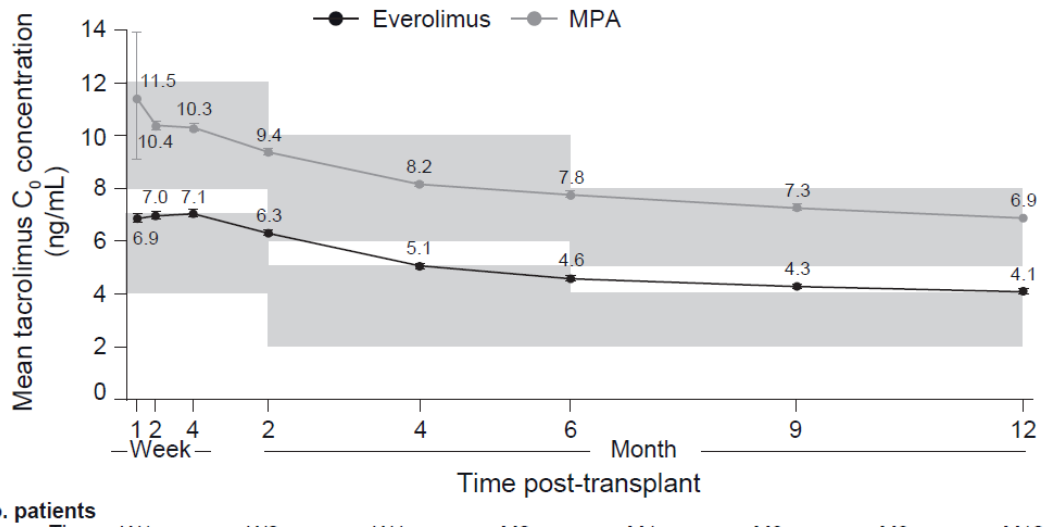
SUPPLEMENTARY TABLE OF CONTENTS

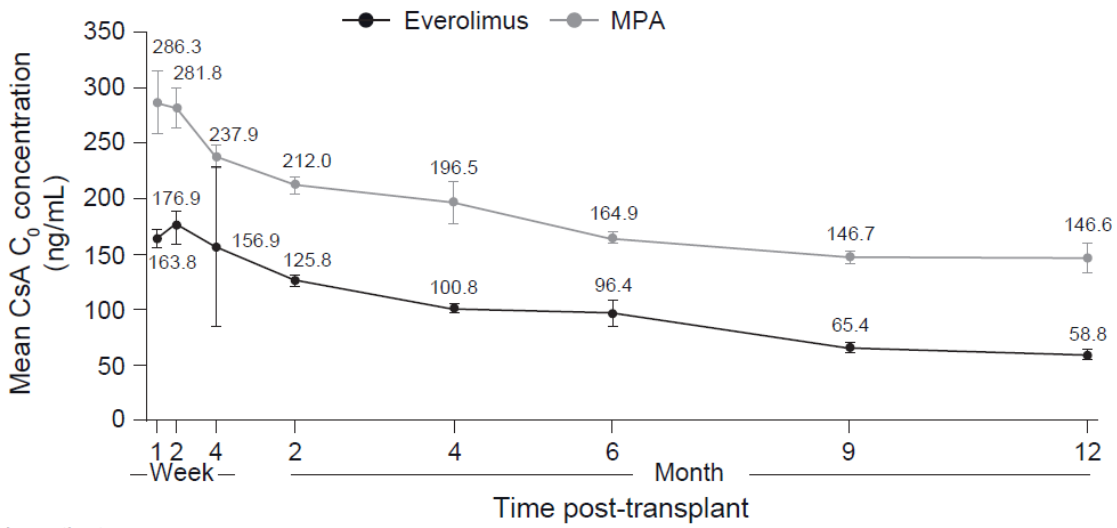
Figure S1. Trough (C_0) concentration of (a) tacrolimus (b) cyclosporine [CsA] (on-treatment analysis). Shaded areas indicate target ranges for the everolimus group (lower ranges) and the MPA group. Values are shown as mean (SE)

(a)



