American Journal of Transplantation 2010; 10: 1401–1413
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2010.03129.x

Everolimus Plus Reduced-Exposure CsA versus Mycophenolic Acid Plus Standard-Exposure CsA in Renal-Transplant Recipients

H. Tedesco Silva Jr.[a,*,†], D. Cibrik[b,†], T. Johnston[c], E. Lackova[d], K. Mange[e], C. Panis[e], R. Walker[f], Z. Wang[e], G. Zibari[g] and Y. S. Kim[h]

[a] *Hospital do Rim e Hipertensão, São Paulo, Brazil*
[b] *Department of Internal Medicine, University of Michigan, Ann Arbor, MI*
[c] *University of Kentucky, Lexington, KY*
[d] *NSP F.D. Roosevelta, Banska Bystrica, Slovak Republic*
[e] *Novartis Pharmaceuticals Corporation, East Hanover, NJ*
[f] *The Royal Melbourne Hospital, Parkville, Victoria, Australia*
[g] *Louisiana State Health Sciences Center, Shreveport, LA*
[h] *Yonsei University College of Medicine Severance Hospital, Seoul, Korea*
**Corresponding author: H. Tedesco Silva Jr., heliotedesco@hrim.com.br*
†H. Tedesco Silva Jr. and D. Cibrik contributed equally to this work.

Everolimus allows calcineurin-inhibitor reduction without loss of efficacy and may improve renal-transplant outcomes. In a 24-month, open-label study, 833 *de novo* renal-transplant recipients were randomized to everolimus 1.5 or 3.0 mg/day (target troughs 3–8 and 6–12 ng/mL, respectively) with reduced-exposure CsA, or mycophenolic acid (MPA) 1.44 g/day plus standard-exposure CsA. Patients received basiliximab ± corticosteroids. The primary endpoint was composite efficacy failure (treated biopsy-proven acute rejection, graft loss, death or loss to follow-up) and the main safety endpoint was renal function (estimated glomerular filtration rate [eGFR], by Modification of Diet in Renal Disease [MDRD]) at Month 12 (last-observation-carried-forward analyses). Month 12 efficacy failure rates were noninferior in the everolimus 1.5 mg (25.3%) and 3.0 mg (21.9%) versus MPA (24.2%) groups. Mean eGFR at Month 12 was noninferior in the everolimus groups versus the MPA group (54.6 and 51.3 vs 52.2 mL/min/1.73 m^2 in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively; 95% confidence intervals for everolimus 1.5 mg and 3.0 mg vs MPA: −1.7, 6.4 and −5.0, 3.2, respectively). The overall incidence of adverse events was comparable between groups. The use of everolimus with progressive reduction in CsA exposure, up to 60% at 1 year, resulted in similar efficacy and renal function compared with standard-exposure CsA plus MPA.

Key words: Calcineurin inhibitor toxicity, cyclosporine, everolimus, renal function, renal transplantation, therapeutic drug monitoring

Received 23 December 2009, revised 26 February 2010 and accepted for publication 10 March 2010

Introduction

Although advances in immunosuppressive therapy have dramatically improved short-term outcomes following renal transplantation, long-term graft survival has not improved to the same extent. The nephrotoxicity of calcineurin inhibitors (CNIs) contributes to chronic graft dysfunction (1), and since renal function at 12 months posttransplant potentially predicts long-term graft function (2–4), optimizing renal function is critical. Thus, a key challenge is to develop immunosuppressive strategies that allow early CNI minimization or elimination and lead to the reduction of CNI-related adverse events (AEs) while maintaining current low acute-rejection rates.

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor/proliferation-signal inhibitor (PSI) with potent immunosuppressive and antiproliferative effects (5), and is highly effective in preventing acute rejection in renal-transplant recipients (6–9). Although, in initial trials, everolimus plus standard-exposure CsA (ST-CsA) demonstrated equivalent efficacy to MMF plus ST-CsA in *de novo* renal-transplant recipients, renal function was reduced in everolimus-treated patients (6,9,10). However, Phase III studies have demonstrated that everolimus allows early CNI minimization while maintaining good efficacy and renal function (7). Various everolimus and CsA dosing regimens have been assessed (11–14), culminating in a regimen that minimizes the risk of rejection by targeting specific everolimus trough levels, while reducing the risk of CNI nephrotoxicity by CNI minimization.

The A2309 study assessed the efficacy and safety of two regimens of everolimus plus reduced-exposure CsA (RD-CsA) compared with mycophenolic acid (MPA) plus ST-CsA in *de novo* renal-transplant recipients over 24 months. This report details the 12-month results.

Materials and Methods

Study design

This study was a Phase IIIb, 24-month, multicenter, open-label trial. Eligible patients were randomized (1:1:1) to one of three treatment groups within 24 hours posttransplantation:

- Everolimus 1.5 mg (0.75 mg p.o. b.i.d. targeted to 3–8 ng/mL) + RD-CsA.
- Everolimus 3.0 mg (1.50 mg p.o. b.i.d. targeted to 6–12 ng/mL) + RD-CsA.
- MPA 1.44 g (720 mg p.o. b.i.d.) + ST-CsA.

All patients received basiliximab induction therapy ± corticosteroids. Patients were assigned a randomization number, which was linked to one of the three treatment groups, using an interactive voice-response system. The randomization scheme was reviewed and approved by the Biostatistics Quality Assurance Group. The institutional review board of each center approved the study protocol, and all patients provided written informed consent.

Patients

Patients aged 18–70 years undergoing primary kidney transplantation were eligible. Key exclusion criteria included, kidneys donated after cardiac death or with a cold ischemia time >40 hours; donor age >65 years; recipients of multiorgan-, ABO-incompatible-, positive T-cell cross-match- or HLA-identical living-related-donor transplants; or most recent anti-HLA Class I panel-reactive antibodies (PRA) >20% by a CDC (complement-dependent cytotoxicity)-based assay or >50% by flow cytometry or ELISA.

Immunosuppressive therapy

Eligible patients received basiliximab (20 mg) within the 2 hours prior to transplantation and 20 mg at Day 4, or according to local practice. Patients received their first dose of study drug within 24 hours posttransplantation. From Day 5, CsA dose adjustments were made based on trough levels (Supporting Table 1). Everolimus doses were adjusted from Day 5 onward:

- Everolimus 1.5 mg group: targeted to 3–8 ng/mL.
- Everolimus 3.0 mg group: targeted to 6–12 ng/mL.

Trough levels were assessed at a central laboratory using liquid chromatography-mass spectrometry. Blood samples were taken 3–7 days following each visit in which patients' everolimus or CsA doses were changed. Corticosteroids were administered according to local practice.

Dose reductions were permitted for patients experiencing decreases in white blood cell (WBC) or platelet counts, increases in cholesterol or triglyceride levels, or other AEs, to keep patients on the study drug. Study drug interruptions were permitted during antibody treatment of rejection episodes.

CMV prophylaxis (≥30 days; ganciclovir, CMV hyperimmune globulin, acyclovir or valacyclovir; according to local practice) was mandatory for all CMV-negative recipients who received a kidney from a CMV-positive donor. Other patients received CMV prophylaxis according to local practice. *Pneumocystis carinii* pneumonia prophylaxis was initiated when oral medication was tolerated and continued for the first year of the study.

Efficacy and safety

Efficacy: The primary endpoint was efficacy failure, defined as the composite of treated biopsy-proven acute rejection (BPAR), graft loss, death or loss to follow-up at Month 12. The main secondary endpoint was the composite of graft loss, death or loss to follow-up at Month 12. In suspected rejection episodes, regardless of antirejection treatment, an allograft-core biopsy was performed within 48 hours. Biopsies were read by local pathologists according to 1997 updated Banff criteria (15) and by a central pathologist, blinded to the patient's treatment. The primary endpoint was assessed using the local pathologists' readings. Other secondary endpoints included the components of the primary endpoint.

Safety: The main safety endpoint was renal function at Month 12, assessed by estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) formula (16). Renal function was also assessed by using the Nankivell formula (17) to calculate eGFR, the Cockcroft–Gault formula to estimate creatinine clearance and by measuring serum creatinine. Other safety assessments included AEs, serious AEs (SAEs), clinical laboratory measurements (biochemistry, hematology and urinalysis) and vital signs.

