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Early Conversion From Calcineurin Inhibitor- to Everolimus-Based Therapy Following Kidney Transplantation: Results of the Randomized ELEVATE Trial

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In a 24-month, multicenter, open-label, randomized trial, 715 *de novo* kidney transplant recipients were randomized at 10–14 weeks to convert to everolimus (n = 359) or remain on standard calcineurin inhibitor (CNI) therapy (n = 356; 231 tacrolimus; 125 cyclosporine), all with mycophenolic acid and steroids. The primary endpoint, change in estimated glomerular filtration rate (eGFR) from randomization to month 12, was similar for everolimus versus CNI: mean (standard error) 0.3(1.5) mL/min/1.73^2 versus −1.5(1.5) mL/min/1.73^2 (p = 0.116). Biopsy-proven acute rejection (BPAR) at month 12 was more frequent under everolimus versus CNI overall (9.7% vs. 4.8%, p = 0.014) and versus tacrolimus-treated patients (2.6%, p < 0.001) but similar to cyclosporine-treated patients (8.8%, p = 0.755). Reporting on *de novo* donor-specific antibodies (DSA) was limited but suggested more frequent anti-HLA Class I DSA under everolimus. Change in left ventricular mass index was similar. Discontinuation due to adverse events was more frequent with everolimus (23.6%) versus CNI (8.4%). In conclusion, conversion to everolimus at 10–14 weeks posttransplant was associated with renal function similar to that with standard therapy overall. Rates of BPAR were low in all groups, but lower with tacrolimus than everolimus.

Abbreviations: ANCOVA, analysis of covariance; BPAR, biopsy-proven acute rejection; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CsA, cyclosporine; DSA, donor-specific antibodies; EC-MPS, enteric-coated mycophenolate sodium; eGFR, estimated glomerular filtration rate; IFTA, interstitial fibrosis and tubular atrophy; ITT, intention-to-treat; LOCF, last observation carried forward; LS, least square; LVMi, left ventricular mass index; MDRD4, four-variable Modification of Diet in Renal Disease; MFI, mean fluorescence intensity; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin

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Introduction

As the risk of kidney allograft loss due to acute rejection has declined, the goal of management has switched to long-term preservation of kidney function. Minimizing calcineurin inhibitor (CNI)-related nephrotoxicity is a key component of this objective (1). One significant development has been the introduction of mammalian target of rapamycin (mTOR) inhibitors which, in addition to their immunomodulatory effect, inhibit tumor growth and posttransplant malignancies (2,3), and are associated with a lower frequency of cytomegalovirus (CMV) infections than conventional CNI-based regimens (4). Moreover, there is growing evidence that inhibition of mTOR signaling may offer cardioprotective benefits, including an anti-atherogenic effect (5) and reduction of cardiac hypertrophy (6–10) and fibrosis (11), and possibly attenuation of arterial stiffness (12,13).

In a series of randomized trials, kidney transplant patients were converted pre-emptively from CNI therapy to an mTOR inhibitor agent between day 30 and month 6 posttransplant (14–18). Results showed a benefit in renal function compared to conventional CNI therapy, although higher rates of mild acute rejection were observed after switch in some studies (14–17). All but one trial (18) included only cyclosporine (CsA) in the CNI comparator arm, whereas tacrolimus is now used by a majority of centers in the *de novo* setting.

The ELEVATE study was an international 2-year study in which over 700 *de novo* kidney transplant patients were randomized to convert to everolimus at 10–14 weeks posttransplant or to remain on their CNI therapy (19). The primary objective was to assess the renal effect of early conversion from CNI therapy to everolimus, but also included novel secondary endpoints including left ventricular mass index (LVMi) and prevalence of antibodies against HLA donor-specific antigens in addition to efficacy variables.

Methods

Study design and conduct

This was a 24-month, multicenter, open-label, randomized, controlled trial in which *de novo* kidney allograft recipients were randomized at 10–14 weeks posttransplant to convert from CNI therapy to everolimus or remain on a standard CNI regimen (Figure S1A) (NCT01114529). The study was carried out at 72 centers in 20 countries in Europe, Asia, Australia, and South America. A detailed description of the study methodology has been published previously (19).

The study was undertaken in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki following approval from the institutional review board at participating centers. Written informed consent was obtained from all participants.

Study population

Adult recipients of a first or second kidney transplant from a deceased or living donor with a cold ischemia time <24 h were eligible for the study. Key exclusion criteria were multiorgan transplantation, ABO incompatible allograft or a positive cross-match, and panel reactive antibodies ≥30% within 3 months of baseline. At randomization, patients were required to be receiving CNI therapy (tacrolimus or CsA) with enteric-coated mycophenolate sodium (EC-MPS) and steroids, with serum creatinine <250 μmol/L and estimated glomerular filtration rate ([eGFR], four-variable Modification of Diet in Renal Disease [MDRD4] (20) formula) ≥25 mL/min/1.73 m^2 without dialysis. Key exclusion criteria at randomization were graft loss, severe humoral and/or cellular rejection (Banff ≥ IIb) or two or more episodes of acute rejection or antibody treatment for rejection prior to randomization; ongoing or currently treated acute rejection within 2 weeks prior to randomization; proteinuria >1 g/day; focal segmental glomerulosclerosis; white blood cell count ≤2000/mm^3 or absolute neutrophil count ≤1500/mm^3 with platelet count ≤50 000/mm^3; and hemoglobin <8 g/dL.

Study medication

An interactive voice response/interactive web response system was responsible for generating the randomization listing using a validated system that automated the random assignment of patient numbers to randomization numbers. The randomization scheme is fixed block with block size of 4. Patients were stratified according to (i) eGFR (MDRD4) <30, 30 to <60, 60 to <90, or ≥90 mL/min/1.73 m^2 and (ii) previous cardiovascular events (yes/no), defined as myocardial infarction or percutaneous coronary intervention.

All patients received basiliximab induction (20 mg on days 0 and 4), with tacrolimus (target C_0 6–12 ng/mL) or CsA (150–300 ng/mL), EC-MPS (1080–1440 mg/day), and steroids administered according to local practice but at a minimum dose of 5 mg/day, until randomization. Patients randomized to everolimus (C_0 target 6–10 ng/mL) could be converted from CNI therapy either overnight or stepwise over 1 week, but were to be CNI-free by the end of week 16 (Figure S1B). In the control arm, tacrolimus or CsA was continued (target C_0 5–10 ng/mL for tacrolimus, 100–250 ng/mL for CsA).

In both treatment groups, EC-MPS was continued (1080–1440 mg/day), with steroids at a minimum dose of 5 mg/day, until the end of the study.

Study endpoints

The primary endpoint was the change in eGFR (MDRD4 (20)) from randomization to month 12. Key secondary efficacy endpoints were (i) a composite efficacy endpoint of treated biopsy-proven acute rejection (BPAR) (Banff ≥ IB), graft loss or death at month 12, and (ii) the change in LVMi from randomization to month 12, as measured by echocardiogram. All secondary endpoints were exploratory.

CMV and BK infection was assessed centrally. CMV infection was defined as laboratory-defined CMV (antigenemia-positive or polymerase chain reaction positive), CMV syndrome (fever for the preceding 2 days with neutropenia, leukopenia, viral syndrome), or CMV disease (organ involvement). Delayed graft function was defined as requirement for dialysis during the first week posttransplant. New-onset diabetes mellitus was assessed among patients who were not diabetic at transplantation, comprising patients for whom the reason for transplantation was not diabetes, diabetes was not included in the medical history, and random glucose was <11 mmol/L with HbA1c < 5.7% at the time of transplantation. New-onset diabetes was defined as diabetes reported as an adverse event, random glucose ≥11 mmol/L, diabetes recorded as indication for a medication, or two HbA1c values ≥6.5%, all at more than 28 days posttransplantation.