No. patients								
Time	W1	W2	W4	M2	M4	M6	M9	M12
Everolimus	843	866	826	784	756	727	684	658
MPA	850	876	864	847	806	775	736	712
% patients								
Everolimus								
Above target	39.5	40.7	37.4	24.9	42.6	30.5	43.8	40.0
Below target	16.0	10.3	8.0	15.4	0.8	1.6	2.2	2.1
MPA								
Above target	18.1	23.2	19.9	10.8	15.6	9.8	27.4	22.9
Below target	42.8	27.1	25.3	38.1	19.9	22.8	12.9	15.0

(b)



No. patients								
Time	W1	W2	W4	M2	M4	M6	M9	M12
Everolimus	94	95	92	90	84	81	76	76
MPA	83	87	87	85	84	80	75	74
% patients								
Everolimus								
Above target	50.0	52.6	40.0	17.4	31.8	20.2	61.3	47.6
Below target	20.8	12.6	20.0	39.1	5.7	17.9	6.3	2.4
MPA								
Above target	25.9	31.9	12.2	6.7	16.7	12.6	10.5	9.1
Below target	30.6	28.6	30.0	48.3	41.1	41.4	8.1	19.3

Figure S2. Estimated GFR (eGFR, MDRD) according to treatment groups (ITT population). Data are shown as mean values and 95% CI ranges, using multiple imputation for missing values. BL, baseline; D, day.

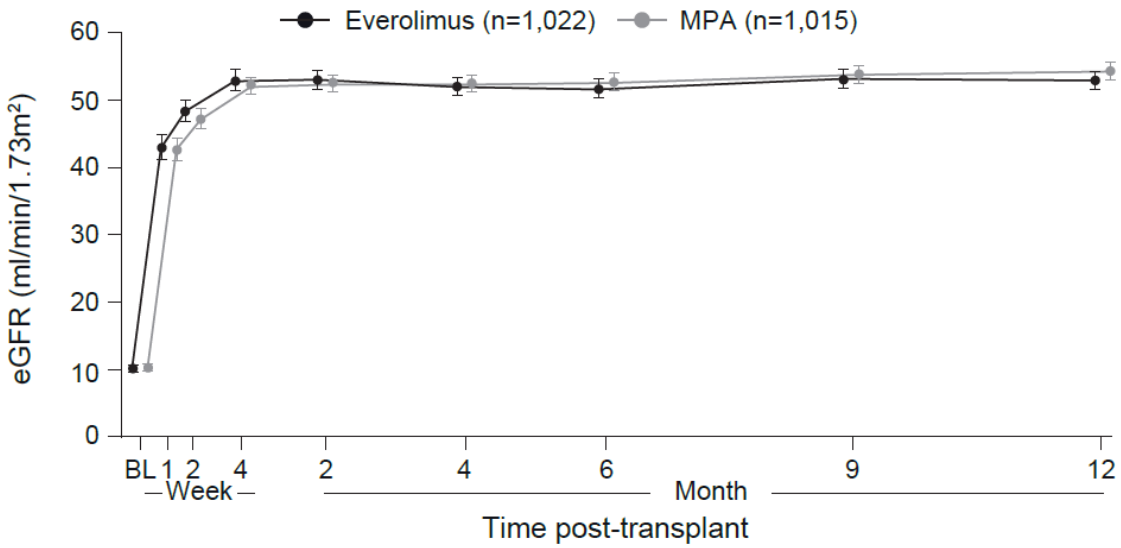
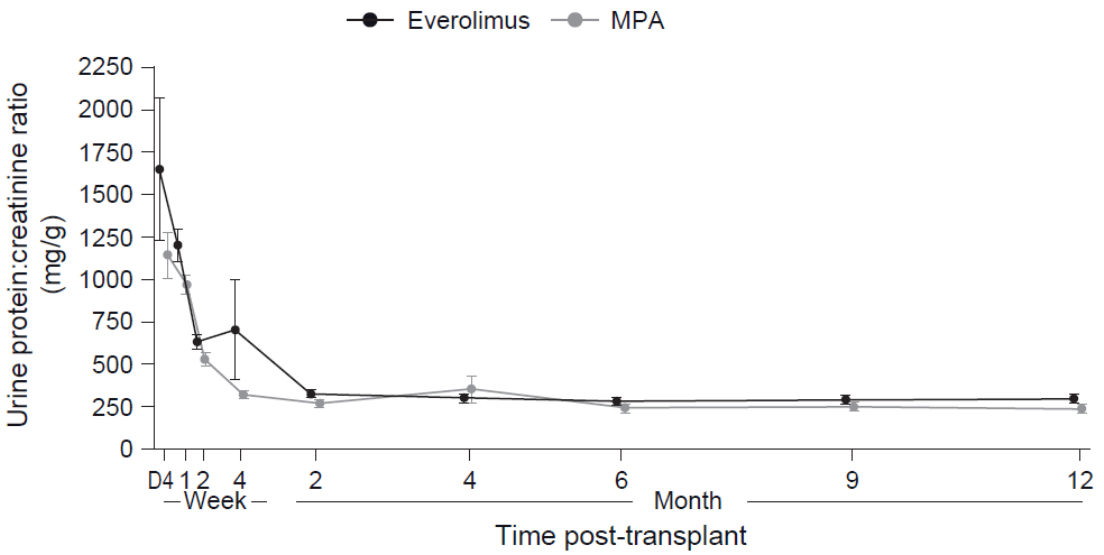


