NOVARTIS

Sponsor

Novartis

GenericDrugName

Everolimus

TrialIndication(s).

Renal transplantation

ProtocolNumber

CRAD001A2429

ProtocolTitle

A 24-month, multi-center, open-label, randomized, controlled trial to investigate efficacy, safety and evolution of cardiovascular parameters in de novo renal transplant recipients after early calcineurin inhibitor to everolimus conversion.

ClinicalTrialPhase IIIB

PhaseofDrugDevelopment

IV

StudyStart/EndDates

09-Aug-2010 to 30-Oct-2014

ReasonforTermination(Ifapplicable)

Not applicable

StudyDesign/Methodology

This was a 24-month, multi-center, randomized, open-label trial with two parallel arms in adult de novo renal allograft recipients. The study consisted of a run-in period from transplantation to Randomization and a treatment period from Randomization until Month 24. At baseline visit, patients were transplanted and entered the run-in period from transplantation (Baseline) to Randomization (week 10-14 post-transplantation). At Week 10-14, eligible patients were randomized into one of the 2 treatment arms: standard CNIs and Myfortic versus everolimus and Myfortic and entered the treatment period of the study from Randomization to Month 24. Patients in both arms received steroids as per center practice and in any caseat least 5 mg/Day. At Randomization, patients were stratified according to their renal allograft function and previous cardiovascular events. The main analysis was performed at Month 12 and the follow-up analysis was performed at Month 24.

Centers

Participating countries and number of centers in each were: Germany (8), Spain (6), France (5), Belgium (1), Romania (1), Argentina (7), Mexico (4), Austria (2), Turkey (3), Australia (4), Norway (1), Netherlands (3), Thailand (2), Latvia (1), Estonia (1), Portugal (3), India (5), Russia (8), Greece (3), Italy (4).

Publication

None

Objectives:

Primary objective

To show that the everolimus group is superior to the standard CNI group with respect to renal function assessed by change from Randomization in estimate glomerular filtration rate using the Modification of Diet in Renal Disease [eGFR (MDRD4)] at 12 months.

Key Efficacy secondary objective (s)

To demonstrate non-inferior efficacy (defined by a composite efficacy endpoint of treated Biopsy Proven Acute Rejection (tBPAR)≥IB, graft loss or death) at Month 12.

To demonstrate improvement of Left Ventricular Hypertrophy (LVH) as assessed by LV mass index (LVMi) using echocardiogram at Month 12.

To evaluate the incidence, time to event and severity of Treated BPAR ≥ IB, incidence of BPAR that needs antibody treatment, incidence of antibody mediated (humoral) rejection, incidence of treated BPAR ≥ IB at 12 and 24 months post-transplantation.

To evaluate the incidence, time to event and severity of any suspected acute rejection, treated acute rejection, biopsy proven acute rejection, treated biopsy proven acute rejection and subclinical acute rejection at 12 and 24 months post-transplantation.

To evaluate the incidence of adverse events and serious adverse events at 12 and 24 months post-transplantation.

TestProduct(s),Dose(s),andMode(s)ofAdministration

Investigational drug: Everolimus (labeled as RAD001) as commercially available tablets (0.25 mg, 0.5 mg, 0.75 mg or 1.0 mg). Dose adjustments were based on blood levels, tolerability, or change in co-medications or clinical conditions.

Non-investigational/ concomitant medications:

- Neoral (cyclosporine A) as commercially available capsules (10, 25, 50, or 100 mg). Taken twice a Day at 12-hour intervals, with dose according to blood levels.
- Tacrolimus as commercially available capsules (0.5 mg, 1 mg, or 5 mg). Taken twice a Day at 12-hour intervals, with dose according to blood levels.

StatisticalMethods

Data was analyzed for CSR when all patients completed 24 months or discontinued study early, and were declared clean and accurate. Both 12-Month and 24-Month analysis were performed as planned.

The primary efficacy endpoint was the change from randomization in eGFR (MDRD4) at 12 months post-transplantation. Analysis of covariance (ANCOVA) was applied with the primary endpoint as the response variable; treatment, center (as a random effect),

donor type, age and cold ischemia time as factors; and eGFR at randomization as a covariate. The analysis was performed on full analysis set (FAS) with Type I error probability set at 0.05, two-sided.