Donor-specific antibodies (DSA) were assessed at baseline, randomization, months 12 and 24, and at the time of clinically indicated biopsies in a central laboratory using a single antigen bead assay (Luminex® One Lambda, Canoga Park, CA).

Statistical analysis

The primary endpoint, change in eGFR (MDRD4) from randomization to month 12, was compared at the significance level of 0.05 (two-sided) between groups using analysis of covariance (ANCOVA) with treatment, center (as a random effect), donor type, age (<50 vs. ≥50 years), and cold ischemia time (≤24 vs. >24 h) as factors, and eGFR at randomization as a covariate, based on least square (LS) mean values. Patients with graft loss were assigned a zero value for eGFR at month 12, with the last observation carried forward (LOCF) method applied for other missing values at month 12. For the key composite efficacy secondary endpoint, the noninferiority margin of 10% for the everolimus group versus the CNI group at 12 months was tested via Z-test based two-sided 95% confidence interval (CI). The null hypothesis was that the proportion of patients experiencing efficacy failure at 12 months in the everolimus group was higher than that of the CNI group by 10% or more. For this analysis, the incidence rate of the composite efficacy endpoint was estimated using Kaplan–Meier product-limit formula and Greenwood's formula was used to estimate the variance. The other secondary key secondary endpoint, LVMi at 12 months, was compared between groups in evaluable patients using ANCOVA with treatment, center (as a random effect), and donor type as factors and LVMi at randomization as covariate. All other analyses were exploratory.

The intent-to-treat (ITT) population included all transplanted, randomized patients. The safety population included all patients who received at least one dose of randomized study drug and provided at least one postrandomization safety assessment.

The sample size calculation showed that 304 patients randomized per group (338 to allow for 10% dropout) would provide 86% power to detect a difference of 5 mL/min/1.73 m^2 in the primary endpoint (change of eGFR [MDRD4] from randomization to month 12) between treatment groups, assuming a standard deviation of 20 mL/min/1.73 m^2 and a two-sided type I error rate of 0.05.

Results

Patients

A total of 992 patients were screened; 930 were enrolled in the study, of whom 717 were eligible for randomization. The criteria for inclusion in the ITT population were met by 715 patients (everolimus 359, CNI 356) (Figure 1). The 12-month study visit was completed by

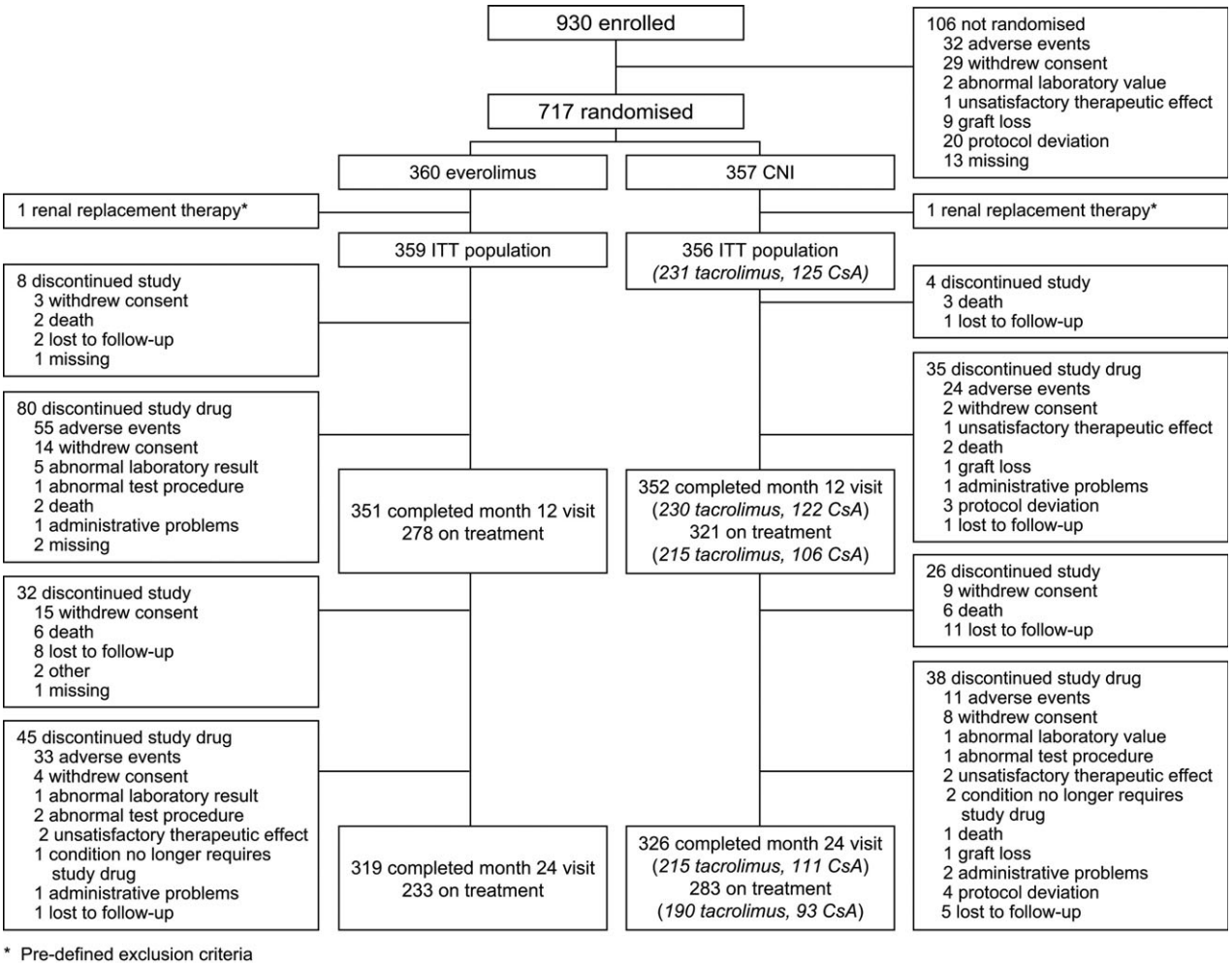

Figure 1: Patient disposition. CNI, calcineurin inhibitor; CsA, cyclosporine; ITT, intention-to-treat.

703/715 patients (98.3%; everolimus 351, CNI 352), and 645/715 completed the 24-month study visit (90.2%; everolimus 319, CNI 326). In total, 711 patients (everolimus 352, CNI 359) met the criteria for inclusion in the safety set. At months 12 and 24, 77.4% (278/359) and 64.9% (233/359) of ITT patients in the everolimus group were still in the study and receiving randomized therapy, compared to 90.2% (321/356) and 79.5% (283/356) in the CNI arm.

Patient characteristics and demographics were generally similar between groups (Table 1).

Immunosuppression and concomitant medication

In the everolimus group, 64.9% (233/359) of patients were switched from tacrolimus and 35.1% (126/359) from CsA. In the CNI control group, 64.9% (231/356) and 35.1% (125/356), respectively, were receiving tacrolimus and CsA as they entered the postrandomization phase (Table 1). Mean everolimus trough concentration was 7.0–7.4 ng/mL throughout the study, with 50–60% of patients within the everolimus target range (6–10 ng/mL) at any study visit. In the CNI control arm, 70–75% of tacrolimus-treated patients and 60–80% of the CsA-treated patients were within target range at postrandomization visits.

Mean daily EC-MPS dose was similar in the everolimus and CNI cohorts at month 24 (Table 1). The mean EC-MPS dose at month 24 was 956 mg/day in patients receiving tacrolimus versus 1215 mg/day in patients receiving CsA. The mean (standard deviation [SD]) dose of steroids during the 24-month study was 7.9 (7.6) mg/day and 5.4 (5.5) mg/day in the everolimus and CNI groups, respectively.

Inhibitors of the renin–angiotensin system were prescribed during the study for 62.2% (219/352) and 67.1% (241/359) patients in the everolimus and CNI groups, respectively, with lipid-lowering therapy in 70.7% (249/352) and 57.4% (206/359).

