and pyrexia. Fewer differences in the proportions of patients with SAEs were seen between the EVR+Reduced TAC group and the TAC Control group.

Other Relevant Findings

Not applicable

Date of Clinical Trial Report 6-Sep-2012
Date Inclusion on Novartis Clinical Trial Results Database 10 April 2013
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