There were two key secondary objectives: 1) to demonstrate non-inferior efficacy (defined by composite efficacy endpoint of treated BPAR ≥ IB, graft loss or death) at Month 12; 2) to demonstrate improvement of left ventricular hypertrophy (LVH) as assessed by LV mass index (LVMi) at Month 12. A hierarchical fixed hypothesis test procedure was used to maintain the overall Type I error level of 0.05 with above order. The analysis was performed on full analysis set.

The rate of composite efficacy endpoint was estimated with Kaplan-Meier formula and the variance was from Greenwood's formula. The everolimus group was compared against the standard CNI group for non-inferiority with an NI-margin of 10%. A two-sided 95% confidence interval was derived based on normal distribution approximation (Z-test based).

The central laboratory LVH data was used for the second key secondary analysis. When central data was not available, the local data was used for missing data imputation. Analysis of covariance (ANCOVA) was applied with LVMi change from randomization at Month 12 as the response variable; treatment plus variables which resulted in significant association with the change in LVMi by univariate ANCOVA analysis.

All efficacy events that occurred from randomization until month 12/24 post-transplantation (whether experienced on or off study treatment) were included in the analysis. All acute rejections were identified through local pathologists' evaluation of all biopsy readings. Between-treatment comparisons were made using the Pearson Chi-square test or Exact test for events with low event rates (<5%). Evaluation of each of the components of the composite efficacy endpoint, tBPAR≥1B, graft loss or death at 12/24 months, was performed similarly to the analysis of the composite efficacy endpoint as described above but without non-inferiority test.

Treatment-emergent adverse events were defined as**:**
adverse events or infections that started after the first dose of randomized study medication or events present prior to the first dose of randomized study medication but that increased in severity, up until last dose of study regimen (cyclosporine, everolimus, tacrolimus & Myfortic) + 7-day rule. Generally, infections data were analyzed together with Adverse Event (AE) data. In addition, infection data were analyzed separately.
AEs and infections collected were to be coded with the MedDRA dictionary (Version 17.1) that gave preferred term and primary system organ class information. AEs and infection preferred terms were to be analyzed as a whole under the heading of AEs for each treatment arm. The incidence of AEs was summarized by body system, severity and relationship to study drug by the following:

- Incidence rates of (frequent) AEs / infections by primary system organ class, preferred term, and treatment group (regardless of study drug relationship).
- Incidence rates of AEs / infections suspected related to study drug by system organ class, preferred term, and treatment group.
- Incidence rates of AEs / infections requiring study drug dose adjustment or interruption by system organ class, preferred term, and treatment group (regardless of study drug relationship).

The incidence of Serious AEs/Infections (all reported events, e.g. no 7-day rule) was summarized by primary system organ class and preferred term. Serious Infections were summarized separately also. In addition, onset and duration of Serious AEs/Infections were summarized by primary system organ class and treatment.

StudyPopulation:KeyInclusion/ExclusionCriteria

Inclusion Criteria at Baseline:

• Male or female renal allograft recipients at least 18 years old.

• Written informed consent.

• Patient receiving a primary or secondary kidney transplant from a cadaveric or living unrelated-/related donor.

• Cold ischemia time (CIT) < 24 hours.

• Negative pregnancy test for female patients. Inclusion Criteria at Randomization:

• Patients on CNI (TAC or CsA) + Myfortic + steroids.

• Serum creatinine < 2.8 mg/dL (250 µmol/L) and an actual eGFR (MDRD4) ≥ 25 mL/min/1.73m exp2 (without renal replacement therapy).