Renal function

The primary endpoint, change in eGFR (MDRD4) from randomization to month 12 was not significantly different after adjustment for factors/covariates applying the LOCF method: 0.3 (1.5) mL/min/1.73 m^2 in the everolimus group versus −1.5 (1.5) in the CNI group. The difference was 1.8 (1.1) mL/min/1.73 m^2, 95% CI [−0.4, 4.0 mL/min/1.73 m^2], p = 0.116 (LS mean [standard error] values, ANCOVA) (Table 2). The primary endpoint showed no relevant difference in the tacrolimus or CsA subpopulations of the CNI group (Table 3).

Observed values for mean eGFR were significantly higher in the everolimus group at all points after randomization in the ITT population other than at month 12 (Figure 2A). At month 12, mean (SD) eGFR was 64.1 (22.3) mL/min/1.73 m^2 and 60.4 (19.8) mL/min/1.73 m^2, respectively, in the everolimus and CNI groups (p = 0.042). At month 24, observed mean (SD) values were 62.5 (22.4) mL/min/1.73 m^2 and 57.4 (19.9) mL/min/1.73 m^2 (p = 0.005), respectively. The difference in observed eGFR for everolimus versus the tacrolimus-treated subpopulation of the CNI group was significant only at week 16 and month 9, with similar values at month 24 (mean [SD] eGFR was 59.7 [20.5] mL/min/1.73 m^2 for tacrolimus-treated patients) (Figure 2B). The difference was more marked between everolimus and the CsA-treated patients, remaining significantly higher in the everolimus cohort at all postrandomization time points (Figure 2C). Mean (SD) eGFR for the CsA subpopulation at month 24 was 53.0 (18.0) mL/min/1.73 m^2.

Proteinuria: At month 24, 80.4%, 11.2%, 7.3%, and 1.0% of patients in the everolimus group had proteinuria in the ranges <0.5 g/day, 0.5–0.9 g/day, 1.0–2.9 g/day and in the nephrotic range (≥3.0 g/day), respectively, compared to 93.2%, 3.6%, 2.6%, and 0.6% of patients in the CNI group. The mean (SD) urinary protein/creatinine ratio was significantly higher in the everolimus group versus the CNI group at month 24 (36.4 [53.4] mg/mmol versus 19.1 [26.9] mg/mmol, p < 0.001). Values were similar in the tacrolimus- and CsA-treated subgroups of the CNI arm (19.1 [24.3] and 19.0 [31.8] mg/mmol, respectively). Proteinuria was reported by investigators as an adverse event in 15.3% of everolimus-treated patients (54/352) and in 3.6% of CNI-treated patients (13/356).

Efficacy endpoints

Composite efficacy endpoint, graft loss, and death: The everolimus group was statistically noninferior to the CNI group in terms of the composite efficacy endpoint of treated BPAR ≥ 1B, graft loss, or death at month 12, with a difference in incidence of 2.3%, 95% CI [−1.1, 5.7%], p < 0.001 for noninferiority (p = 0.187 for no difference). Graft loss occurred in four everolimus-treated patients by month 24 (Table 2). Eight patients died in the everolimus group and nine died in the CNI group (Table 2).

BPAR: The incidences of treated BPAR and any BPAR were significantly higher in the everolimus group versus the CNI cohort (Table 2). All episodes of treated BPAR were mild (Banff grade 1 or 2A) except for two patients in the everolimus group who experienced grade 2B BPAR by month 24. When treated BPAR and any BPAR were analyzed according to type of CNI, incidences were significantly lower for tacrolimus versus everolimus but not for CsA versus everolimus

Table 1: Patient characteristics and immunosuppression (ITT population)

		CNI		
	Everolimus (n = 359)	Total (n = 356)	Tacrolimus (n = 231)	CsA (n = 125)
Recipient characteristics				
Age, years	45.9 (14.5)	46.7 (14.9)	47.3 (14.5)	45.4 (15.6)
Male gender, n (%)	245 (68.2)	252 (70.8)	160 (69.3)	92 (73.6)
Race				
White, n (%)	252 (70.2)	270 (75.8)	173 (74.9)	97 (77.6)
Black, n (%)	4 (1.1)	5 (1.4)	5 (2.2)	0
Other, n (%)	103 (28.7)	81 (22.8)	53 (22.9)	28 (22.4)
End-stage disease leading to transplantation, n (%)				
Glomerular disease	61 (17.0)	66 (18.5)	38 (16.5)	28 (22.4)
Polycystic disease	48 (13.4)	35 (9.8)	20 (8.7)	15 (12.0)
Diabetes mellitus	28 (7.8)	19 (5.3)	12 (5.2)	7 (5.6)
Hypertension/nephrosclerosis	55 (15.3)	56 (15.7)	35 (15.2)	21 (16.8)
IgA nephropathy	27 (7.5)	39 (11.0)	32 (13.9)	7 (5.6)
Other	76 (21.2)	70 (19.7)	42 (18.2)	28 (22.4)
Unknown/missing	64 (17.8)	71 (19.9)	52 (22.5)	19 (15.2)
Peak PRA ≥20%, n (%)	11 (3.1)	11 (3.1)	7 (3.0)	4 (3.2)
Preformed DSA (pretransplant), n/N (%)[1]				
HLA A	11/206 (5.3)	9/229 (3.9)	7/153 (4.6)	2/76 (2.6)
HLA B	10/225 (4.4)	12/244 (4.9)	9/159 (5.7)	3/85 (3.5)
HLA DR	14/195 (7.2)	8/197 (4.1)	6/132 (4.5)	2/65 (3.1)
HLA DQ	7/72 (9.7)	6/85 (7.1)	4/18 (8.3)	2/37 (5.4)
DSA at randomization, n/N (%)[2]				
HLA A	4/206 (1.9)	7/232 (3.0)	4/153 (2.6)	3/79 (3.8)
HLA B	6/228 (2.6)	14/251 (5.6)	9/162 (5.6)	5/89 (5.6)
HLA DR	7/203 (3.4)	6/202 (3.0)	6/134 (4.5)	0/68 (0)
HLA DQ	11/80 (13.8)	12/89 (13.5)	7/53 (13.2)	5/36 (13.9)
eGFR at randomization (mL/min/1.73 m^2)				
Mean (SD)	59.9 (20.5)	58.8 (20.0)	60.0 (20.3)	56.7 (19.4)
tBPAR ≥ 1B prior to randomization	11 (3.1)	8 (2.2)	4 (1.7)	4 (3.2)
Donor characteristics				
Age, years	46.7 (14.7)	47.7 (15.6)	48.1 (15.1)	46.9 (16.5)
Deceased, noncardiac death, n (%)	164 (45.7)	151 (42.4)	85 (36.8)	66 (52.8)
Deceased, cardiac death, n (%)	32 (8.9)	47 (13.2)	35 (15.2)	12 (9.6)
Living, n (%)	162 (42.1)	156 (43.8)	109 (47.2)	47 (37.6)
Information on type of donor missing	1 (0.3)	2 (0.6)	2 (0.9)	0 (0.0)
Expanded criteria, n (%)	114 (31.8)	118 (33.1)	66 (28.6)	52 (41.6)
Transplant characteristics				
Cold ischemia time, hours[2]	8.9 (7.7)	8.9 (7.7)	8.3 (7.5)	10.1 (8.1)
Delayed graft function, n (%)[3]	38 (10.8)	51 (14.3)	31 (13.4)	20 (16.0)
HLA mismatch, n (%)				
0	23 (6.5)	25 (7.0)	15 (6.5)	10 (8.0)
1–3	168 (46.8)	179 (50.3)	119 (51.5)	60 (48.0)
>3	142 (39.6)	133 (37.6)	85 (36.8)	48 (38.4)
Missing	26 (7.4)	19 (5.3)	12 (5.2)	7 (5.6)
Retransplant, n (%)	17 (4.8)	9 (2.5)	8 (3.5)	1 (0.8)
Immunosuppression[4]				
Previous CNI therapy, n (%)				
Tacrolimus	233 (64.9)	231 (64.9)	231 (100.0)	–
CsA	126 (35.1)	125 (35.1)	–	125 (100.0)
Tacrolimus C_0 (ng/mL)				
Randomization	8.2 (2.8)	–	8.3 (2.9)	–
Month 24	–	–	6.3 (2.0)	–
CsA C_0 (ng/mL)				
Randomization	180 (79)	–	–	178 (59)
Month 24	–	–	–	120 (43)