Statistical analyses

The primary efficacy analyses were conducted on the intent-to-treat (ITT) population (all patients randomized). Noninferiority was assessed using a two-sided 0.025-level *z*-test analyzed by the modified Bonferroni testing procedure (18) to control for multiple comparisons and maintain the overall Type I error rate at $\alpha = 0.05$. Everolimus was considered noninferior to MPA if the upper limit of the 95% confidence interval (CI) was less than 10%. Additional supportive analyses of the primary efficacy endpoint included repeating the *z*-test using the per-protocol population (ITT minus patients with major protocol deviations), performing a Kaplan–Meier (K–M) survival analysis and analyzing BPAR based on central pathologist readings. A K–M analysis of BPAR was used to estimate the probability of experiencing an event and to compare the time to event between treatment groups. The method used for the primary efficacy analyses was also used for the main secondary efficacy endpoints. For the main safety endpoint, renal function was compared using *t*-test-based 95% CI for the difference in mean eGFR at Month 12 between everolimus and MPA (ITT population). A last-observation-carried-forward (LOCF) approach was used to impute missing eGFR values for the 12-month analyses, with a value of zero entered for patients with graft loss. Everolimus was considered noninferior to MPA if the lower limit of the 95% CI was greater than −8 mL/min/1.73 m^2. Summary statistics were provided for calculated eGFRs and differences between everolimus and MPA responses were compared by the Wilcoxon Rank–Sum test. Renal function was also assessed using data observed while patients remained on treatment (no later than 2 days after the discontinuation of study medication). Except for the renal-function analyses, safety analyses were performed on the safety population (patients who received at least one dose of study drug and had a postbaseline safety assessment).

Sample size calculation

The efficacy failure rates at Month 12 for the everolimus and MPA groups were assumed to be 19% and 20%, respectively. A sample size of 825 patients (275 per group) was calculated to have an 84% power to demonstrate that everolimus was not more than 10% inferior to MPA with respect to the primary endpoint.

For the mean eGFR (MDRD) noninferiority assessment, the sample-size calculation was based on the 95% CI of a two-sided *t*-test. A significance level of 0.025 was used to control for multiple comparisons. It was assumed that the MPA and everolimus groups would have a 12-month mean eGFR of 50 mL/min/1.73 m^2 and a SD of 22 mL/min/1.73 m^2. Based on these

assumptions, a sample size of 825 patients (275 per group) would have 97% power to demonstrate that mean eGFR in the everolimus groups was noninferior to the MPA group by ≥8 mL/min/1.73 m^2.

Results

Baseline demographics

In total, 833 patients were randomized to the everolimus 1.5 mg (n = 277), 3.0 mg (n = 279), or MPA (n = 277) groups. A total of 595 (71.4%) patients remained on study medication at Month 12; AEs were the most frequent reason for study-drug discontinuation in all groups (Figure 1). Donor and recipient characteristics were generally comparable between groups (Table 1).

Immunosuppressive therapy

Mean everolimus trough levels were within the target ranges at all time points (Figure 2). From Month 1 onward 76–85% of patients in the 1.5 mg group were within the target range versus 60–69% in the 3.0 mg group (Supporting Table 2).

Per protocol, CsA doses were reduced over time. In the everolimus groups, >50% of patients had CsA trough levels within the target range from Day 14 onward, with the exception of Months 4, 6 and 7. In the MPA group, >50% of patients had trough levels within the target range from Month 1 onward (Figure 3; Supporting Table 2). Compared with the MPA group, the percentage reductions in mean CsA trough levels at Months 1, 6 and 12 were 31%, 46% and 60%, respectively, for the everolimus 1.5 mg and 29%, 51% and 64%, respectively, for the 3.0 mg groups. Mean MPA doses in the control group were constant throughout the study; the overall mean dose (SD) of MPA was 1.34 g/day (0.210).

Efficacy

Primary efficacy endpoint: Composite efficacy failure event rates at Month 12 were 25.3%, 21.9% and 24.2% in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively; both everolimus groups were statistically noninferior to MPA (Table 2). No statistical differences were observed between the groups in terms of the K–M estimate of the proportion of patients free from composite efficacy failure at Month 12 (74.7%, 78.1% and 75.8% in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively; p ≥ 0.300 for all comparisons).

Per-protocol population analyses confirmed the primary ITT analyses findings, with similar composite efficacy failure rates reported for the everolimus 1.5 mg (15.8%), 3.0 mg (12.2%) and MPA groups (15.7%). Similar results were reported when the incidence of treated BPAR was based on central laboratory biopsy analyses (data not shown).

Secondary efficacy endpoints: The combined incidence of death, graft loss and loss to follow-up at Month 12 was 11.6%, 11.1% and 9.4% in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively (statistically noninferior for everolimus vs MPA) (Table 2). In total, 53, 42 and 54 treated BPARs were reported in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively. A majority were Banff type IA (Table 2). The K–M estimate of patients free from treated BPAR (95% CI) at Month 12 (ITT population) was 82.7% (78.1, 87.3) in the everolimus 1.5 mg, 86.0% (81.9, 90.2) in the 3.0 mg and 82.4% (77.8, 87.0) in the MPA groups (Figure 4). Rates of antibody-treated rejection were similar between groups: 3.6%, 4.3% and 5.4%, respectively (statistically noninferior for the everolimus vs MPA groups). Differences in the incidence of graft loss were not significant between the groups with 4.3% of patients in the everolimus 1.5 mg, 4.7% in the 3.0 mg and 3.2% in the MPA groups experiencing graft loss by Month 12 (p = 0.504 and p = 0.393 vs MPA, respectively) (Table 2).

Safety

Renal function: For the main safety endpoint analyses at Month 12 (LOCF analyses), mean eGFR (MDRD) was 54.6, 51.3 and 52.2 mL/min/1.73 m^2 in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively. Renal function in both everolimus groups was statistically noninferior to MPA, since the lower limits of the 95% CI for the mean eGFR difference in the everolimus 1.5 mg (−1.7, 6.4) and 3.0 mg (−5.0, 3.2) versus MPA groups were greater than −8 mL/min/1.73 m^2. Mean and median calculated eGFR (MDRD) showed similar patterns of renal function over the 12-month period (on-treatment population). Significantly higher eGFR values were reported at Months 1, 6, 7 and 9 in the everolimus 1.5 mg versus MPA groups (Table 3, Figure 5). When renal function was assessed by creatinine clearance (Cockcroft–Gault) and Nankivell eGFR methods, a similar pattern was observed with the highest values generally in the everolimus 1.5 mg group (targeted to 3–8 ng/mL) (Table 3). The National Kidney Foundation (NKF) criteria for chronic kidney disease Stage 3 (eGFR 30–59 mL/min/1.73 m^2) and Stage 4 (eGFR 15–29 mL/min/1.73 m^2) were used as a guide to evaluate renal function by category. Of the patients whose renal function was <60 mL/min/1.73 m^2 at Month 1 (<30 and 30–<60 mL/min/1.73 m^2 categories), a total of 20% (25/127) of patients in the everolimus 1.5 mg group experienced an increase in GFR to ≥60 mL/min/1.73 m^2 by Month 12 versus only 15% (20/132) and 12% (18/145) in the 3.0 mg and MPA groups, respectively. The mean eGFR changes in individual categories are presented in Table 3. Delayed graft function was comparable between treatment groups (10.2%, 10.4% and 9.2% in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively).

Adverse events: The overall incidence of AEs was comparable between groups: 98.9%, 99.3% and 98.9% of patients in the everolimus 1.5 mg, 3.0 mg and MPA groups,