Exclusion Criteria at Baseline:

•Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

- Recipient of multiple organ transplants.
- Recipient of ABO incompatible allograft or a positive cross-match.
- Panel Reactive Antibodies (PRA) level ≥ 30 %.
- Positive test for human immunodeficiency virus (HIV).
- Patient receiving an allograft from a Hepatitis B surface Antigen (HBsAg) or a Hepatitis C Virus (HCV) positive donor.
- HBsAg and/or a HCV positive patient with evidence of elevated LFTs (ALT/AST levels ≥ 2.5 times ULN).
- Severe restrictive or obstructive pulmonary disorders.
- Patient with severe allergy requiring acute or chronic treatment or hypersensitivity to any of the study drugs or similar drugs.
- Severe hypercholesterolemia or hypertriglyceridemia.
- Low platelet count.
- Low white blood cell count.
- History of malignancy of any organ system Exclusion Criteria at Randomization:
- Graft loss.
- Patient on renal replacement therapy.
- Patient who experienced severe humoral and/or cellular rejection (BANFF ≥ IIb).
- Patient with ≥ 2 episodes of AR or an AR episode that needed antibody treatment.
- Patient with ongoing or currently treated AR (2 weeks prior to randomization).
- Proteinuria > 1 g/day.
- Patients with recurrence of Focal Segmental Glomerulosclerosis (FSGS).

- Low platelet count; Low white blood cell count; Low absolute neutrophil count; Low hemoglobin.
- Severe liver disease.
- Systemic infection requiring continued therapy that would interfere with the objectives of the study.
- Severe hypercholesterolemia or hypertriglyceridemia.
- Patients with ongoing wound healing problems, clinically significant infection requiring continued therapy.
- Presence of intractable immunosuppressant complications or side effects.
- Patients on anticoagulants that prevents renal allograft biopsy.
- Use of prohibited medication.
- Use of immunosuppressive agents not utilized in the protocol.
- Pregnant or nursing (lactating) women.
- Women of child-bearing potential not using a highly effective method of birth control

ParticipantFlowTable

Patient disposition – n (%) of patients by treatment group at Month 12 and Month 24 (Full analysis set - 24 month analysis)

	M 0-12 study				M 0-24 study			
		Standard CNI n (%)				Standard CNI n (%)		
	Everolimus N=353	Total N=356	Tac N=231	CsA N=125	Everolimus N=353	Total N=356	Tac N=231	CsA N=125
Total no. of patients	353 (100.0)	356 (100.0)	231 (100.0)	125 (100.0)	353 (100.0)	356 (100.0)	231 (100.0)	125 (100.0)
Completed study medication	273 (77.3)	321 (90.2)	215 (93.1)	106 (84.8)	229 (64.9)	283 (79.5)	190 (82.3)	93 (74.4)
Completed study phase	345 (97.7)	352 (98.9)	230 (99.6)	122 (97.6)	313 (88.7)	326 (91.6)	215 (93.1)	111 (88.8)
Discontinued study medication	80 (22.7)	35 (9.8)	16 (6.9)	19 (15.2)	124 (35.1)	73 (20.5)	41 (17.7)	32 (25.6)
Adverse Event(s)	55 (15.6)	24 (6.7)	11 (4.8)	13 (10.4)	87 (24.6)	35 (9.8)	18 (7.8)	17 (13.6)
Abnormal laboratory value(s)	5 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.7)	1 (0.3)	0 (0.0)	1 (0.8)
Abnormal test procedure result(s)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	1 (0.3)	0 (0.0)	1 (0.8)
Unsatisfactory therapeutic effect	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	2 (0.6)	3 (0.8)	1 (0.4)	2 (1.6)
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.6)	1 (0.4)	1 (0.8)
Subject withdrew consent	14 (4.0)	2 (0.6)	1 (0.4)	1 (0.8)	18 (5.1)	10 (2.8)	8 (3.5)	2 (1.6)
Lost to follow-up	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.3)	6 (1.7)	4 (1.7)	2 (1.6)
Administrative problems	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.8)	2 (0.6)	3 (0.8)	1 (0.4)	2 (1.6)
Death	2 (0.6)	2 (0.6)	0 (0.0)	2 (1.6)	2 (0.6)	3 (0.8)	1 (0.4)	2 (1.6)
Graft loss	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.9)	0 (0.0)
Protocol Deviation	0 (0.0)	3 (0.8)	1 (0.4)	2 (1.6)	0 (0.0)	7 (2.0)	5 (2.2)	2 (1.6)
Missing	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued study	8 (2.3)	4 (1.1)	1 (0.4)	3 (2.4)	40 (11.3)	30 (8.4)	16 (6.9)	14 (11.2)
Subject withdrew consent	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	18 (5.1)	9 (2.5)	6 (2.6)	3 (2.4)
Lost to follow-up	2 (0.6)	1 (0.3)	1 (0.4)	0 (0.0)	10 (2.8)	12 (3.4)	5 (2.2)	7 (5.6)
Death	2 (0.6)	3 (0.8)	0 (0.0)	3 (2.4)	8 (2.3)	9 (2.5)	5 (2.2)	4 (3.2)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