(*Continued*)

Table 1. *Continued*

	Everolimus (n = 359)	CNI		
		Total (n = 356)	Tacrolimus (n = 231)	CsA (n = 125)
Everolimus C_0 (ng/mL)				
Week 14	7.2 (3.1)	–	–	–
Month 24	7.2 (3.2)	–	–	–
EC-MPS dose (mg/day)				
Randomization	1205 (324)	1187 (315)	1129 (318)	1300 (276)
Month 24	1080 (337)	1039 (339)	956 (313)	1215 (325)

Continuous variables are shown as mean (SD). C_0, trough concentration; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CsA, cyclosporine; DSA, donor-specific antibodies; EC-MPS, enteric-coated mycophenolate sodium; eGFR, estimated glomerular filtration rate; HLA, human leukocyte antibody; ITT, intention-to-treat; PRA, panel reactive antibodies; tBPAR, treated biopsy-proven acute rejection.
[1]Defined as mean fluorescence intensity (MFI) ≥500.
[2]Includes deceased and living donor recipients. Four patients in the everolimus group and five patients in the CNI group had CNI >24 h against protocol.
[3]Delayed graft function as defined by the investigator.
[4]Mean (standard deviation [SD]) values provided for patients in the safety population receiving each medication.

(Table 3, Figure 3). The occurrence of BPAR was not associated with subsequent DSA.

Antibody-mediated rejection confirmed on histology was rare in both groups, but was more frequent in everolimus- versus CNI-treated patients at month 12 although not month 24 (everolimus 4.5% [16/353], CNI 2.0% [7/356], p = 0.059) (Table 2). The difference at month 12 was largely accounted for by a significantly lower rate of antibody-mediated rejection in the tacrolimus cohort versus everolimus (Table 2).

DSA

Data on DSA against different HLA loci at time of transplant were available in between 54% and 62% of patients randomized to everolimus, and in between 55% and 69% of CNI patients (Table 1). In the subset of patients with data on DSA, the incidence of *de novo* DSA (i.e. in patients with overall mean fluorescence intensity [MFI] <500 at randomization) at month 24 using a cut-off of MFI 500 was 8.9% (11/124) and 6.2% (6/97) for Class I and Class II DSA in the everolimus group, compared to 3.0% (5/166) and 6.3% (8/128) in the CNI group (Table 4). When assessed according to the type of CNI, the proportions of patients with Class I and Class II *de novo* DSA at month 24 were 4.3% (5/116) and 5.6% (5/89) for tacrolimus compared to 0% (0/50) and 8.1% (3/37) for CsA (Table 4). When *de novo* DSA was assessed at months 12 and 24 in patients with no DSA at time of transplant, Class II DSA was more frequent in the everolimus cohort at month 12 (18.4% [30/163] vs. 11.1% [22/199] in the CNI group), but showed less difference at month 24 (13.1% [17/130] vs. 10.7% [18/169]) (Table 4).

The incidence of all *de novo* anti-HLA antibodies (MFI ≥500 in patients with MFI <500 at randomization) regardless of donor status, among patients who provided data at randomization, month 12, and month 24, was 8.1% (10/124) for Class I and 19.6% (9/46) for Class II DSA in the everolimus group at month 12, compared to 4.8% (8/166) and 17.1% (6/35) in the CNI group. At month 24, the incidence was 8.9% (11/124) for Class I and 16.7% (6/36) for Class II with everolimus, compared to 3.0% (5/166) and 15.6% (7/45) with CNI. Overall, for any patient with DSA data at month 24, *de novo* anti-HLA antibodies (either Class I or Class II) were present in 18.2% of everolimus-treated patients (31/170) and 15.5% of CNI-treated patients (34/219).

IFTA on protocol biopsies

The proportion of patients with protocol biopsy data at month 12 and month 24 did not vary markedly between the two treatment groups or within the tacrolimus- and CsA-treated subpopulations at months 12 and 24 (range 79.0–88.8% of patients) (Table S1). The incidence of interstitial fibrosis and tubular atrophy (IFTA) on centrally read protocol biopsies was similar between the everolimus and CNI groups overall, and between everolimus and either the tacrolimus-treated or CsA-treated subpopulations (Table S1). The severity of IFTA at months 12 and 24, assessed as the frequency of Banff grade I, II, or III, was also similar between treatment groups (Table S1).

Cardiovascular endpoints

Echocardiographic data were available at randomization and at month 12 in 531 patients (247 everolimus, 284 CNI). Mean (SD) LVMi was 50.3 (11.6) versus 51.1 (13.6) g/m$^{2.7}$ for everolimus versus CNI at randomization, 50.0 (12.6) versus 49.6 (14.1) g/m$^{2.7}$ at month 12, and 46.7 (12.2) versus 46.4 (13.3) g/m$^{2.7}$ at month 24 for patients with echocardiographic measurements at all three time points (everolimus 180, CNI 231). The LS mean change in LVMi from randomization to month 12 in

Table 2: Renal and efficacy endpoints from randomization (ITT population). Significant p values are shown in bold

	Everolimus (n = 359)	CNI (n = 356)	Difference (95% CI)	p value
Primary endpoint				
Change in eGFR to month 12, LS mean (SE), mL/min/1.73 m^2 [1]	0.3 (1.5)	−1.5 (1.5)	1.8 (1.1) (−0.4, 4.0)	0.116
Secondary endpoints				
Composite efficacy endpoint[2,3]				
Month 12	21 (6.1)	12 (3.8)	2.3 (−1.1, 5.7)	0.187
Treated BPAR	17	7		
Graft loss	1	2		
Death	3	3		
Month 24	27 (8.0)	16 (4.5)	3.6 (−0.2, 7.1)	0.064
Treated BPAR	18	8		
Graft loss	3	2		
Death	6	6		
Graft loss, n (%)[3,4]				
Month 12	2 (0.6)	4 (1.2)	−0.6 (−2.0, 0.8)	0.407
Month 24	4 (1.2)	4 (1.1)	0.0 (−1.6, 1.6)	0.955
Death, n (%)[3,5]				
Month 12	5 (2.0)	4 (1.5)	0.4 (−2.1, 2.9)	0.741
Month 24	8 (2.6)	9 (2.6)	0.0 (−2.5, 2.5)	0.990
Treated BPAR (Banff ≥ 1b), n (%)[3]				
Month 12	17 (4.8)	7 (2.0)	2.8 (0.2, 5.5)	**0.037**
Month 24	18 (5.1)	8 (2.3)	2.9 (0.1, 5.6)	**0.045**
Any BPAR, n (%)[6]				
Month 12	35 (9.7)	17 (4.8)	5.0 (−2.3, 12.3)	**0.014**
Month 24	39 (10.9)	21 (5.9)	5.0 (0.9, 9.0)	**0.017**
Any treated BPAR, n (%)[6]				
Month 12	29 (8.2)	17 (4.8)	3.4 (−4.0, 10.7)	0.068
Banff IA	14 (4.0)	9 (2.5)	1.4 (−6.0, 8.8)	0.230
Banff IB	13 (3.7)	7 (2.0)	1.7 (−5.7, 9.0)	0.181
Banff IIA	3 (0.8)	1 (0.3)	0.6 (−6.8, 7.9)	0.372
Banff IIB	2 (0.6)	0	0.6 (−6.8, 7.9)	0.248
Banff III	0	0		
Subclinical	0	0		
Month 24	32 (9.1)	20 (5.6)	3.4 (−0.4, 7.3)	0.078
Banff IA	16 (4.5)	11 (3.1)	1.4 (−6.0, 8.8)	0.334
Banff IB	14 (4.0)	8 (2.2)	1.7 (−5.7, 9.0)	0.201
Banff IIA	3 (0.8)	1 (0.3)	0.6 (−6.8, 7.9)	0.372
Banff IIB	2 (0.6)	0	0.6 (−6.8, 7.9)	0.248
Banff III	0	0		
Subclinical	0	0		
Antibody-mediated rejection, n (%)[6]				
Month 12	13 (3.7)	2 (0.6)	3.1 (−4.3, 10.4)	**0.004**
Month 24	16 (4.5)	7 (2.0)	2.6 (−4.8, 9.9)	**0.059**

BPAR, biopsy-proven acute rejection; CNI, calcineurin inhibitor; eGFR, estimated GFR (four-variable Modification of Diet in Renal Disease); ITT, intention-to-treat; LS, least means; SE, standard error.