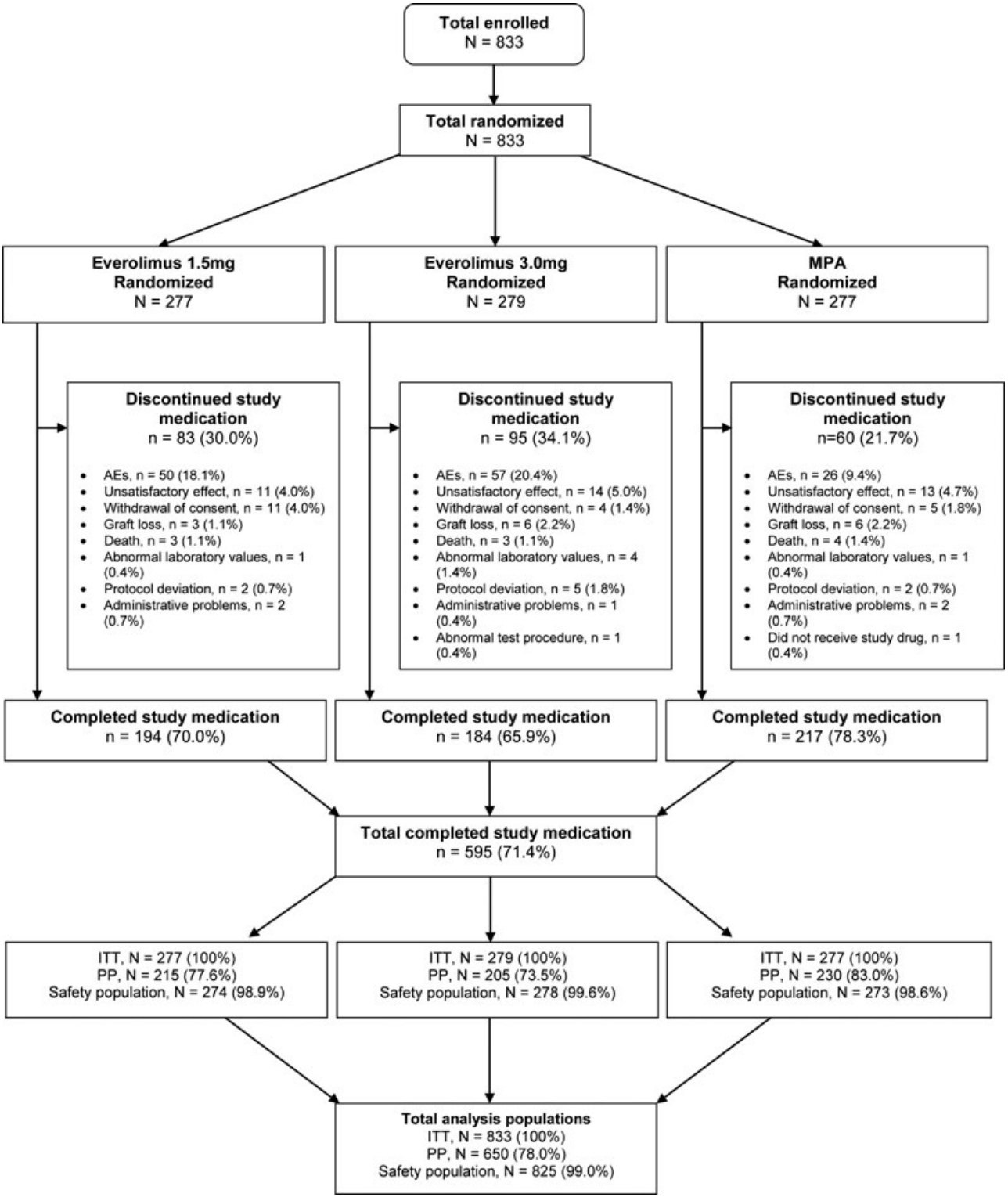

Figure 1: Patient disposition. ITT population = all patients randomized after transplantation; PP population = all patients who completed study without major protocol deviations, i.e. patients who had received multiple or previous transplants; kidneys with cold ischemia time >40 hours; or a kidney from a donor aged >65 years; Safety population: all patients who received at least one dose of study drug and had at least one postbaseline safety assessment; *primary reason for discontinuation listed; AEs = adverse events; ITT = intention-to-treat; MPA = mycophenolic acid; PP = per protocol.

Table 1: Baseline demographics and clinical characteristics of renal-transplant recipients and donors (intent-to-treat population)

	Everolimus 1.5 mg (N = 277)	Everolimus 3.0 mg (N = 279)	MPA 1.44 g (N = 277)
Recipient characteristics			
Age, years ± SD	45.7 ± 12.7	45.3 ± 13.4	47.2 ± 12.7
Male, n (%)	176 (63.5)	191 (68.5)	189 (68.2)
Caucasian, n (%)	193 (69.7)	180 (64.5)	190 (68.6)
BMI, n (%)			
≤25th percentile (22.2)	71 (25.6)	73 (26.2)	57 (20.6)
>25th percentile, ≤50th percentile (25.1)	64 (23.1)	57 (20.4)	70 (25.3)
>50th percentile, ≤75th percentile (29.0)	69 (24.9)	60 (21.5)	75 (27.1)
>75th percentile	61 (22.0)	74 (26.5)	62 (22.4)
Unknown	12 (4.3)	15 (5.4)	13 (4.7)
Primary disease leading to transplantation, n (%)			
Hypertension/nephrosclerosis	50 (18.1)	56 (20.1)	45 (16.2)
Glomerulonephritis/glomerular disease	43 (15.5)	55 (19.7)	40 (14.4)
Diabetes mellitus	39 (14.1)	29 (10.4)	45 (16.2)
Polycystic disease	36 (13.0)	29 (10.4)	33 (11.9)
Unknown	34 (12.3)	37 (13.3)	39 (14.1)
Other[1]	74 (26.7)	73 (26.2)	74 (26.7)
Missing	1 (0.4)	0 (0.0)	1 (0.4)
Current dialysis, n (%)[†]			
Hemodialysis	182 (65.7)	197 (70.6)	188 (67.9)
Peritoneal dialysis	48 (17.3)	45 (16.1)	42 (15.2)
None	46 (16.6)	37 (13.3)	46 (16.6)
Number of HLA mismatches, n (%)			
0	10 (3.6)	15 (5.4)	15 (5.4)
1	19 (6.9)	18 (6.5)	19 (6.9)
2	37 (13.4)	51 (18.3)	40 (14.4)
≥3	210 (75.8)	194 (69.5)	202 (72.9)
CMV serology status, n (%)			
Negative	94 (33.9)	83 (29.7)	104 (37.5)
Positive	180 (65.0)	188 (67.4)	170 (61.4)
CMV donor/recipient serology status, n (%)			
Donor positive/recipient positive	140 (50.5)	139 (49.8)	125 (45.1)
Donor positive/recipient negative	30 (10.8)	28 (10.0)	42 (15.2)
Donor negative/recipient positive	36 (13.0)	44 (15.8)	39 (14.1)
Donor negative/recipient negative	62 (22.4)	53 (19.0)	60 (21.7)
Missing	9 (3.2)	15 (5.4)	11 (4.0)
Donor characteristics			
Age, years ± SD	41.4 ± 13.9	41.1 ± 13.0	41.8 ± 13.6
Male, n (%)	154 (55.6)	139 (49.8)	136 (49.1)
Caucasian, n (%)	193 (69.7)	191 (68.5)	197 (71.1)
Deceased donor heart beating, n (%)	128 (46.2)	126 (45.2)	127 (45.8)
Donated after cardiac death, n (%)	1 (0.4)	2 (0.7)	1 (0.4)
Living related, n (%)	99 (35.7)	111 (39.8)	101 (36.5)
Living unrelated, n (%)	48 (17.3)	40 (14.3)	47 (17.0)
Missing, n (%)	1 (0.4)	0 (0.0)	1 (0.4)

[1]Includes pyelonephritis, drug-induced toxicity, interstitial nephritis, vasculitis, obstructive disorder/reflux, renal hyperplasia/dysplasia, IgA nephropathy and other causes; [†]Data not available for one patient in the everolimus 1.5 mg and MPA groups.
ITT = intent-to-treat; MPA = mycophenolic acid; SD = standard deviation.

respectively. SAEs were also comparable (56.6%, 60.4% and 53.8%, respectively) (Table 4). The incidence of AEs by system organ class was generally similar between groups and a majority were mild-to-moderate in severity. Neoplasms were infrequent in all groups (3.3%, 2.9% and 5.9% of patients in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively) while AEs generally ascribed to CsA or PSI/mTOR inhibitors were reported more frequently in the MPA and everolimus groups, respectively (Table 4). Posttransplant diabetes mellitus, as assessed by the investigator, was reported as an AE in a similar percentage of patients in each group (5.1%, 7.9% and 7.0% in the 1.5 mg, 3.0 mg and MPA groups, respectively).

Infections and infestations were reported as AEs in 61.7%, 64.0% and 67.8% of patients in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively. The most frequent was urinary tract infection (Table 4), with comparable