BaselineCharacteristics

Recipient demographic summary by treatment group (Full analysis set - 24 month analysis)

			Standard CNI		
		Everolimus N=353	Total N=356	Tac N=231	CsA N=125
Age (Years)	Mean ± SD	46.0± 14.4	46.7± 14.9	47.3± 14.5	45.4± 15.6
	Median (range)	47.0 (18.0- 76.0)	47.0 (18.0- 81.0)	48.0 (18.0- 74.0)	44.0 (19.0- 81.0)
Gender - n (%)	Male	242 (68.6)	252 (70.8)	160 (69.3)	92 (73.6)
	Female	111 (31.4)	104 (29.2)	71 (30.7)	33 (26.4)
Race - n (%)	Caucasian	246 (69.7)	270 (75.8)	173 (74.9)	97 (77.6)
	Black	4 (1.1)	5 (1.4)	5 (2.2)	0 (0.0)
	Asian	66 (18.7)	61 (17.1)	41 (17.7)	20 (16.0)
	Native American	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
	Pacific Islander	0 (0.0)	2 (0.6)	1 (0.4)	1 (0.8)
	Other	36 (10.2)	18 (5.1)	11 (4.8)	7 (5.6)

SummaryofEfficacy

PrimaryOutcomeResult(s)

Comparison between treatment arms for change from randomization to Month 12 in eGFR (MDRD4) (Full analysis set - 24 month analysis)

Treatment	N	LS Mean (SE)	Difference (Everolimus - Standard CNI) LS Mean (SE)	95% CI	p-value
Everolimus	321	1.61 (1.48)	1.90 (1.10)	(-0.26, 4.07)	0.0847
Standard CNI	329	-0.29 (1.45)			
Everolimus	321	1.93 (1.65)	1.68 (1.30)	(-0.87, 4.24)	0.1963
Standard CNI:Tac	213	0.25 (1.74)			
Everolimus	321	1.98 (1.71)	2.08 (1.59)	(-1.05, 5.22)	0.1917
Standard CNI:CsA	116	-0.10 (2.03)			

1. Least squares (LS) means, 95% confidence intervals, and p-values are from an ANCOVA model containing treatment, center (as a random effect), donor type, age (<65 vs. >=65) and cold ischemia time (<20 vs. >=20 hours) as factors, and eGFR at randomization as a covariate.
2. Imputation for missing Month 12 eGFR (MDRD4) values: Patients who lost their graft = 0; otherwise, using the last non-missing post-randomization observation carried forward (LOCF).

SecondaryOutcomeResult(s)

Comparison between treatment arms for Kaplan-Meier incidence rates of composite efficacy endpoint at Month 12 and at Month 24 (Full analysis set - 24 month analysis)

	Efficacy endpoint at Month 12				Efficacy endpoint at Month 24			
Statistic	Everolimus N=353	Standard CNI N=356			Everolimus N=353	Standard CNI N=356		
		Total N=356	Tac N=231	CsA N=125		Total N=356	Tac N=231	CsA N=125
Number of composite endpoint *	21	12	4	8	27	16	8	8
KM estimate of incidence rate (%)	6.2%	3.8%	2.4%	6.4%	8.1%	4.5%	3.5%	6.4%
Difference in KM estimates (%) (Everolimus - Standard CNI)		2.4%	3.9%	-0.2%		3.6%	4.6%	1.7%
95% CI for difference (%)		(-1.0%, 5.8%)	(0.2%,7.5%)	(-5.2%, 4.8%)		(-0.1%, 7.3%)	(0.8%,8.4%)	(-3.5%, 6.9%)
p-value of z-test for no difference		0.172	0.036	0.939		0.057	0.018	0.520
p-value of z-test for non-inferiority		<0.001						