[1]Last observation carried forward method (analysis of covariance).

[2]Treated BPAR (Banff ≥ 1b), graft loss or death.

[3]Percentages based on Kaplan–Meier estimates; p values indicate the difference in risk based on Kaplan–Meier estimates.

[4]Causes of graft loss by month 24; everolimus: decreased immunosuppression in response to severe fungal infection (104 days after switch to tacrolimus), chronic rejection, infection and urological complications; CNI: acute rejection, urological complications, noncompliance, and neoplasia transmitted from the donor.

[5]Causes of death by month 24; everolimus: cardiac arrest, myocardial ischemia, sudden death (2), pneumonia, sepsis/septic shock (2), renal failure; CNI: cardiac arrest (2), myocardial infarction, chronic renal failure, malignancies (4; gastric adenocarcinoma, brain tumor, small-cell lung cancer, hepatic cancer), carbon monoxide poisoning.

[6]Observed values; p values calculated by Fisher exact test.

this cohort was 0.05 g/$m^{2.7}$ in the everolimus cohort and −1.14 g/$m^{2.7}$ in the CNI cohort, a difference of 1.19 (0.86) g/$m^{2.7}$; 95% CI [−0.50, 2.89], p = 0.168. Mean systolic blood pressure at month 24 was 132/79 mmHg in both the everolimus and CNI groups (tacrolimus 132/79 mmHg, CsA 134/80 mmHg).

Table 3: Renal and efficacy endpoints from randomization according to type of CNI therapy (ITT population). Significant p values are shown in bold

		Tacrolimus			CsA		
	Everolimus (n = 359)	Tacrolimus (n = 231)	Difference vs everolimus (95% CI)	p value	CsA (n = 125)	Difference vs everolimus (95% CI)	p value
Primary endpoint							
Change in eGFR to month 12, LS mean (SE), mL/min/1.73 m^2 [1]	0.3 (1.5)	−0.6 (1.8)	1.4 (1.3) (−1.2, 4.0)	0.281	−1.8 (2.1)	2.3 (1.7) (−1.0, 5.5)	0.171
Secondary endpoints							
Composite efficacy endpoint[2,3]							
Month 12	21 (6.1)	4 (2.4)	3.8 (−0.2, 7.3)	**0.040**	8 (6.4)	−0.3 (−5.3, 4.7)	0.907
Treated BPAR	17	2			5		
Graft loss	1	1			1		
Death	3	1			2		
Month 24	27 (8.0)	8 (3.5)		**0.020**	8 (6.4)		
Treated BPAR	18	7	4.5 (0.7, 8.3)		4	1.6 (−3.6, 6.8)	0.551
Graft loss	3	1			1		
Death	6	0			3		
Graft loss, n (%)[3]							
Month 12	2 (0.6)	2 (1.0)	−0.4 (−1.9, 1.2)	0.636	2 (1.6)	−1.0 (−3.4, 1.3)	0.388
Month 24	4 (1.2)	2 (0.9)	0.3 (−1.4, 2.0)	0.714	2 (1.6)	−0.4 (−3.0, 2.1)	0.730
Death, n (%)[3]							
Month 12	5 (2.0)	1 (1.0)	1.0 (−1.8, 3.7)	0.508	3 (2.4)	−0.4 (−3.7, 2.8)	0.793
Month 24	8 (2.6)	5 (2.2)	0.4 (−2.3, 3.0)	0.778	4 (3.2)	−0.6 (−4.3, 3.0)	0.726
Treated BPAR (Banff ≥ 1b), n (%)[3]							
Month 12	17 (4.8)	2 (0.9)	4.0 (1.4, 6.5)	**0.002**	5 (4.1)	0.8 (−3.4, 4.9)	0.716
Month 24	18 (5.1)	3 (1.3)	3.8 (1.1, 6.6)	**0.006**	5 (4.1)	1.1 (−3.1, 5.3)	0.616
Any BPAR, n (%)[4]							
Month 12	35 (9.7)	6 (2.6)	7.2 (−1.1, 15.3)	**<0.001**	11 (8.8)	0.9 (−4.9, 6.8)	0.755
Month 24	39 (10.9)	8 (3.5)	7.4 (−0.9, 15.6)	**0.001**	13 (10.4)	0.5 (−5.8, 6.7)	0.885
Antibody-mediated rejection, n (%)[4]							
Month 12	13 (3.7)	1 (0.4)	3.2 (−5.0, 11.5)	**0.011**	1 (0.8)	2.9 (−7.3, 13.0)	0.128
Month 24	16 (4.5)	4 (1.7)	2.8 (−5.5, 11.1)	0.101	3 (2.4)	2.1 (−8.1, 12.3)	0.426

BPAR, biopsy-proven acute rejection; CNI, calcineurin inhibitor; CsA, cyclosporine; eGFR, estimated GFR (four-variable Modification of Diet in Renal Disease); ITT, intention-to-treat;. LS, least means; SE, standard error.
[1]Last observation carried forward method (analysis of covariance).
[2]Treated BPAR (Banff ≥ 1b), graft loss or death.
[3]Percentages based on Kaplan–Meier estimates; p values indicate the difference in risk based on Kaplan–Meier estimates.
[4]Observed values; p values calculated by Fisher exact test.

Major adverse cardiac events occurred in 4 everolimus patients by month 12 compared to 15 CNI-treated patients (1.1% [4/353] vs. 4.2% [15/356], p = 0.018). By month 24, the difference in incidence had become non-significant (2.2% [8/359] vs. 4.5% [16/356], p = 0.145). Events occurring by month 24 are listed in Table S2.

Safety

The proportion of patients who reported at least one adverse event between randomization and by month 24 was similar in both groups (everolimus 91.5% [322/352], CNI 88.9% [319/359]). Pyrexia, peripheral edema, and mouth ulceration were more frequent in the everolimus group than in CNI-treated patients; diarrhea and anemia were less frequent under CsA than either tacrolimus or everolimus, but increased blood creatinine and hypertriglyceridemia, as defined by the investigator, were more frequent with CsA (Table 5). Diabetes was reported as an adverse event in 4.3% (15/352) of everolimus-treated patients and 6.4% (23/359) of CNI-treated patients (19/238 receiving tacrolimus [8.0%], 4/121 receiving CsA [3.3%]). The protocol-specified criteria for new-onset diabetes mellitus were met by 10.7% of patients in the everolimus group (27/252 patients without diabetes at randomization) and 10.1% of patients in the CNI group (28/278) (p = 0.887) (Table 5). The incidence was 13.3% (24/181) under tacrolimus (p = 0.452 vs. everolimus) and 4.1% (4/97) under CsA (p = 0.059 vs. everolimus) (Table 5).