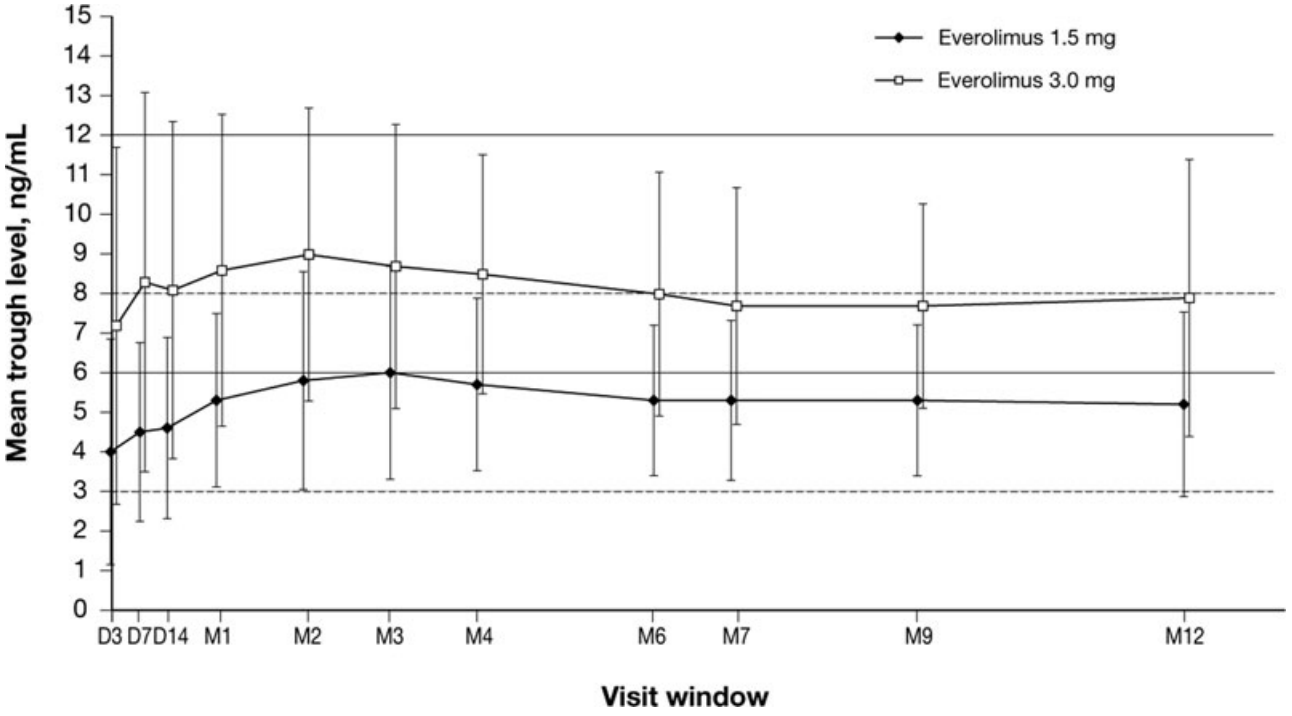

Figure 2: Target range and actual mean trough levels of everolimus achieved (ng/mL) over time in the everolimus 1.5 mg and 3.0 mg groups (safety population). Everolimus target ranges were 3–8 ng/mL and 6–12 ng/mL in the 1.5 mg and 3.0 mg everolimus groups, respectively; mean everolimus doses in mg/day (SD) at Day 1, Month 6 and Month 12 were 3.2 (22.6), 2.5 (10.1) and 2.6 (10.6) in the 1.5 mg group and 2.7 (0.5), 2.7 (1.0) and 3.4 (9.8) in the 3.0 mg group, respectively; the maximum doses of everolimus reported in some cases were implausibly high and these were likely to be administrative errors.

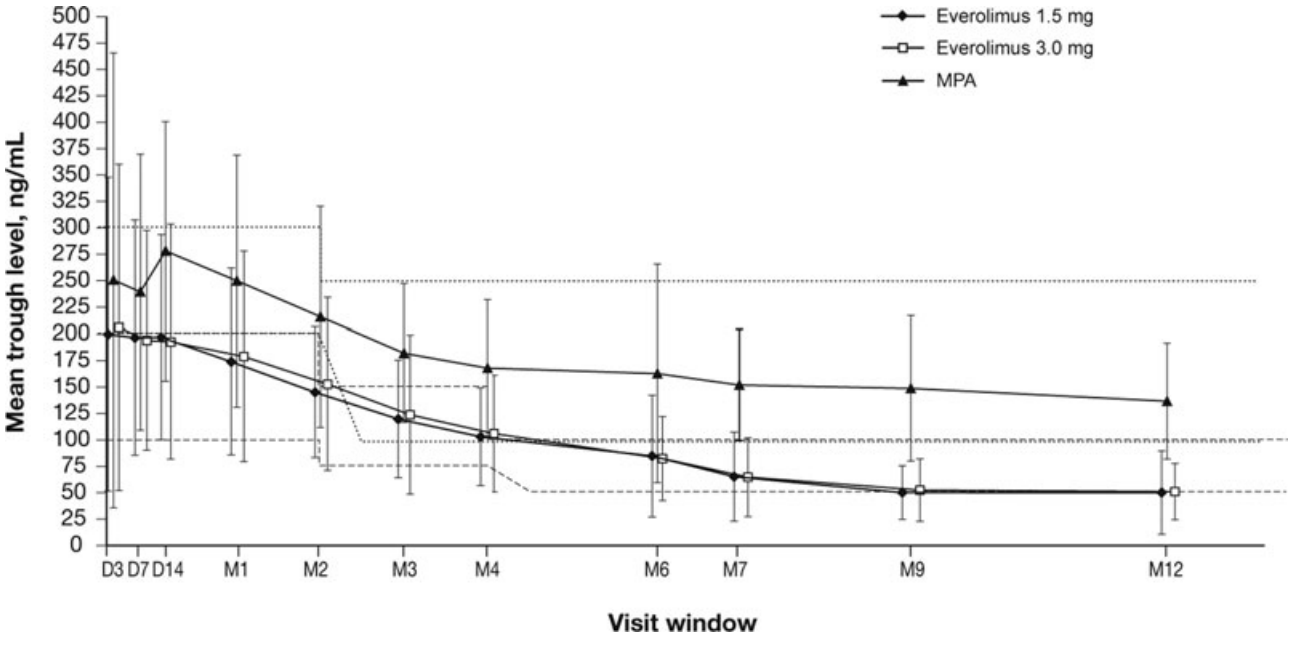

Figure 3: Target range and actual mean trough levels of CsA achieved (ng/mL) over time in the everolimus 1.5 mg, 3.0 mg and mycophenolic acid 1.44 g groups (safety population). CsA target ranges for the everolimus groups were 100–200 ng/mL from Day 3 decreasing to 75–150 ng/mL from Month 2, 50–100 ng/mL from Month 4 and 25–50 ng/mL from Months 6 to 12; CsA target ranges for the MPA groups were 200–300 ng/mL from Day 3 decreasing to 100–250 ng/mL from Months 2 to 12; MPA = mycophenolic acid.

Table 2: Summary of efficacy-related results over 12 months of treatment (ITT population[1])

	Everolimus 1.5 mg N = 277		Everolimus 3.0 mg N = 279		MPA 1.44 g N = 277
	n (%)	Event rate difference (95% CI) *vs* control	n (%)	Event rate difference (95% CI) *vs* control	n (%)
Primary composite endpoint[2]	70 (25.3)	1.1 (−6.1, 8.3)	61 (21.9)	−2.7 (−9.3, 4.7)	67 (24.2)
Death	7 (2.5)		9 (3.2)		6 (2.2)
Graft loss	12 (4.3)		13 (4.7)		9 (3.2)
Loss to follow up[3]	12 (4.3)		8 (2.9)		9 (3.2)
Treated BPAR[4]	45 (16.2)		37 (13.3)		47 (17.0)
Number of treated BPAR of any grade[5]	53		42		54
Patients with treated BPAR by Banff grade					
IA	21 (7.6)		16 (5.7)		22 (7.9)
IB	11 (4.0)		8 (2.9)		7 (2.5)
IIA	7 (2.5)		9 (3.2)		15 (5.4)
IIB	1 (0.4)		3 (1.1)		2 (0.7)
III	1 (0.4)		0 (0.0)		1 (0.4)
Missing	6 (2.2)		4 (1.4)		3 (1.1)
Death, graft loss or loss to follow up[2,6,7]	32 (11.6)	2.2 (−2.9, 7.3)	31 (11.1)	1.7 (−3.3, 6.8)	26 (9.4)
Death or graft loss	18 (6.5)	1.1 (−2.9, 5.0)	21 (7.5)	2.1 (−2.0, 6.2)	15 (5.4)

[1]Last-observation-carried-forward analyses; [2]Both everolimus groups were non-inferior to the MPA group; [3]Loss to follow-up patient for primary composite endpoint is a patient who did not experience treated BPAR, graft loss or death and whose last day of contact is prior to Day 316; [4]First treated BPAR; [5]Some patients experienced >1 BPAR; [6]Main secondary endpoint; [7]Loss to follow-up patient for secondary endpoint is a patient who did not experience graft loss or death and whose last day of contact is prior to Day 316.
BPAR = biopsy-proven acute rejection; CI = confidence interval; ITT = intent-to-treat; MPA = mycophenolic acid.

severity between groups. A higher incidence of BK viruria and BK viremia was observed in the MPA (3.3% and 1.8%) versus everolimus groups (everolimus 1.5 mg: 0.7% and 1.1%; and 3.0 mg: 0.4% and 0.7%) and a further three BK nephropathy cases were confirmed by histology: 0.4%, 0.0% and 0.7% in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively. CMV infection was observed in a higher proportion of patients in the MPA (5.9%) versus everolimus groups (0.7% and 0.0% in the everolimus 1.5 mg and 3.0 mg groups, respectively). Similarly, the incidence of CMV syndrome and CMV disease was higher in the MPA group (everolimus 1.5 mg: 1.5% and 0.7%;