Statistic	Efficacy endpoint at Month 12		Efficacy endpoint at Month 24	
	Everolimus N=353	Standard CNI N=356	Everolimus N=353	Standard CNI N=356

*Composite endpoint = tBPAR>=IB, graft loss or death.
1. tBPAR = treated biopsy proven acute rejection. Local biopsy results are used to define tBPAR.
2. P-values and 95% CI are obtained using Kaplan-Meier (KM) probability estimates of composite efficacy failure rates and standard error derived based on Greenwood's formula.
3. In Kaplan-Meier estimate, the censoring day for patients without event is the last contact day.

Comparison between treatment arms for change from randomization to Month 12 in left ventricular mass index (LVMi) (FAS - 12 month analysis)

			Difference (Everolimus - Standard CNI)		
Treatment	**N**	**LS Mean**	**LS Mean (SE)**	**95% CI**	**p-value**
Everolimus	247	0.05			
Standard CNI	284	-1.14	1.19 (0.86)	(-0.50, 2.89)	0.1677
Tac	187	-1.76	1.81 (0.97)	(-0.09, 3.71)	0.0612
CsA	97	0.06	0.00 (1.19)	(-2.34, 2.33)	0.9968

1.Least squares (LS) means, 95% confidence intervals, and p-values are from an ANCOVA model containing treatment center (as a random effect), and covariates from Table 14.2-1.3a0 with p-value < 0.15.
2. Only patients with both randomization and Month 12 LVMi values are included in the analysis.
3. P-value: two-sided test for no difference at 0.05 level.

Comparison between treatment arms for incidence rates of efficacy endpoints (Full analysis set - 24 month analysis)

	Everolimus vs. Standard CNI

Efficacy endpoints	Everolimus N=353 n (%)	Standard CNI N=356 n (%)	Total N=709	Risk diff(%)	95% CI	p-value
Composite efficacy failure: tBPAR>=IB, graft loss, death*	27 (7.6)	16 (4.5)	43 (6.1)	3.2%	(-4.3,10.4)	0.0850
Composite of tBPAR>=IB, graft loss, death or loss to follow up	35 (9.9)	29 (8.1)	64 (9.0)	1.8%	(-2.4, 6.0)	0.4112
Composite of graft loss or Death*	10 (2.8)	10 (2.8)	20 (2.8)	0.0%	(-7.4, 7.4)	1.0000
tBPAR>=IB*	18 (5.1)	8 (2.2)	26 (3.7)	2.9%	(-4.5, 10.2)	0.0472
Graft loss*	4 (1.1)	4 (1.1)	8 (1.1)	0.0%	(-7.4, 7.4)	1.0000
Death*	8 (2.3)	9 (2.5)	17 (2.4)	-0.3%	(-7.6, 7.1)	1.0000
Suspected AR	61 (17.3)	46 (12.9)	107 (15.1)	4.4%	(-0.9, 9.6)	0.1050
Subclinical AR	0	0	0			
AR	52 (14.7)	29 (8.1)	81 (11.4)	6.6%	(1.9,11.2)	0.0059
tAR BPAR	40 (11.3)	23 (6.5)	63 (8.9)	4.9%	(0.7, 9.0)	0.0227
tBPAR	37 (10.5)	21 (5.9)	58 (8.2)	4.6%	(0.6, 8.6)	0.0260
tBPAR=IA*	32 (9.1)	20 (5.6)	52 (7.3)	3.4%	(-0.4, 7.3)	0.0783
tBPAR=IB*	16 (4.5)	11 (3.1)	27 (3.8)	1.4%	(-6.0, 8.8)	0.3338
tBPAR=IIA*	14 (4.0)	8 (2.2)	22 (3.1)	1.7%	(-5.7, 9.0)	0.2013
tBPAR=IIB*	3 (0.8)	1 (0.3)	4 (0.6)	0.6%	(-6.8, 7.9)	0.3718
tBPAR=III	2 (0.6)	0	2 (0.3)	0.6%	(-6.8, 7.9)	0.2475
	0	0	0			
Antibody tBPAR*		2 (0.6)	4 (0.6)	0.0%	(-7.4, 7.4)	1.0000
AMR*	16 (4.5)	7 (2.0)	23 (3.2)	2.6%	(-4.8,9.9)	0.0588

1. AR = Acute rejection; tAR = treated AR; BPAR = biopsy proven acute rejection; tBPAR = treated BPAR; AMR = Antibody mediated rejection. Local biopsy results are used.