Figure S3. Urinary protein:creatinine ratio (on-treatment analysis). Values are shown as mean (SE)



No. patients									
Time	D4	W1	W2	W4	M2	M4	M6	M9	M12
Everolimus	79	899	936	895	865	832	799	754	728
MPA	54	903	929	926	924	864	836	799	793

Table S1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
– Male or female subject ≥18 years – Randomized <24 hours after transplant surgery – Cold ischemia time <30 hours – Recipient of a primary (or secondary, if first graft was not lost due to immunological reasons) kidney transplant from a deceased heart beating donor, living unrelated donor, living related non-human leukocyte antigen (HLA) identical donor, or an expanded criteria donor[a]	– Use of other investigational drugs at the time of enrollment, or within 30 days or five half-lives of enrollment, whichever is longer (except for dialysis-related drugs which are not expected to interact with the study regimens) – Multi-organ transplant recipient – ABO incompatible allograft or complement-dependent lymphocytotoxic (CDC) crossmatch positive transplant – High immunological risk for rejection[b] – Recipient or donor positive for HIV, hepatitis B surface antigen (HBsAg) or hepatitis C (HCV) – Body mass index (BMI) >35kg/m^2 – Severe systemic infection (current or with 2 weeks prior to randomization) – Requirement for systemic anticoagulation that cannot be temporarily interrupted and which would preclude renal biopsy – History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases – Severe restrictive or obstructive pulmonary disorders – Severe uncontrolled hypercholesterolemia or hypertriglyceridemia – White blood cell count ≤2,000 /mm^3 or platelet count ≤50,000 /mm^3 – Pregnant or nursing (lactating) women – Women of child-bearing potential, unless they are using effective methods of contraception during dosing of study treatment

[a] Defined as brain-dead donor aged >60 years or donor aged >50 years with two of the following: history of hypertension, terminal serum creatinine ≥1.5 mg/dL (132 µmol/L) or death resulting from cerebrovascular accident

[b] As determined by local practice for assessment of anti-donor reactivity e.g. high panel reactive antibodies (PRA), presence of pre-existing donor specific antigen (DSA)