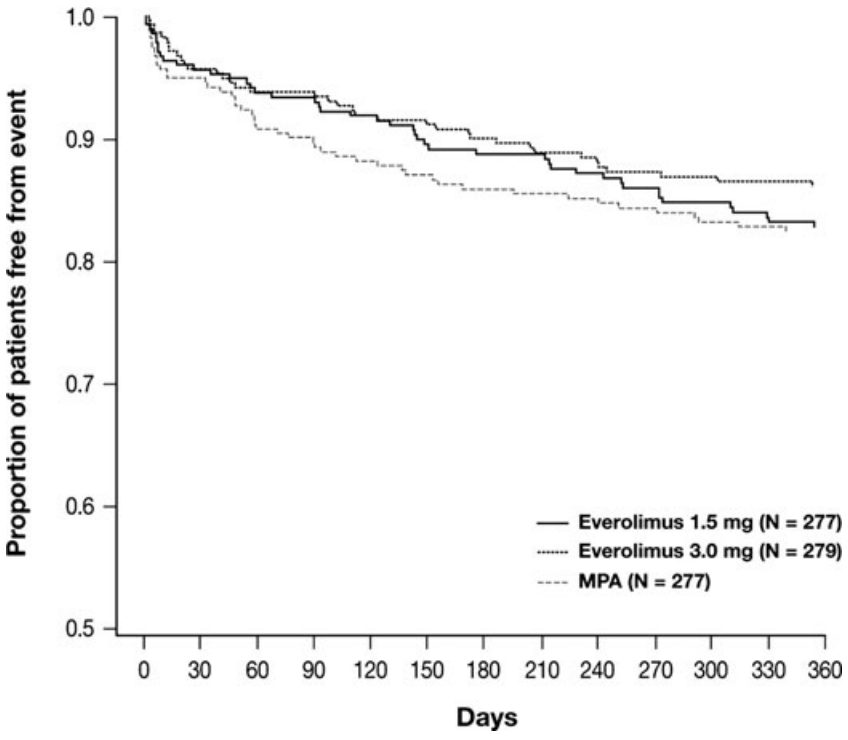

Figure 4: Kaplan–Meier estimate of time to biopsy-proven acute rejection over 12 months of treatment (intent-to-treat population). Analyses are based on local laboratory data; MPA = mycophenolic acid.

Table 3: Renal function over 12 months (ITT population[1])

	Everolimus 1.5 mg (N = 277)				Everolimus 3.0 mg (N = 279)				MPA 1.44 g (N = 277)		
	n	Mean (SD)	Median (range)	p-Value[2]	n	Mean (SD)	Median (range)	p-Value[2]	n	Mean (SD)	Median (range)
eGFR (MDRD) (mL/min/1.73 m^2)											
Baseline	267	9.3 (7.9)	8.0 (2.8–83.4)	0.840	270	9.1 (5.4)	7.8 (2.9–49.8)	0.379	271	8.7 (4.5)	7.6 (2.1–27.2)
Day 1	241	18.0 (13.5)	13.8 (3.5–91.0)	0.542	237	18.1 (13.2)	13.8 (3.1–68.5)	0.596	242	17.0 (12.1)	14.3 (3.5–73.5)
Day 3	261	39.0 (30.6)	35.6 (2.8–323.5)	0.097	270	37.7 (26.0)	33.5 (2.7–158.3)	0.199	259	35.1 (25.8)	29.5 (3.2–128.2)
Day 7	269	48.7 (33.5)	48.6 (3.7–345.9)	0.316	273	45.6 (26.2)	45.7 (3.5–121.7)	0.763	267	45.9 (27.6)	42.8 (3.6–145.5)
Day 14	257	55.1 (25.4)	54.0 (3.5–199.3)	0.056	252	50.9 (24.4)	50.8 (4.3–124.9)	0.936	251	51.6 (23.5)	49.7 (4.1–151.3)
Month 1	251	59.7 (22.5)	56.9 (6.8–181.2)	0.029	252	54.9 (21.4)	54.6 (6.5–137.1)	0.713	251	55.9 (21.4)	52.7 (5.1–153.9)
Month 2	237	58.8 (22.9)	57.2 (6.2–229.2)	0.169	240	55.3 (20.7)	53.5 (6.5–148.8)	0.757	245	55.7 (19.8)	54.4 (7.2–139.4)
Month 3	253	57.9 (20.8)	54.7 (8.9–175.9)	0.077	252	53.2 (19.7)	51.9 (7.1–119.0)	0.430	256	54.5 (20.2)	52.2 (5.9–133.2)
Month 6	232	57.2 (19.9)	53.6 (6.4–138.4)	0.013	241	53.7 (18.6)	52.6 (7.2–137.5)	0.503	249	52.1 (18.0)	51.1 (6.8–111.2)
Month 7	214	58.6 (19.2)	55.6 (6.9–166.0)	0.016	205	55.7 (18.8)	52.9 (7.8–122.0)	0.369	229	54.0 (17.8)	52.6 (8.3–113.5)
Month 9	234	55.9 (18.2)	54.8 (5.8–131.5)	0.021	248	54.1 (18.8)	53.2 (8.9–145.5)	0.459	250	52.5 (17.5)	50.7 (6.3–127.8)
Month 12	245	56.3 (20.1)	55.3 (4.6–140.9)	0.057	244	55.0 (19.8)	53.8 (8.7–124.0)	0.480	248	54.4 (26.4)	50.8 (6.8–366.4)
eGFR (Nankivell) (mL/min)											
Month 12	192	65.8 (16.7)	64.7 (22.6–124.8)	0.030	182	64.0 (18.6)	65.6 (10.0–107.0)	0.161	208	62.6 (21.7)	61.6 (10.0–234.7)
Serum creatinine (μmol/L)											
Month 12	245	142.4 (108.3)	122.0 (47.0–1124.0)	0.073	244	141.1 (63.9)	129.5 (56.0–660.0)	0.970	248	142.2 (74.8)	128.0 (28.0–864.0)
Creatinine clearance (Cockcroft–Gault) (mL/min)											
Month 12	244	68.8 (23.3)	67.8 (8.8–137.9)	0.253	244	67.27 (23.7)	64.9 (11.6–153.2)	0.870	248	67.9 (25.7)	63.2 (10.5–205.3)

eGFR (MDRD) categories (mL/min/1.73 m^2)	Everolimus 1.5 mg (N = 277)			Everolimus 3.0 mg (N = 279)			MPA 1.44 g (N = 277)		
	<30	30–60	≥60	<30	30–60	≥60	<30	30–60	≥60
eGFR (MDRD) category at Month 1	19 (8.2)	108 (46.6)	105 (45.3)	20 (8.7)	112 (48.9)	97 (42.4)	16 (6.9)	129 (55.4)	88 (37.8)
eGFR achieved at Month 12 for patients in <30 category at Month 1	6 (31.6)	8 (42.1)	5 (26.3)	6 (30.0)	13 (65.0)	1 (5.0)	6 (37.5)	9 (56.3)	1 (6.3)
eGFR achieved at Month 12 for patients in 30–60 category at Month 1	6 (5.6)	82 (75.9)	20 (18.5)	8 (7.1)	85 (75.9)	19 (17.0)	5 (3.9)	107 (82.9)	17 (13.2)
eGFR achieved at Month 12 for patients in ≥60 category at Month 1	2 (1.9)	36 (34.3)	67 (63.8)	2 (2.1)	43 (44.3)	52 (53.6)	1 (1.1)	35 (39.8)	52 (59.1)

[1]On-treatment analyses; [2]Wilcoxon Rank–Sum test comparing everolimus and MPA values.

eGFR = glomerular filtration rate; ITT = intent-to-treat; MDRD = Modification of Diet in Renal Disease; MPA = mycophenolic acid; SD = standard deviation.