Infections were reported as adverse events in 57.4% and 49.0% of everolimus- and CNI-treated patients, respectively, comprising bacterial, fungal, and viral infections in 33.2%, 2.3%, and 19.3% of patients in the

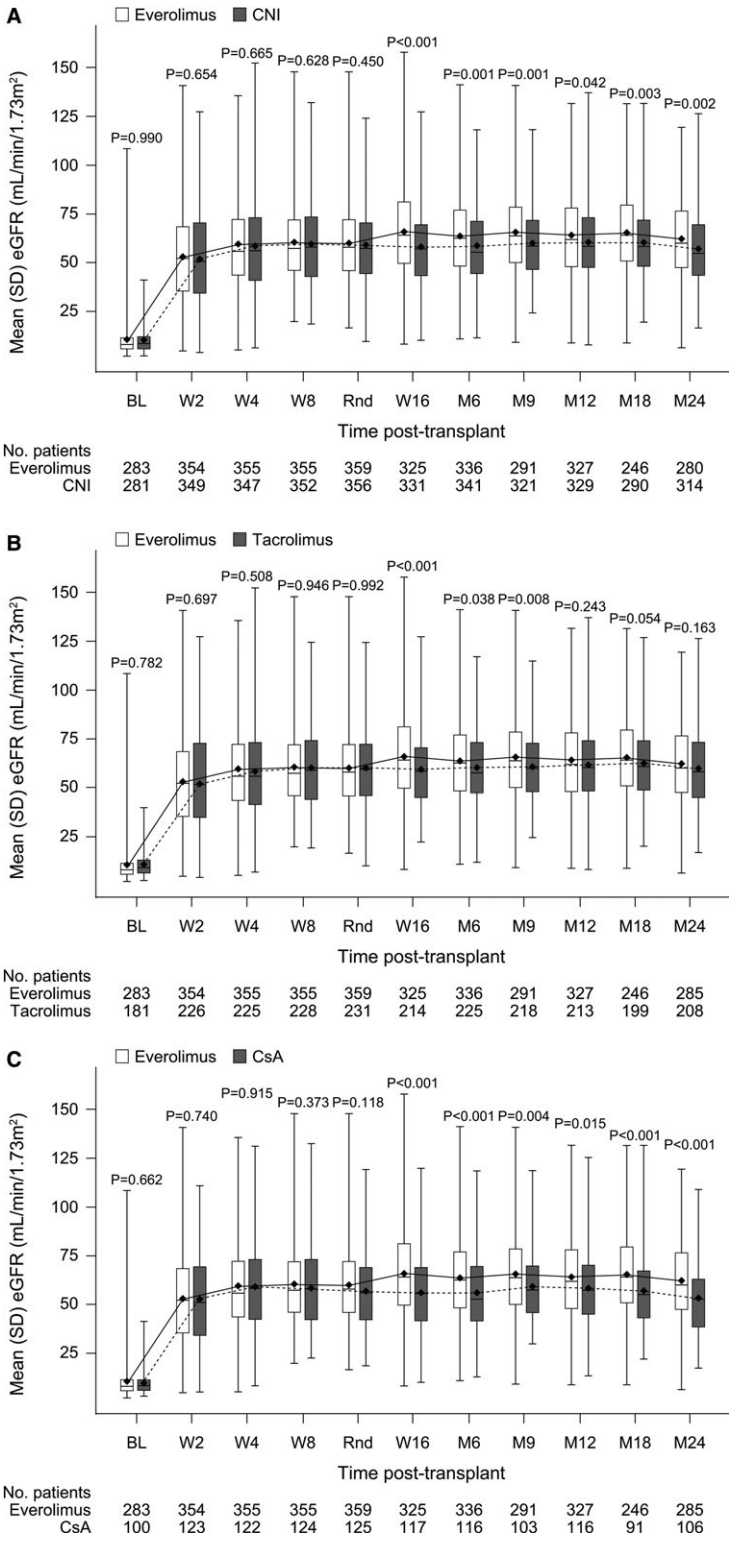

Figure 2: Mean (SD) eGFR (MDRD4) from randomization (Rnd) to month 24 (A) everolimus versus CNI, (B) everolimus versus tacrolimus (C), everolimus versus CsA (ITT population). Means are joined by a horizontal line. Boxes indicate the 10th and 90th percentile, with horizontal lines showing the median. Vertical lines indicate minimum and maximum values. CNI, calcineurin inhibitor; CsA, cyclosporine; eGFR, estimated GFR (four-variable Modification of Diet in Renal Disease); ITT, intention-to-treat; SD, standard deviation.

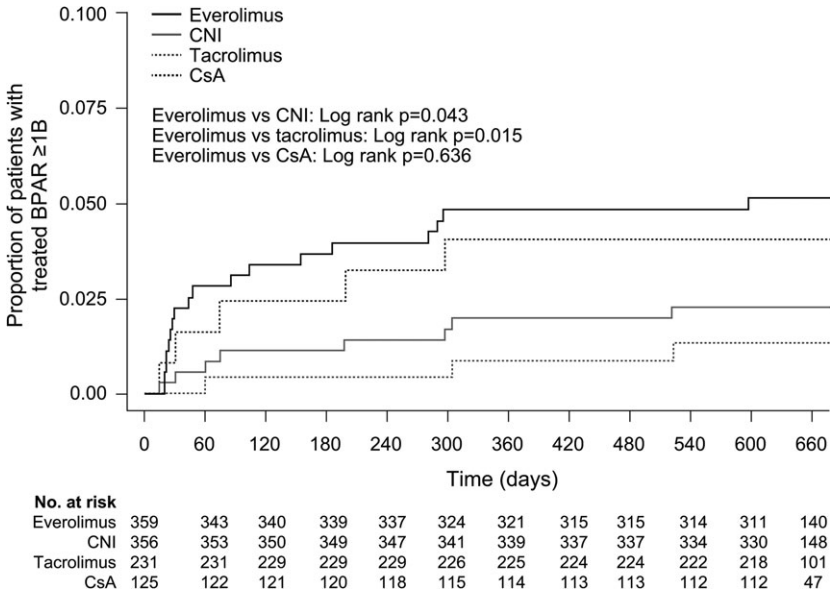

Figure 3: Kaplan–Meier estimates of freedom from treated biopsy-proven acute rejection (BPAR) ≥1B ITT population. CNI, calcineurin inhibitor; CsA, cyclosporine; ITT, intention-to-treat.

everolimus group and 24.2%, 3.9%, and 22.6% of patients in the CNI group. CMV infection was reported as an adverse event in 14 and 22 patients (4.0% vs. 6.1%) and BKV infection in 5 and 18 patients (1.4% vs. 5.0%). Protocol-specified central assessments at month 24 detected CMV infection in 9.4% of everolimus-treated patients (33/352) and 12.3% of CNI-treated patients (44/359), with BKV infection in 3.8% (7/185) and 9.0% (19/211), respectively, for patients in whom data were provided.

The rate of wound healing events was similar between groups (everolimus, 23/352 [6.5%]; CNI 21/359 [5.8%]).

The incidence of serious adverse events between randomization and month 24 was comparable (everolimus 54.8% [193/3526], CNI 49.0% [176/359]). Other than episodes of rejection, the most frequent serious adverse events were urinary tract infection (everolimus 7.1%, CNI 7.5%), pyrexia (7.1%, 2.5%), gastroenteritis (3.1%, 3.9%), diarrhea (4.3%, 3.6%), pneumonia (4.0%, 2.5%), and pyelonephritis (3.7%, 2.5%). Ten patients in the everolimus group (2.8%) and 17 patients (4.7%) in the CNI group developed malignancy.

Prior to randomization, 15 patients (2.1%) discontinued CNI therapy due to adverse events. Discontinuation of study drug between randomization and month 24 due to adverse events was more frequent in the everolimus group (23.6% [83/352]) than the CNI group (8.4% [30/359]; tacrolimus 15/238 [6.3%], CsA 15/121 [12.4%]). The most common event to result in everolimus discontinuation was allograft rejection (Table S3).