Table S2. Study endpoints

Primary endpoint	– Binary composite endpoint of treated BPAR or eGFR <50mL/min/1.73m^2 (MDRD4) at month 12 post-transplant
Key secondary endpoint	– Composite endpoint of treated BPAR, graft loss or death at month 12 post-transplant
Other secondary endpoints	– Binary composite endpoint of treated BPAR or eGFR <50 mL/min/1.73m^2 (MDRD4) at month 24 – Binary composite endpoint of treated BPAR (excluding Banff grade 1A acute rejection) or eGFR <50 mL/min/1.73m^2 (MDRD4) at month 24 – Binary composite endpoint of treated BPAR or eGFR <50 mL/min/1.73m^2 (MDRD4) at month 12 in predefined subgroups – Composite endpoint of treated BPAR, graft loss or death at month 24 post-transplant – Composite endpoint of treated BPAR, graft loss, death or loss to follow-up at months 12 and 24 – Composite endpoint of treated BPAR, graft loss, death or eGFR <50 mL/min/1.73m^2 (MDRD4) at months 12 and 24 – Composite endpoint of graft loss or death at months 12 and 24 – Individual endpoints of graft loss, death, treated BPAR, BPAR, treated acute rejection, acute rejection or antibody-mediated rejection at months 12 and 24 – Treated BPAR by severity and time to event – Treated BPAR excluding grade 1A rejections – eGFR <50 mL/min/1.73m^2 at months 12 and 24 – Renal function (eGFR) and change in renal allograft function from month 1 to months 12 and 24 – Evolution of renal function (eGFR) over time by slope analysis – Renal function assessed by cystatin C-based and other alternate formulae (e.g. CKD-EPI[2], Hoek's formula[3]) based on on-treatment analysis without imputation – Adverse events, serious adverse events, and adverse events leading to study regimen discontinuation – Cytomegalovirus infection, BK virus infection, new onset diabetes mellitus, chronic kidney disease with associated proteinuria, and CNI-associated adverse events – Urinary protein and albumin excretion estimated by urinary protein/creatinine and urinary albumin/creatinine ratios – Major cardiovascular events – Malignancies
Exploratory endpoints	– The incidence of DSA by treatment group, and in relation to acute rejection, in a subset of patients at participating centers – Development of chronic allograft nephropathy/interstitial fibrosis-tubular atrophy on protocol renal biopsy in a subset of patients at participating centers

1. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461-70.
2. Hoek FJ, Kemperman FA, Krediet RT. A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. Nephrol Dial Transplant 2003;18:2024-31.
3. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.

BPAR, biopsy-proven acute rejection; CNI, calcineurin inhibitor; DSA, donor specific antibody; eGFR, estimated glomerular filtration rate; MDRD4, four-variable Modification of Diet in Renal Disease

Table S3. Statistical methods

Multiple imputation for missing eGFR values	– Multiple imputation (MI) was used as the primary method for handling missing eGFR data. – For the component of eGFR < 50 mL/min/1.73m^2 in the composite endpoint, a value for missing eGFR as a continuous variable was imputed, then dichotomized it to derive this endpoint. – The MI first created 100 imputations imputed datasets of missing eGFR (MDRD4) values. The imputation model assumed a multivariate normal model for the eGFR (MDRD4) measurements. This model was estimated separately within each treatment stratum. – Under the assumption of missing not at random (MNAR), patients who lost their grafts will be assigned a value of zero for their missing eGFR at the visits on and after graft loss – Otherwise, under the assumption of missing at random (MAR), patients who had missing values including those who died with a functioning graft would have a 12-month eGFR imputed using multiple imputation method based on the covariates/factors CNI, region, donor type, HLA mismatch (≤3 vs >3), induction therapy, recipient gender, recipient age, donor age, and DGF, and all eGFR (MDRD4) data collected at the visit windows during the analysis period of interest. Together with the tBPAR data, the binary composite endpoint of tBPAR or eGFR (MDRD4) <50 mL/min/1.73m^2 at Month 12 post-transplantation was derived.
Statistical testing	– For primary endpoint: To the resulting 100 imputed datasets, the proportion of patients meeting the endpoint was estimated, yielding 100 sets of parameter estimates and associated covariance matrices. The analysis results were then combined according to Rubin's rules to derive overall estimates and confidence intervals that adequately reflect missing data uncertainty as well as associated p-values – Key secondary endpoint: the event rate was estimated with Kaplan-Meier product-limit formula. Greenwood's formula were used to estimate variance of failure rates and to derive Z-test based confidence interval for the difference. Patients with missing efficacy evaluation for the 12-month analysis were censored at the last day known to be free of the event.
Populations for analysis	– The intention-to-treat (ITT) population consists of all randomized and transplanted patients. Patients randomized but not transplanted were excluded from the ITT set. Patients who were mis-randomized due to documented (IVRS) administrative error (eligibility criteria) and had no study drug received were excluded from the ITT set. Following the ITT principle, patients were analyzed according to their randomized treatment assignment and according to the actual stratum to which they initially belonged. – The per protocol population includes ITT patients who completed the study without any major deviations from protocol procedures. – The safety set consists of all patients who received at least one dose of study drug. Patients were analyzed according to their actual treatment regimen and according to the actual stratum they initially belong to. All safety analyses were performed on the safety set.