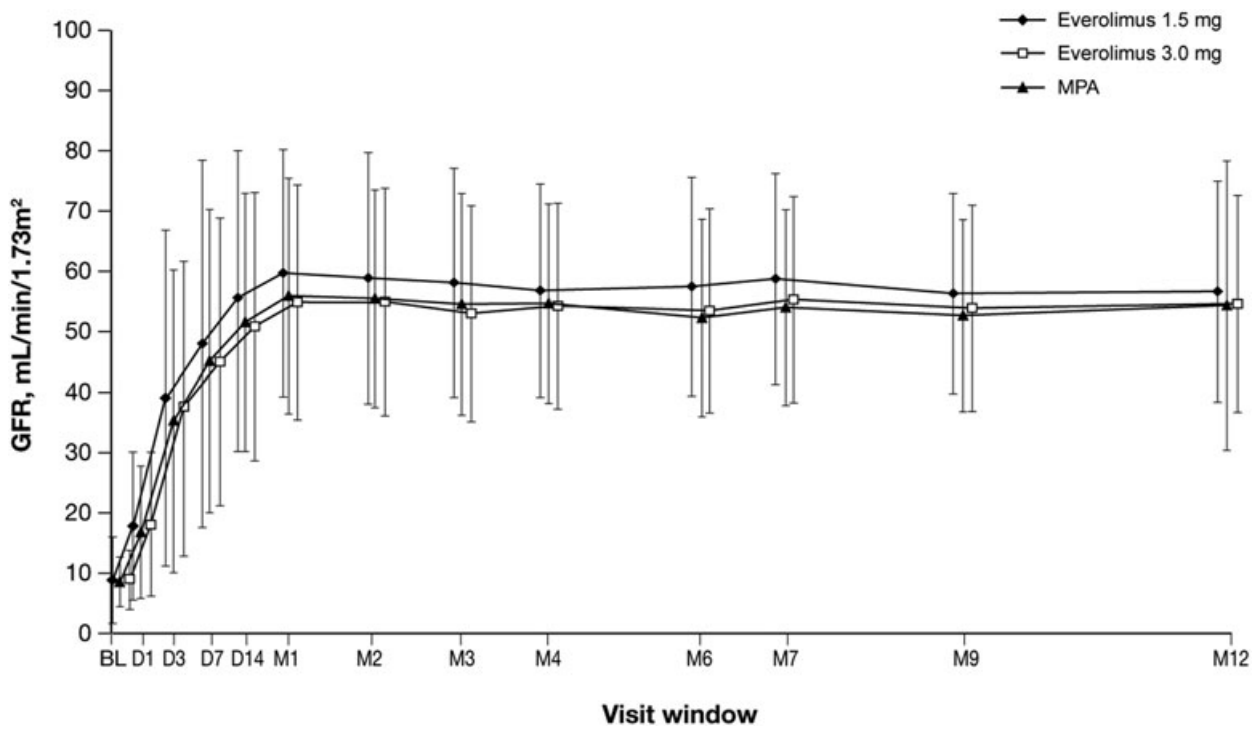

Figure 5: Mean calculated glomerular filtration rate (Modification of Diet in Renal Disease formula) over time by treatment group (intent-to-treat population; on-treatment values). On-treatment values include any assessment obtained no later than 2 days after discontinuation of study medication; mean eGFR was numerically higher (1.9 mL/min/1.73 m^2) in the everolimus 1.5 mg versus the MPA group at Month 12 with the mean increase from Months 1 to 12 ranging from 1.8–5.1 mL/min/1.73 m^2; eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; MPA = mycophenolic acid.

3.0 mg: 1.4% and 0.7%; and MPA: 4.4% and 2.2%, respectively).

Higher levels of proteinuria were observed early after transplantation and fell rapidly in the first month. Mean urinary protein:creatinine ratios at Month 12 were comparable in the everolimus 1.5 mg and MPA groups but higher in the everolimus 3.0 mg group. Nephrotic proteinuria was rare in all groups (Table 5). Severe proteinuria (assessed by the investigator) was infrequent (0.7%, 1.4% and 0.4% in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively) (Table 4).

Adverse wound-healing events were reported in 35.0%, 38.8% and 25.6% of patients in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively; 10.6%, 12.6% and 6.6% required surgical intervention. A greater proportion of wound-healing events were reported in patients in BMI categories >50th percentile. In the everolimus groups, wound-healing events were reported in 46–50% of patients with a BMI >75th percentile versus 27% of patients in the MPA group ($p < 0.05$; Chi-squared test).

The only system-organ class for which severe AEs were reported in >10% of patients was infections and infestations (5.8%, 10.1% and 7.3% in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively). Peripheral edema, headache and hyperlipidemia were reported as severe AEs by patients receiving everolimus but not MPA (peripheral edema: 2.6% and 1.4%; headache: 1.1% and 0.4%; and hyperlipidemia: 0.7% and 0.0%, in the everolimus 1.5 mg and 3.0 mg groups, respectively). High total cholesterol and triglyceride levels were more frequent in the everolimus versus MPA groups (Table 5) and lipid-modifying agents were prescribed to 64.6%, 72.3% and 57.5% of patients in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively. Low lymphocyte counts were the most commonly reported hematologic parameter; high and low WBC counts and low neutrophil counts were more frequently observed in the MPA versus everolimus groups.

There were seven (2.6%), nine (3.2%) and six (2.2%) deaths in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively. The main causes were cardiac disorders (four in each group), and infections and infestations (two, four and one in the everolimus 1.5 mg, 3.0 mg and MPA groups, respectively). Two deaths were suspected by the center investigator to be related to the study drug: malignant melanoma in the everolimus 1.5 mg group (the patient had a history of melanoma prior to transplantation) and chronic bronchopneumonia and congestive heart failure in the everolimus 3.0 mg group.

Table 4: Summary of adverse events over 12 months of treatment (safety population)

	Everolimus 1.5 mg (N = 274)	Everolimus 3.0 mg (N = 278)	MPA 1.44 g (N = 273)
Any AE	271 (98.9)	276 (99.3)	270 (98.9)
SAEs	155 (56.6)	168 (60.4)	147 (53.8)
Severe AEs	88 (32.1)	111 (39.9)	98 (35.9)
Any notable event[1]	165 (60.2)	183 (65.8)	155 (56.8)
AEs leading to study drug discontinuation[2]	64 (23.4)	79 (28.4)	43 (15.8)
AEs leading to study drug dose adjustment	61 (22.3)	75 (27.0)	95 (34.8)
Most frequently reported AEs and infections (≥20% of patients in any treatment group)[3]			
Blood and lymphatic system disorders	93 (33.9)	112 (40.3)	111 (40.7)
Anemia	70 (25.5)	86 (30.9)	68 (24.9)
Gastrointestinal disorders	196 (71.5)	208 (74.8)	207 (75.8)
Constipation	105 (38.3)	122 (43.9)	117 (42.9)
Nausea	79 (28.8)	80 (28.8)	85 (31.1)
Vomiting	40 (14.6)	48 (17.3)	60 (22.0)
General disorders and administration site conditions	181 (66.1)	185 (66.5)	160 (58.6)
Peripheral edema	123 (44.9)	120 (43.2)	108 (39.6)
Infections and infestations	169 (61.7)	178 (64.0)	185 (67.8)
Urinary tract infection	60 (21.9)	57 (20.5)	63 (23.1)
Investigations	137 (50.0)	120 (43.2)	133 (48.7)
Increased blood creatinine	48 (17.5)	52 (18.7)	59 (21.6)
Metabolism and nutrition disorders	222 (81.0)	233 (83.8)	199 (72.9)
Hyperkalemia	49 (17.9)	58 (20.9)	48 (17.6)
Hyperlipidemia	57 (20.8)	60 (21.6)	43 (15.8)
Vascular disorders	122 (44.5)	137 (49.3)	124 (45.4)
Hypertension[4]	81 (29.6)	76 (27.3)	82 (30.0)
AEs commonly ascribed to CsA treatment			
Tremor	23 (8.4)	22 (7.9)	38 (13.9)
Gingival hyperplasia	2 (0.7)	1 (0.4)	8 (2.9)
Gingival hypertrophy	3 (1.1)	2 (0.7)	6 (2.2)
Hirsutism	8 (2.9)	11 (4.0)	15 (5.5)
Renal and urinary disorders	112 (40.9)	143 (51.4)	124 (45.4)
AEs commonly associated with PSI/mTOR inhibitor treatment			
Hyperlipidemia[4]	57 (20.8)	60 (21.6)	43 (15.8)
Proteinuria	25 (9.1)	36 (12.9)	20 (7.3)
Severity			
Asymptomatic	1 (0.4)	1 (0.4)	0 (0.0)
Mild	15 (5.5)	18 (6.5)	14 (5.1)
Moderate	7 (2.6)	13 (4.7)	5 (1.8)
Severe	2 (0.7)	4 (1.4)	1 (0.4)
Mouth ulceration	9 (3.3)	14 (5.0)	5 (1.8)
Wound-healing event	96 (35.0)	108 (38.8)	70 (25.6)
Lymphocele	18 (6.6)	31 (11.2)	14 (5.1)
Impaired healing	5 (1.8)	11 (4.0)	3 (1.1)
Wound dehiscence	4 (1.5)	9 (3.2)	4 (1.5)

Data are n (%).

[1]Defined as death, nonfatal SAEs, AEs leading to discontinuation of study medication and adverse drop-out (drop-out due to AE, abnormal laboratory values, or abnormal test procedure results); [2]Patients with AEs leading to discontinuation of study medication may have had another reason cited as their primary reason for discontinuation (see Figure 1); [3]By primary system organ class and preferred term; [4]Data are included in both categories. The AE database was searched for potential wound-healing events, and additional information to determine the nature of these events was collected retrospectively, as outlined in the study protocol. This is the source for the wound-healing data presented here.