2. * stands for exact confidence interval and two-sided Fisher exact test p-value presented for that variable.
For others, asymptotic confidence interval and Pearson Chi-square test p-value are presented.
3. All p-values are for two-sided test and should be compared to 0.05 significance level.

SummaryofSafety

SafetyResults

Number (%) of patients experiencing adverse events/infections by SOC and treatment group (Safety set - 24 month analysis)

		Standard CNI n(%)		
System organ class	**Everolimus N=346 n(%)**	**Total (N=359)**	**Tac (N=238)**	**CsA (N=121)**
Any system organ class	316 (91.3)	319 (88.9)	216 (90.8)	103 (85.1)
Blood and lymphatic system disorders	103 (29.8)	89 (24.8)	69 (29.0)	20 (16.5)
Cardiac disorders	31 (9.0)	36 (10.0)	22 (9.2)	14 (11.6)
Congenital, familial and genetic disorders	1 (0.3)	2 (0.6)	2 (0.8)	0 (0.0)
Ear and labyrinth disorders	9 (2.6)	12 (3.3)	4 (1.7)	8 (6.6)
Endocrine disorders	9 (2.6)	16 (4.5)	12 (5.0)	4 (3.3)
Eye disorders	22 (6.4)	20 (5.6)	16 (6.7)	4 (3.3)
Gastrointestinal disorders	144 (41.6)	127 (35.4)	97 (40.8)	30 (24.8)
General disorders and administration site conditions	137 (39.6)	90 (25.1)	58 (24.4)	32 (26.4)
Hepatobiliary disorders	7 (2.0)	13 (3.6)	12 (5.0)	1 (0.8)
Immune system disorders	45 (13.0)	33 (9.2)	14 (5.9)	19 (15.7)
Infections and infestations	206 (59.5)	198 (55.2)	142 (59.7)	56 (46.3)
Injury, poisoning and procedural complications	63 (18.2)	85 (23.7)	60 (25.2)	25 (20.7)
Investigations	74 (21.4)	85 (23.7)	51 (21.4)	34 (28.1)
Metabolism and nutrition disorders	147 (42.5)	166 (46.2)	120 (50.4)	46 (38.0)
Musculoskeletal and connective tissue disorders	62 (17.9)	77 (21.4)	61 (25.6)	16 (13.2)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	22 (6.4)	32 (8.9)	23 (9.7)	9 (7.4)
Nervous system disorders	52 (15.0)	59 (16.4)	43 (18.1)	16 (13.2)
Psychiatric disorders	24 (6.9)	32 (8.9)	24 (10.1)	8 (6.6)
Renal and urinary disorders	115 (33.2)	86 (24.0)	65 (27.3)	21 (17.4)
Reproductive system and breast disorders	26 (7.5)	20 (5.6)	16 (6.7)	4 (3.3)
Respiratory, thoracic and mediastinal disorders	65 (18.8)	51 (14.2)	40 (16.8)	11 (9.1)

System organ class	Everolimus N=346 n(%)	Standard CNI n(%) Total (N=359)	Tac (N=238)	CsA (N=121)
Skin and subcutaneous tissue disorders	75 (21.7)	55 (15.3)	40 (16.8)	15 (12.4)
Surgical and medical procedures	0 (0.0)	2 (0.6)	1 (0.4)	1 (0.8)
Vascular disorders	67 (19.4)	73 (20.3)	51 (21.4)	22 (18.2)

Note: AE/infections with an onset date ≥ 8 days after the discontinuation of randomized study medication are not included in this analysis.