Table S4. Doses of mycophenolic acid (MPA) and steroids (safety population)

	Everolimus (n=1,014)		**MPA (n=1,012)**	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)
MPA, mg/day				
Week 1	-	-	1563 (338)	1440 (0, 3000)
Month 1	-	-	1316 (348)	1440 (0, 2880)
Month 4	-	-	1158 (407)	1080 (0, 3000)
Month 6	-	-	1123 (417)	1080 (0, 3000)
Month 12	-	-	1110 (398)	1080 (0, 2880)
Steroid dose, mg/kg/day				
Week 1	0.67 (1.33)	0.35 (0.0, 16.9)	0.67 (1.51)	0.36 (0.1, 21.9)
Month 1	0.27 (0.43)	0.21 (0.1, 8.4)	0.32 (0.81)	0.22 (0.1, 14.9)
Month 4	0.50 (4.78)	0.12 (0.0, 101.3)	0.25 (0.91)	0.12 (0.0, 9.7)
Month 6	0.42 (2.05)	0.10 (0.0, 27.3)	0.35 (1.34)	0.10 (0.0, 13.7)
Month 12	0.53 (2.29)	0.09 (0.0, 16.0)	0.45 (2.22)	0.09 (0.0, 25.4)

Table S5. Safety endpoints at month 12 (safety population)

	Everolimus (n=1,014)	**MPA (n=1,012)**	**Risk ratio (95% CI)**
Pre-specified adverse events of interest, n (%)[a]	851 (83.9)	731 (72.2)	1.16 (1.11, 1.22)
Anemia	245 (24.2)	249 (24.6)	0.98 (0.84, 1.14)
Gastrointestinal ulcers	7 (0.7)	12 (1.2)	0.58 (0.23, 1.47)
Hyperlipidemia	340 (34.5)	188 (18.6)	1.86 (1.59, 2.17)
Interstitial lung disease	11 (1.1)	3 (0.3)	3.66 (1.02, 13.08)
Major cardiovascular events	56 (5.5)	74 (7.3)	0.76 (0.54, 1.06)
Malignancy	26 (2.6)	24 (2.4)	1.08 (0.63, 1.87)
Peripheral edema	373 (36.8)	262 (25.9)	1.42 (1.25, 1.62)
Pleural effusion	11 (1.1)	11 (1.1)	1.00 (0.43, 2.29)
Proteinuria	136 (13.4)	68 (6.7)	2.00 (1.51, 2.64)
Renal failure, excluding proteinuria	280 (27.6)	278 (27.5)	1.01 (0.87, 1.16)
Stomatitis and mouth ulceration	78 (7.7)	21 (2.1)	3.71 (2.31, 5.95)
Thrombocytopenia	82 (8.1)	40 (4.0)	2.05 (1.42, 2.96)
Thrombotic and thromboembolic events	119 (11.7)	84 (8.3)	1.41 (1.08, 1.84)
Thrombotic microangiopathy	16 (1.6)	7 (0.7)	2.28 (0.94, 5.52)
New-onset diabetes mellitus[†]	134 (13.2)	122 (12.1)	1.10 (0.87, 1.38)
Other adverse events of interest, n (%)[b]			
Leukopenia	94 (9.3)	192 (19.0)	0.49 (0.39, 0.62)
Anemia	227 (22.4)	233 (23.0)	0.97 (0.78, 1.06)
Lymphocele	74 (7.3)	52 (5.1)	1.42 (1.01, 20.0)
Diarrhea	219 (21.6)	316 (31.2)	0.69 (0.60, 0.80)
Nausea	177 (17.5)	214 (21.1)	0.83 (0.69, 0.99)
Vomiting	110 (10.8)	141 (13.9)	0.78 (0.62, 0.98)
Tremor	98 (9.7)	137 (13.5)	0.71 (0.56, 0.91)
Insomnia	91 (9.0)	130 (12.8)	0.70 (0.54, 0.90)
Proteinuria	128 (12.6)	57 (5.6)	2.24 (1.66, 3.02)
Hypokalemia	144 (14.2)	82 (8.1)	1.75 (1.36, 2.27)
Wound healing complications	395 (39.0)	341 (33.7)	1.16 (1.03, 1.30)
Procedural pain	96 (9.5)	104 (10.3)	0.92 (0.71, 1.20
Lymphocele	74 (7.3)	52 (5.1)	1.42 (1.00, 2.00
Incision site pain	50 (4.9)	59 (5.8)	0.85 (0.59, 1.22)
Wound dehiscence	39 (3.8)	18 (1.8)	2.16 (1.25, 3.75
Abnormal healing	35 (3.5)	8 (1.8)	4.37 (2.04, 9.37)
Wound infection	17 (1.7)	7 (0.7)	2.42 (1.01, 5.82)
Any adverse event leading to study drug discontinuation, n (%)	233 (23.0)	120 (11.9)	1.94 (1.58, 2.37)
Adverse events leading to study drug discontinuation in ≥0.5% of patients in either group, n (%)			
Proteinuria	22 (2.2)	0 (0.0)	-
Leukopenia	4 (0.4)	9 (0.9)	0.44 (0.14, 1.44)
Diarrhea	-	6 (0.6)	-
Graft loss	8 (0.8)	9 (0.9)	0.89 (0.34, 2.29)
Transplant rejection	15 (1.5)	1 (0.1)	14.97 (1.98, 113.1)
Acute kidney injury	7 (0.7)	-	-
Renal impairment	5 (0.5)	2 (0.2)	2.50 (0.49, 12.83)
Impaired healing	12 (1.2)	1 (0.1)	11.98 (1.56, 91.93)
Lymphocele	5 (0.5)	0 (0.0)	-
CMV infection	1 (0.1)	5 (0.5)	0.20 (0.02, 1.71)
Polyomavirus-associated nephropathy	5 (0.5)	14 (1.4)	0.36 (0.13, 0.99)
BK virus infection	3 (0.3)	12 (1.2)	0.25 (0.07, 0.88)
Laboratory values			
Urinary protein:creatinine ratio (mg/g),	100 (0-9,300)	100 (0-1,000)	-