AE = adverse event; MPA = mycophenolic acid; mTOR = mammalian target of rapamycin; PSI = proliferation-signal inhibitor; SAE = serious adverse event.

Discussion

The A2309 study met its Month 12 primary endpoints: both everolimus groups showed similar and statistically noninferior outcomes to the MPA group with respect to primary efficacy failure and renal function. Efficacy and safety outcomes with everolimus treatment were maintained with CsA minimization of ∼50% and ∼60% versus the MPA group by Months 6 and 12, respectively.

Table 5: Laboratory abnormalities over 12 months of treatment (safety population, on-treatment analysis)

	Everolimus 1.5 mg (N = 274)	Everolimus 3.0 mg (N = 278)	MPA 1.44 g (N = 273)
Hemoglobin <6 g/dL	4 (1.5)	1 (0.4)	0 (0.0)
White blood cells			
$<2.1 \times 10^9$/L	3 (1.1)	7 (2.5)[1]	10 (3.7)[2]
$>15.9 \times 10^9$/L	69 (25.2)	67 (24.2)[1]	85 (31.3)[2]
Absolute neutrophils $<1.1 \times 10^9$/L	5 (1.8)	10 (3.6)	17 (6.3)
Absolute lymphocytes $<1.1 \times 10^9$/L	247 (90.1)	253 (91.3)	248 (91.2)
Eosinophils >11%	4 (1.5)	2 (0.7)	5 (1.8)
Platelets			
$<50 \times 10^9$/L	0 (0.0)	3 (1.1)[1]	1 (0.4)[2]
$>699 \times 10^9$/L	3 (1.1)	1 (0.4)[1]	1 (0.4)[2]
Lipids			
Cholesterol (total) >350 mg/dL	43 (15.7)	46 (16.5)	17 (6.3)[2]
Triglycerides >750 mg/dL	12 (4.4)	17 (6.1)	7 (2.6)[2]
High-density lipoprotein			
≥193–270 mg/dL	68 (26.3)[3]	95 (36.7)[3]	81 (31.0)[4]
>270 mg/dL	20 (7.7)[3]	13 (5.0)[3]	17 (6.5)[4]
Lipid-modifying agents	177 (64.6)	201 (72.3)	157 (57.5)
Glucose			
<2.5 mmol/L	25 (9.1)	16 (5.8)	31 (11.4)[2]
>13 mmol/L	39 (14.2)	42 (15.1)	46 (16.9)[2]
Urinary protein:creatinine ratio mg/g at Month 12			
Mean (SD)	35.6 (66.3)	61.4 (165.2)	31.1 (68.7)
<30 (normal)	1 (0.5)	1 (0.6)	4 (2.0)
30–<300 (mild)	134 (71.3)	122 (68.5)	158 (77.1)
300–<3000 (subnephrotic)	46 (24.5)	44 (24.7)	26 (12.7)
≥3000 (nephrotic)	2 (1.1)	6 (3.4)	4 (2.0)

Data are mean n (%) unless otherwise stated.
Abnormality criteria were predefined.
[1]n = 277; [2]n = 272; [3]n = 259; [4]n = 261.
MPA = mycophenolic acid.

Attempts to minimize CNI nephrotoxicity by reducing or eliminating CNIs from immunosuppressive regimens have often been limited by an increase in acute rejection (19–21). Building upon previous data (8,12,13,22), this study demonstrated that everolimus with RD-CsA was as effective as MPA plus ST-CsA in preventing BPARs; graft and patient survival rates were also comparable between groups. Patients in the 3.0 mg everolimus group (targeted to 6–12 ng/mL) had the lowest BPAR rates while the time to BPAR as estimated by the K–M analysis was similar between groups. The incidence of ≥Banff IIA BPARs was numerically lower with the everolimus versus MPA regimens. The incidence of AEs commonly associated with CNI exposure—tremor, hirsutism, gingival hyperplasia and hypertrophy—were lower in the everolimus groups. These differences are potentially attributable to everolimus-facilitated CNI minimization.

Previous studies showed that compared with MPA, patients receiving everolimus with ST-CsA display worse renal function at the end of the first year (6,9). These differences are due to a clinically recognized drug–drug synergistic mechanism between PSIs/mTORs and CsA. In the A2309 study, mean eGFR at Month 12 was similar between groups (MDRD; LOCF analyses), although the everolimus 1.5 mg regimen (targeted to 3–8 ng/mL) was associated with numerically higher mean and median eGFR versus the MPA regimen at Month 1, which persisted over 12 months (on-treatment analyses). These data were supported by sensitivity analyses including LOCF for patients who died or experienced graft loss prior to Month 12, and different methods of calculating renal function. As improvements in 12-month eGFR are associated with improvements in long-term graft function (2–4,23), these findings are clinically significant. In addition, categorizing eGFR by NKF categories demonstrated that a greater proportion of patients in the everolimus 1.5 mg group (targeted to 3–8 ng/mL) achieved eGFR ≥60 mL/min/1.73 m^2 at Month 12 versus the 3.0 mg and MPA groups. Also, a greater proportion of patients with eGFR in the <30 or 30–60 mL/min/1.73 m^2 NKF categories at Month 1 experienced improvement in their renal function to eGFR ≥60 mL/min/1.73 m^2 by Month 12.

The overall safety profile of everolimus was similar to that seen in previous studies (8,11–14); approximately 50 000 patient-years of everolimus experience now exists (24). AEs associated with everolimus treatment appear to be dose related, indicating that a trough level targeted to 3–8 ng/mL has the optimal benefit:risk profile.

A greater proportion of patients in the everolimus versus MPA groups discontinued study drug due to an AE. These differences were most likely due to the study's open-label design; investigators are likely to have a lower threshold for discontinuing everolimus treatment due to unfamiliarity with this drug. In addition, study-drug discontinuation as a result of an AE is unlikely with MPA, as viable alternatives are not available. In contrast, a lower number of patients required dose reduction due to an AE in the everolimus groups versus the MPA group and, in total, the incidence of patients discontinuing plus those requiring study-drug adjustment due to an AE was lower in the everolimus 1.5 mg compared with the 3.0 mg and MPA groups. A *post hoc* regression analysis demonstrated that there was no significant relationship between the everolimus trough level and the rate of discontinuation (data not shown).

Certain AEs are more prevalent with mTOR inhibitors/PSIs, namely hematologic disorders, wound-healing events, hyperlipidemia and proteinuria. A higher incidence of wound-healing events was observed with everolimus versus MPA treatment with the highest percentage in the everolimus 3.0 mg (targeted to 6–12 ng/mL) group. The incidence of impaired-healing events and wound dehiscence were similar between the MPA and everolimus 1.5 mg (targeted to 3–8 ng/mL) groups. Higher BMI is a well-known factor associated with wound-healing complications (25–27) and, as expected, patients with a BMI >75th percentile in the everolimus groups had a higher number of wound-healing events. In contrast, only 27% of wound-healing events occurred in the >75th percentile in the MPA group. A lower incidence of leukopenia was observed in the everolimus groups, while the incidence of anemia and thrombocytopenia were similar in all groups. Total cholesterol values and the use of lipid-modifying agents were higher in the everolimus groups; these events were seldom reported as SAEs and rarely led to study-drug discontinuation. In addition, proteinuria was reported in a greater proportion of patients in the everolimus 3.0 mg versus 1.5 mg and MPA groups; severe proteinuria was infrequent in all groups.

A lower incidence of infections, particularly BK virus and CMV were observed with everolimus versus MPA treatment. The reduced incidence of CMV infections in the present study is consistent with other clinical trials of everolimus versus azathioprine and MMF in *de novo* renal-transplant recipients (10,28). The incidence of CMV syndrome and CMV disease was also lower in the everolimus versus MPA groups. A lower incidence of neoplasms was observed in the everolimus versus MPA groups with the only case of melanoma (everolimus 1.5 mg group; targeted to 3–8 ng/mL) being a recurrence of a pretransplantation event. These trends are consistent with the antiproliferative effects of everolimus and its FDA approval for advanced renal-cell carcinoma treatment after vascular endothelial growth-factor-receptor inhibitor failure.

Several limitations should be considered when interpreting these results. Some inaccuracy in AE reporting is perhaps inevitable when assessed by individual investigators, with AEs generally being underreported; however, investigators may be more likely to report AEs in an open-label trial including an unfamiliar drug, which may partially explain the higher discontinuation rate ascribed to AEs in patients in the everolimus versus MPA groups. Since the study population was at low immunological-risk and a majority of patients were Caucasian with low PRA levels, these results may not be directly transferable to other transplant populations. In addition, noninferiority studies determine that the study-drug-group response is noninferior to the control but do not test for clinical differences. Lastly, although the degree of proteinuria did not differ between the everolimus 1.5 mg (targeted to 3–8 ng/mL) versus the MPA groups, these results are based on 12-month data and further follow-up is required.