Laboratory data at randomization and month 24 for patients who remained on their randomized treatment are summarized in Table S3. Levels of lipids and liver enzymes were higher in the everolimus group, while levels of hemoglobin, white blood cells, and fasting blood glucose were lower; but mean values remained within normal ranges.

Discussion

In this randomized, multicenter, 2-year study, more than 709 patients were investigated and 359 were converted from CNI therapy to everolimus at 10–14 weeks after kidney transplantation. The primary endpoint, change in eGFR from randomization to month 12, was similar in patients who were switched to everolimus or who remained on standard CNI immunosuppression. When analyzed according to the type of CNI therapy in the control arm, observed eGFR was significantly higher with everolimus versus CsA, but not versus tacrolimus. Both the CNI-free patients receiving everolimus and the CNI-treated cohort showed low rates of treated BPAR or any BPAR throughout follow-up, although these were approximately twice as frequent in the everolimus group, a difference driven by significantly lower frequencies of rejection among patients who remained on tacrolimus.

Although mean eGFR was significantly higher in the everolimus group versus control patients from randomization onwards (with the exception of the month 12 time point), the primary endpoint of adjusted change in eGFR from

Table 4: *De novo* DSA at months 12 and 24 in patients with overall mean fluorescence intensity (MFI) <500 at (a) randomization (b) transplantation (safety population)

	Everolimus (n = 352)	CNI (n = 359)	Tacrolimus (n = 238)	CsA (n = 121)
(a) MFI <500 at randomization				
Month 12				
Anti class I	10/124 (8.1)	8/166 (4.8)	8/116 (6.9)	0/50 (0.0)
HLA A	6/98 (6.1)	4/142 (2.8)	4/97 (4.1)	0/45 (0.0)
HLA B	5/114 (4.4)	4/148 (2.7)	4/102 (3.9)	0/46 (0.0)
Anti class II	9/97 (9.3)	6/126 (4.8)	2/89 (2.2)	4/37 (10.8)
HLA DR	3/91 (3.3)	0/119 (0.0)	0/86 (0.0)	0/33 (0.0)
HLA DQ	6/36 (16.7)	6/47 (12.8)	2/32 (6.3)	4/15 (26.7)
Month 24				
Anti class I	11/124 (8.9)	5/166 (3.0)	5/116 (4.3)	0/50 (0.0)
HLA A	8/98 (8.2)	3/142 (2.1)	3/97 (3.1)	0/45 (0.0)
HLA B	3/114 (2.6)	1/148 (0.7)	1/102 (1.0)	0/46 (0.0)
Anti class II	6/97 (6.2)	8/126 (6.3)	5/89 (5.6)	3/37 (8.1)
HLA DR	3/91 (3.3)	2/119 (1.7)	2/86 (2.3)	0/33 (0.0)
HLA DQ	3/36 (8.3)	6/47 (12.8)	3/32 (9.4)	3/15 (20.0)
(b) MFI <500 at transplantation				
Month 12				
Anti class I	25/198 (12.6)	24/250 (9.6)	20/171 (11.7)	4/79 (5.1)
HLA A	16/161 (9.9)	13/216 (6.0)	12/149 (8.1)	1/67 (1.5)
HLA B	11/181 (6.1)	13/228 (5.7)	10/153 (6.5)	3/75 (4.0)
Anti class II	30/163 (18.4)	22/299 (11.1)	13/135 (9.6)	9/64 (14.1)
HLA DR	12/155 (7.7)	8/185 (4.3)	7/127 (5.5)	1/58 (1.7)
HLA DQ	21/62 (33.9)	16/79 (20.3)	8/49 (16.3)	8/30 (26.7)
Month 24				
Anti class I	19/160 (11.9)	20/216 (9.3)	14/151 (9.3)	6/65 (9.2)
HLA A	13/130 (10.0)	14/190 (7.4)	11/132 (8.3)	3/58 (5.2)
HLA B	5/145 (3.4)	6/195 (3.1)	3/134 (2.2)	3/61 (4.9)
Anti class II	17/130 (13.1)	18/169 (10.7)	12/119 (10.1)	6/50 (12.0)
HLA DR	7/123 (5.7)	7/160 (4.4)	6/114 (5.3)	1/46 (2.2)
HLA DQ	11/50 (22.0)	11/65 (16.9)	6/43 (14.0)	5/22 (22.7)

DSA defined as MFI ≥ 500. CNI, calcineurin inhibitor; CsA, cyclosporine; DSA, donor-specific antibodies.

randomization to month 12 was not significantly different from the CNI continuation group. Progressive lowering of CNI exposure in the control arm may have diminished the between-group difference over time.

The composite efficacy endpoint, and each of its components, occurred at a similar frequency in both treatment arms. Treated BPAR, excluding grade 1A rejections, was infrequent with either regimen (everolimus 5.1%, CNI 2.3% by month 24) although higher in the everolimus group. The difference was due to a lower rate of treated BPAR (and BPAR overall) in the tacrolimus-treated subpopulation. For CsA-treated patients, the rates of both treated BPAR and any BPAR were similar to that seen in the everolimus arm, as described previously in the ZEUS study (16). The incidence and severity of IFTA at month 12 or month 24 was similar in the everolimus group versus the CNI arm, consistent with results from the recent randomized CERTITEM study (21) and versus the tacrolimus- and CsA-treated subpopulations, with comparable severity.

The incidence of antibody-mediated rejection by month 24 was noticeably low in both arms (<5%) but was significantly more frequent in the everolimus group during the first posttransplant year and remained twice as frequent versus the CNI group by month 24. Interpretation of data on DSA development is limited by the low rate of reporting at time of transplant (<70% for any HLA loci) and at month 24 (<50% for Class I or Class II in either treatment arm). Based on the available data, the incidence of *de novo* DSA Class I was 8.9% in the everolimus group versus 3.0% the CNI arm at month 24, while rates of *de novo* DSA Class II were similar between the two treatment groups. Any difference in propensity to develop *de novo* DSA in the two groups does not appear to have resulted in additional antibody-mediated rejection episodes within the 2-year timeframe of this study, but we recognize that this time period may be too short for adequate assessment of an impact of DSA. The low reporting rate for DSA data precludes any firm conclusions, but this observation merits further investigation. Retrospective data have suggested that switch to an

Table 5: Adverse events from randomization to month 24, as reported by the investigators (safety population)

		CNI		
	Everolimus (n = 352)	Total (n = 359)	Tacrolimus (n = 238)	CsA (n = 121)
Any adverse event	322 (91.5)	319 (88.9)	216 (90.8)	103 (85.1)
Any adverse event with suspected relation to study drug	208 (59.1)	154 (42.9)	108 (45.4)	46 (38.0)
Any infection	202 (57.4)	176 (49.0)	123 (51.7)	53 (43.8)
Any serious adverse event	193 (54.8)	176 (49.0)	118 (49.6)	58 (47.9)
Any adverse event leading to study drug discontinuation	83 (23.6)	30 (8.4)	15 (6.3)	15 (12.4)
Adverse events occurring in ≥10% of patients and selected adverse events of interest				
Diarrhea	82 (23.3)	68 (18.9)	55 (23.1)	13 (10.7)
Urinary tract infection	75 (21.3)	65 (18.1)	47 (19.7)	18 (14.9)
Peripheral edema	63 (17.9)	34 (9.5)	21 (8.8)	13 (10.7)
Hypertension	37 (10.5)	36 (10.0)	24 (10.1)	12 (9.9)
Leukopenia	49 (13.9)	46 (12.8)	35 (14.7)	11 (9.1)
Anemia	44 (12.5)	26 (7.2)	21 (8.8)	5 (4.1)
Hypercholesterolemia	41 (11.6)	22 (6.1)	15 (6.3)	7 (5.8)
Hypertriglyceridemia	13 (3.7)	12 (3.3)	4 (1.7)	8 (6.6)
Proteinuria	54 (15.3)	13 (3.6)	11 (4.6)	2 (1.7)
Increased blood creatinine	30 (8.5)	44 (12.3)	24 (10.1)	20 (16.5)
Pyrexia	63 (17.9)	32 (8.9)	20 (8.4)	12 (9.9)
Mouth ulceration	24 (6.8)	3 (0.8)	2 (0.8)	1 (0.8)
Wound healing complication	3 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
New-onset diabetes mellitus according to predefined criteria (>28 days posttransplant)	27 (10.7)	28 (10.1)	24 (13.3)	4 (4.1)
Reported as an adverse event	2 (0.8)	10 (3.6)	10 (5.5)	0
Random glucose ≥11 mmol/L	2 (0.8)	11 (4.0)	11 (6.1)	0
Diabetes as an indication for medication	2 (0.8)	4 (1.4)	3 (1.7)	1 (1.0)
Two HbA1c values ≥6.5%	26 (10.5)	20 (7.2)	16 (8.8)	4 (4.1)