median (range)			
Urinary albumin:creatinine ratio (mg/g), median (range)	30 (0-6,280)	20 (0-7,350)	-
Total cholesterol (mg/dL), mean (SD)	212 (53)	189 (42)	-
LDL-cholesterol (mg/dL), mean (SD)	126 (43)	112 (35)	-
HDL-cholesterol, mg/dL), mean (SD)	59 (18)	55 (18)	-
Total cholesterol:HDL-cholesterol ratio, mean (SD)	3.9 (1.4)	3.7 (1.4)	-
Triglycerides, mean (SD)	203 (146)	161 (90)	-
Leukocytes (10^9/L), mean (SD)	6.9 (2.2)	7.0 (2.3)	-
Platelets (10^9/L), mean (SD)	215 (67)	212 (58)	-

[a] Prespecified adverse events of interest

[b] Events captured by standard adverse event reported which occurred in ≥10%of patients in either group and for which the 95% CI of the risk ratio did not include 1.0 (excluding pre-specified adverse events of interest)

New-onset diabetes mellitus defined by WHO criteria

Table S6. Urine protein:creatinine ratio category (safety population)

	Everolimus, n (%)	**MPA, n (%)**
Baseline, mg/g		
N	348	400
<30	0	0
30 – <500	66 (19.0)	69 (17.3)
500 – <1000	76 (21.8)	91 (22.8)
2000 – <3000	116 (33.3)	149 (37.3)
≥3000	90 (25.9)	91 (22.8)
Month 12 (or end of treatment), mg/g		
N	953	940
<30	0	
30 – <500	760 (79.7)	832 (88.5)
500 – <1000	107 (11.2)	55 (5.9)
2000 – <3000	56 (5.9)	40 (4.3)
≥3000	30 (3.1)	13 (1.4)