In conclusion, the Month 12 outcomes from the A2309 study, the largest registration trial of everolimus in renal transplantation to date, showed that everolimus targeted to 3–8 ng/mL plus RD-CsA was as effective as MPA plus ST-CsA with the best benefit-to-risk profile. CsA minimization facilitated by everolimus treatment is a viable option in the treatment of *de novo* renal-transplant recipients that maintains efficacy and safety and has the potential to offer long-term improvements in renal function. Results at 2 years will provide additional information on the long-term safety of these regimens.

Acknowledgments

The authors would like to thank the study investigators and coordinators for their hard work in making this study possible, and Caroline Barnett and Nina Heath of Purple Hat Communications Ltd for medical-writing support on behalf of Novartis.

Funding sources: This study was funded by Novartis Pharma AG, Basel, Switzerland.

Author disclosures: The authors disclose the following relevant financial relationships: Helio Tedesco Silva Jr has received grant/research support from Novartis, Astellas, Janssen-Cilag, Bristol-Myers Squibb and Wyeth, payment for scientific advice from Novartis and honoraria from Novartis, Astellas, Janssen-Cilag, Bristol-Myers Squibb and Wyeth; Diane Cibrik is a scientific advisor for Novartis, Pfizer and Tolera Therapeutics; Thomas Johnston and Eva Lackova have nothing to declare; Kevin Mange and Charlotte Panis are Novartis Pharmaceuticals Corporation employees and have stock options; Rowan Walker has previously served or is currently serving as a consultant for Novartis, Janssen-Cilag, Roche and Wyeth; Zailong Wang is an employee of Novartis Pharmaceuticals Corporation; and Yu Seun Kim has received grants from Astellas, Novartis, Wyeth, Pfizer and Roche.

Study Investigators

Argentina: P Novoa, R Schiavelli, L Toselli; Australia: S Campbell, S Chadban, B Hutchinson, J Kanellis, P O'Connell, B Pussell, G Russ, R Walker; Brazil: D Carvalho, V Garcia, L Soares, H Tedesco Silva; Canada: M Walsh;

Hong Kong: CS Li; Italy: A Albertazzi, M Carmellini, G Civati, G Colussi, F Schena; Korea: H Duck Jong, SJ Kim, YH Kim, YL Kim, YS Kim, IS Moon; New Zealand: H Pilmore; Slovakia: E Lackova, R Roland; Singapore: T Kee; South Africa: S Naicker; Sweden: G Tufveson; Taiwan: PH Lee; Turkey: E Akin, K Keven, A Uslu; United Kingdom: Y Magdi, H Riad, J Pattison; United States of America: S Abul-Ezz, E Alfrey, K Andreoni, M Aaronson, P Baliga, Y Becker, P Bolin, L Chan, DM Cibrik, M Cooper, A Cotterell, C Foster, C Franklin, S Jensik, TD Johnston, B Kahan, D Katz, D Kim, M Kumar, PC Kuo, J Leone, M Levy, B Marder, B Mistry, S Mulgaonkar, LL Mulloy, T O'Connor, PT Pham, K Rice, V Scantlebury, B Sankari, R Santella, H Shidban, F Shihab, D Slakey, RB Stevens, JR Thistlewaite, JD Welchel, CT Van Buren, N Youssef, C Zayas, G Zibari.

References

1. Chapman JR, Valantine H, Albanell J et al. Proliferation signal inhibitors in transplantation: Questions at the cutting edge of everolimus therapy. Transplant Proc 2007; 39: 2937–2950.
2. Salvadori M, Rosati A, Bock A et al. Estimated one-year glomerular filtration rate is the best predictor of long-term graft function following renal transplant. Transplantation 2006; 81: 202–206.
3. Helal I, Abderrahim E, Ben HF et al. The first year renal function as a predictor of long-term graft survival after kidney transplantation. Transplant Proc 2009; 41: 648–650.
4. Resende L, Guerra J, Santana A, Mil-Homens C, Abreu F, da Costa AG. First year renal function as a predictor of kidney allograft outcome. Transplant Proc 2009; 41: 846–848.
5. Schuler W, Sedrani R, Cottens S et al. SDZ RAD, a new rapamycin derivative: Pharmacological properties in vitro and in vivo. Transplantation 1997; 64: 36–42.
6. Lorber MI, Mulgaonkar S, Butt KM et al. Everolimus versus mycophenolate mofetil in the prevention of rejection in de novo renal transplant recipients: A 3-year randomized, multicenter, phase III study. Transplantation 2005; 80: 244–252.
7. Tedesco-Silva H, Jr, Vitko S, Pascual J et al. 12-month safety and efficacy of everolimus with reduced exposure cyclosporine in de novo renal transplant recipients. Transpl Int 2007; 20: 27–36.
8. Vitko S, Tedesco H, Eris J et al. Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. Am J Transplant 2004; 4: 626–635.
9. Vitko S, Margreiter R, Weimar W et al. Three-year efficacy and safety results from a study of everolimus versus mycophenolate mofetil in de novo renal transplant patients. Am J Transplant 2005; 5: 2521–2530.
10. Vitko S, Margreiter R, Weimar W et al. Everolimus (Certican) 12-month safety and efficacy versus mycophenolate mofetil in de novo renal transplant recipients. Transplantation 2004; 78: 1532–1540.
11. Nashan B, Curtis J, Ponticelli C, Mourad G, Jaffe J, Haas T. Everolimus and reduced-exposure cyclosporine in de novo renal-transplant recipients: A three-year phase II, randomized, multicenter, open-label study. Transplantation 2004; 78: 1332–1340.
12. Chan L, Greenstein S, Hardy MA et al. Multicenter, randomized study of the use of everolimus with tacrolimus after renal transplantation demonstrates its effectiveness. Transplantation 2008; 85: 821–826.
13. Pascual J. Concentration-controlled everolimus (Certican): Combination with reduced dose calcineurin inhibitors. Transplantation 2005; 79: S76–S79.
14. Kovarik JM, Tedesco H, Pascual J et al. Everolimus therapeutic concentration range defined from a prospective trial with reduced-exposure cyclosporine in de novo kidney transplantation. Ther Drug Monit 2004; 26: 499–505.
15. Racusen LC, Colvin RB, Solez K et al. Antibody-mediated rejection criteria – an addition to the Banff 97 classification of renal allograft rejection. Am J Transplant 2003; 3: 708–714.
16. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003; 41: 1–12.
17. Nankivell BJ, Gruenewald SM, Allen RD, Chapman JR. Predicting glomerular filtration rate after kidney transplantation. Transplantation 1995; 59: 1683–1689.
18. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988; 75: 800–802.
19. Frimat L, Cassuto-Viguier E, Charpentier B et al. Impact of cyclosporine reduction with MMF: A randomized trial in chronic allograft dysfunction. The 'reference' study. Am J Transplant 2006; 6: 2725–2734.
20. Grinyo JM, Cruzado JM. Mycophenolate mofetil and sirolimus combination in renal transplantation. Am J Transplant 2006; 6: 1991–1999.
21. Pascual M, Curtis J, Delmonico FL et al. A prospective, randomized clinical trial of cyclosporine reduction in stable patients greater than 12 months after renal transplantation. Transplantation 2003; 75: 1501–1505.
22. Lorber MI, Ponticelli C, Whelchel J et al. Therapeutic drug monitoring for everolimus in kidney transplantation using 12-month exposure, efficacy, and safety data. Clin Transplant 2005; 19: 145–152.
23. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int 2002; 62: 311–318.
24. Novartis Pharma AG. Data on file. 2009.
25. Pedotti P, Cardillo M, Rigotti P et al. A comparative prospective study of two available solutions for kidney and liver preservation. Transplantation 2004; 77: 1540–1545.
26. Tiong HY, Flechner SM, Zhou L et al. A systematic approach to minimizing wound problems for de novo sirolimus-treated kidney transplant recipients. Transplantation 2009; 87: 296–302.
27. Valente JF, Hricik D, Weigel K et al. Comparison of sirolimus vs mycophenolate mofetil on surgical complications and wound healing in adult kidney transplantation. Am J Transplant 2003; 3: 1128–1134.
28. Dunn C, Croom KF. Everolimus: A review of its use in renal and cardiac transplantation. Drugs 2006; 66: 547–570.

Supporting Information

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

Table S1: Target ranges for CsA trough levels

Table S2: Everolimus and CsA dose and trough levels by study visit (safety population)

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.