CNI, calcineurin inhibitor; CsA, cyclosporine.

everolimus-based CNI-free regimen increases the risk for development of *de novo* DSA after transplantation (22,23), although conflicting data have been reported in a series of solid organ transplant patients where 60% continued low-dose CNI (24). A large prospective trial of 202 kidney transplant patients randomized at week 7 posttransplant to remain on CsA or switch to everolimus found a numerical but nonsignificant increase in DSA at 3 years posttransplant in the everolimus group among patients who remained on treatment; renal function remained superior to controls (25). In a single-center analysis, Liefeldt et al reported an increased risk for DSA after kidney transplantation after conversion to CNI-free therapy with introduction of everolimus (26), consistent with findings from the randomized CERTITEM study (21). It seems likely that patients in both the latter studies received inadequate adjunctive immunosuppression (21,27). A recent review concluded that early conversion to CNI-free immunosuppression with an mTOR inhibitor may increase the incidence of *de novo* DSA, but that combined therapy with an mTOR inhibitor and reduced-exposure CNI does not incur an increased risk (28). A randomized, powered trial that includes prespecified, rigorous capture of DSA data under an everolimus-based regimen versus standard therapy, with appropriate concomitant therapy, is awaited.

LVMi remained unchanged in both groups during this 2-year study and no effect of switching to everolimus was observed. This is consistent with data from the randomized CENTRAL study in which kidney transplant recipients were converted from everolimus to CsA at week 7, which showed no effect on LVM at 3 years posttransplant (29). Of note, however, major adverse cardiac events were significantly less frequent in the everolimus group during the first year posttransplant. This has not been reported elsewhere and if confirmed would be of considerable interest.

The profile of adverse events in each group was as expected for these drug classes, showing no new safety concerns. Laboratory data showed higher levels of lipids and liver enzymes, (Table S4) and a lower white blood cell count, in the everolimus group but these rarely led to study drug discontinuation. More patients in the everolimus cohort had proteinuria values >0.5 g/day than in the CNI arm, which is potentially predictive for graft loss (30). There was also a higher ratio of urinary protein/creatinine in the everolimus group, but proteinuria led to discontinuation in only six patients. Additionally, 15 patients who were intolerant to CNI therapy had already discontinued CNI prior to randomization. Importantly, the rate of CMV infection was lower in the everolimus cohort, with numerically

fewer cases of CMV disease, consistent with published data (31), and there were fewer cases of BKV infection in everolimus-treated patients, although absolute numbers were low. Malignancies occurred in 10 everolimus-treated patients and 17 CNI-treated patients (4 of whom died as a result). ELEVATE benefited from a large study population, followed for 2 years, and a randomized, multicenter design. Blinding was not possible due to therapeutic drug dosing for everolimus and CNI agents. As mentioned above, the fact that one in five patients switched from the assigned everolimus treatment regimen complicated the analysis and data capture in the study did not permit a reliable calculation of what proportion resumed CNI therapy. The most notable limitation, however, was the inferior and inconsistent rate of data collection for *de novo* DSA due to varying practices between the 72 participating centers, which limits interpretation.

In conclusion, this trial found no difference in the primary endpoint, change in eGFR from randomization to month 12, between patients randomized to continue CNI therapy or switch to everolimus at 10–14 weeks after kidney transplantation. When analyzed according to type of CNI, a renal benefit is observed following conversion from CsA therapy to everolimus but not after conversion from tacrolimus. Acute rejection was significantly less frequent under tacrolimus–mycophenolic acid (MPA) than everolimus-MPA, although the absolute rates were low in both groups. A small increase in DSA was observed under everolimus versus CNI therapy for Class I, and at month 12 for Class II, but data collection was poor. Discontinuation of study drug was more frequent for everolimus than for CNI therapy. The reduced long-term risks of diabetes, CMV infection, and potentially posttransplant malignancy under everolimus should be considered. These results confirm that early conversion from a CsA-based regimen to everolimus improves renal function, but they do not support switch from tacrolimus-MPA unless specific risk factors for tacrolimus-related complications or other posttransplant morbidities are present that justify introduction of everolimus.

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Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Johan W. de Fijter has taken part in investigator-originated trials supported by Astellas, BMS, and Novartis, has spoken at international scientific meetings funded by Novartis, and is a member of Novartis Advisory Board. Hallvard Holdaas has served as a consultant to Bristol-Myers Squibb, Novartis, AstraZeneca, Astellas, and Schering-Plough, and has received lecture fees from Novartis and AstraZeneca. Ole Øyen has received speaker's honoraria from Novartis. Jan-Stephan Sanders has taken part in investigator-originated trials supported by Astellas and Novartis. Sankaran Sundar is a member of advisory boards for Novartis, Astellas, Panacea Biotec, Biocon, and Dr Reddys Lab, has taken part in investigator-initiated trials supported by Novartis and Astellas, and has received travel grants from Emcure and LG Pharma. Frederike J. Bemelman has taken part in investigator-originated trials supported by Astellas and Novartis. Claudia Sommerer has participated in advisory boards for Novartis and Chiesi, and received research grants from Novartis, Astellas, and Chiesi. Julio Pascual has spoken at international scientific meetings funded by Novartis, and his institution has received research grants from Novartis and Astellas. Yingyos Avihingsanon has received speaker's honoraria and travel funding from Novartis, Astellas, and Pfizer, and has taken part in investigator-originated trials supported by Novartis and Astellas. Cholatip Pongskul has received speaker's honoraria and travel funding from Novartis, Astellas, and Roche. Frederic Oppenheimer has received speaker's honoraria and travel funding from Novartis and Astellas and has taken part in investigator-originated trials supported by Novartis and Astellas. Lorenzo Toselli has no conflicts of interest to declare. Graeme Russ has received speaker's honoraria and travel funding from Novartis and Pfizer and has taken part in investigator-originated trials supported by Novartis and Astellas. Zailong Wang, Patricia Lopez, and Jossy Kochuparampil are Novartis employees. Josep M. Cruzado has received speaker and advisory board honoraria from Novartis, Sandoz, Abbvie, and Alexion and research grants from Amgen and Baxter. Markus van der Giet has taken part in investigator-originated trials supported by Novartis and BMS, has spoken at international scientific meetings funded by Novartis, and is a member of a Novartis Advisory Board.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1: (A) ELEVATE study design. (B) Protocol for conversion to everolimus. CNI, calcineurin inhibitor; EC-MPS, enteric-coated mycophenolate sodium; Tx, transplantation.

Table S1: IFTA on protocol biopsies (ITT population). CNI, calcineurin inhibitor; CsA, cyclosporine; ITT, intention-to-treat.

Table S2: Incidence of major adverse cardiac events by month 24 (ITT population). Patients could have more than one event. CNI, calcineurin inhibitor; CsA, cyclosporine; ITT, intention-to-treat.

Table S3: Adverse events leading to study drug discontinuation in more than one patient in either study group between randomization and month 24 (safety population). CNI, calcineurin inhibitor; CsA, cyclosporine.

Table S4: Laboratory values at month 24. CsA, cyclosporine; SD, standard deviation.

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