Incidence of frequent (more than equal to 10% in any treatment Group) AEs / infections by primary SOC and PT (Safety set - 24 month analysis)

Primary System Organ Class Preferred Term	Everolimus N=346 n(%)	Standard CNI n(%) Total (N=359)	Tac (N=238)	CsA (N=121)
Any frequent AE/Infection	316 (91.3)	319 (88.9)	216 (90.8)	103 (85.1)
Blood and lymphatic system disorders	103 (29.8)	89 (24.8)	69 (29.0)	20 (16.5)
Anaemia	41 (11.8)	26 (7.2)	21 (8.8)	5 (4.1)
Leukopenia	48 (13.9)	46 (12.8)	35 (14.7)	11 (9.1)
Gastrointestinal disorders	144 (41.6)	127 (35.4)	97 (40.8)	30 (24.8)
Diarrhoea	79 (22.8)	68 (18.9)	55 (23.1)	13 (10.7)
General disorders and administration site conditions	137 (39.6)	90 (25.1)	58 (24.4)	32 (26.4)
Oedema peripheral	60 (17.3)	34 (9.5)	21 (8.8)	13 (10.7)
Pyrexia	62 (17.9)	32 (8.9)	20 (8.4)	12 (9.9)
Infections and infestations	206 (59.5)	198 (55.2)	142 (59.7)	56 (46.3)
Urinary tract infection	75 (21.7)	65 (18.1)	47 (19.7)	18 (14.9)
Investigations	74 (21.4)	85 (23.7)	51 (21.4)	34 (28.1)
Blood creatinine increased	30 (8.7)	44 (12.3)	24 (10.1)	20 (16.5)
Metabolism and nutrition disorders	147 (42.5)	166 (46.2)	120 (50.4)	46 (38.0)
Hypercholesterolaemia	40 (11.6)	22 (6.1)	15 (6.3)	7 (5.8)

Primary System Organ Class Preferred Term	Everolimus N=346 n(%)	Standard CNI n(%) Total (N=359)	Tac (N=238)	CsA (N=121)
Renal and urinary disorders	115 (33.2)	86 (24.0)	65 (27.3)	21 (17.4)
Proteinuria	52 (15.0)	13 (3.6)	11 (4.6)	2 (1.7)
Vascular disorders	67 (19.4)	73 (20.3)	51 (21.4)	22 (18.2)
Hypertension	35 (10.1)	36 (10.0)	24 (10.1)	12 (9.9)

Note: AE/infections with an onset date ≥ 8 days after the discontinuation of randomized study medication are not included in this analysis.

Number (%) of patients experiencing notable events by treatment (presented in non-mutually exclusive way) (Safety set - 24 month analysis)

Notable events	Everolimus (N=346) n (%)	Standard CNI n (%) Total (N=359)	Tac (N=238)	CsA (N=121)

Any notable events	207 (59.8)	185 (51.5)	123 (51.7)	62 (51.2)
Death	8 (2.3)	9 (2.5)	5 (2.1)	4 (3.3)
Non-fatal SAE / infection	185 (53.5)	173 (48.2)	116 (48.7)	57 (47.1)
DAE	81 (23.4)	30 (8.4)	15 (6.3)	15 (12.4)
Adverse dropout	92 (26.6)	38 (10.6)	19 (8.0)	19 (15.7)
Adverse events	85 (24.6)	35 (9.7)	18 (7.6)	17 (14.0)
Abnormal lab values	5 (1.4)	2 (0.6)	1 (0.4)	1 (0.8)
Abnormal test procedure results	2 (0.6)	1 (0.3)	0 (0.0)	1 (0.8)

Note: 1. Notable events include death, Non-fatal SAE (including infections), DAE (AE leading to discontinuation of study medication), and Adverse Dropout (recorded on Treatment Completion CRF = Reason for premature discontinuation of study medication: Adverse Events; Abnormal laboratory values; Abnormal test procedure results).

OtherRelevantFindings

None

Conclusion:

In conclusion, this 24-month data confirms that early conversion to an everolimus based- immunosuppressive regimen in combination with Enteric coated mycophenolic sodium (EC-MPS) improved and preserved renal function with comparable overall efficacy and safety versus standard CNI-based therapy and improvement of LVH after kidney transplantation.

DateofClinicalTrialReport

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