At ASTS, transplant is more than your CAREER.
It's your PASSION.

ASTS IS YOUR VOICE

Join. Connect. Succeed.

Learn more at ASTS.org.

ASTS

American Society of Transplant Surgeons®

American Journal of Transplantation 2014; 14: 2796–2806
Wiley Periodicals Inc.

doi: 10.1111/ajt.12955

Novel Once-Daily Extended-Release Tacrolimus (LCPT) Versus Twice-Daily Tacrolimus in *De Novo* Kidney Transplants: One-Year Results of Phase III, Double-Blind, Randomized Trial

K. Budde[1,*], S. Bunnapradist[2], J. M. Grinyo[3], K. Ciechanowski[4], J. E. Denny[5], H. T. Silva[6] and L. Rostaing[7] and on behalf of the Envarsus study group

[1]*Department of Nephrology, Charité Universitätsmedizin, Berlin, Germany*
[2]*David Geffen School of Medicine at UCLA, Los Angeles, CA*
[3]*Department of Nephrology, Hospital Universitari de Bellvitge, Catalunya, Spain*
[4]*Department of Nephrology and Transplantation, Pomeranian Medical University, Szczecin, Poland*
[5]*Henry Ford Transplant Institute, Henry Ford Hospital, Detroit, MI*
[6]*Department of Nephrology, Hospital do Rim e Hipertensao, Sao Paulo, Brazil*
[7]*Department of Nephrology and Transplantation, University Hospital Toulouse-Rangueil, Toulouse, France*
[*]*Corresponding author: Klemens Budde, klemens.budde@charite.de*

This Phase III randomized trial examined efficacy and safety of a novel once-daily extended-release tacrolimus formulation (LCP-Tacro [LCPT]) versus twice-daily tacrolimus in *de novo* kidney transplantation. Primary efficacy end point was proportion of patients with treatment failure (death, graft failure, biopsy-proven acute rejection or lost to follow-up) within 12 months. Starting doses were, LCPT: 0.17 mg/kg/day and tacrolimus twice-daily: 0.1 mg/kg/day; 543 patients were randomized, LCPT: n = 268; tacrolimus twice-daily: n = 275. At 12 months treatment failure was LCPT: 18.3% and tacrolimus twice-daily: 19.6%; the upper 95% CI of the treatment difference was +5.27%, below the predefined +10% noninferiority criteria. There were no significant differences in the incidence of individual efficacy events or adverse events. Target tacrolimus trough levels were more rapidly achieved in the LCPT group. Following initial dose, 36.6% of patients in the LCPT group had rapidly attained trough levels within 6–11 ng/mL versus 18.5% of tacrolimus twice-daily patients; majority of tacrolimus twice-daily patients (74.7%) had troughs <6 ng/mL compared with 33.5% in the LCPT group. Overall, cumulative study dose was 14% lower for LCPT. Results suggest that use of once-daily LCPT in *de novo* kidney transplantation is efficacious and safe. Lower LCPT dose reflects the improved absorption provided by the novel formulation.

Abbreviations: AE, adverse event; AUC, area under the curve; BCS, Biopharmaceutics Classification System; BPAR, biopsy-proven acute rejection; CI, confidence interval; CMH, Cochran Mantel Haenszel; C_{min}, minimum concentration; CNI, calcineurin inhibitor; DGF, delayed graft function; ECG, electrocardiogram; eGFR, estimated GFR; FDA, Food and Drug Administration; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; ITT, intent-to-treat; KDIGO, Kidney Disease: Improving Global Outcomes; LCPT, LCP-Tacro; MDRD, modification of diet in renal disease; mITT, modified ITT; MMF, mycophenolate mofetil; NODM, new-onset diabetes mellitus; PK, pharmacokinetic; PRA, panel reactive antibody; SAE, serious adverse event; TDD, total daily dose; US, United States; UTI, urinary tract infection

Received 22 May 2014, revised 11 July 2014 and accepted for publication 23 July 2014

Introduction

Tacrolimus twice-daily capsules (Prograf®; Astellas Pharma US, Inc., Northbrook, IL) are highly effective in preventing acute rejection after kidney transplantation (1). As such, tacrolimus is used as part of the immunosuppression regimen for the majority of kidney transplant recipients, both early posttransplantation and as part of long-term maintenance regimens (2); and is recommended in the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the care of kidney transplant recipients (3).

Tacrolimus is considered a Narrow Therapeutic Index drug that requires individual dose titration to achieve a satisfactory balance between maximizing efficacy and mininimizing dose-related toxicity (4). In clinical practice, drug monitoring is necessary to facilitate tacrolimus dose titration. Variable patient absorption, interaction with food and concomitant medications and the low bioavailability of tacrolimus from the tacrolimus twice-daily formulation (17 ± 10%) in adult

kidney transplant patients complicate the management of tacrolimus blood levels (5). High intra-individual variability and variable drug exposure are associated with increased risk for graft deterioration and loss (6). In addition, multiple-daily dosing is associated with an increased risk for nonadherence (7–9), which can lead to acute rejection (10) and, in serious cases, graft failure (11). Therefore, a once-daily tacrolimus-dosing regimen could potentially positively affect patient medication adherence.

LCP-Tacro (LCPT) tablets (Envarsus®; Veloxis Pharmaceuticals, Hørsholm, Denmark) is an extended-release formulation of tacrolimus designed for once-daily administration. A hallmark differentiation between LCPT and other forms of once- and twice-daily tacrolimus products is the proprietary MeltDose® drug delivery technology (Veloxis Pharmaceuticals). MeltDose® is designed to improve the bioavailability of drugs with low water solubility (i.e. Biopharmaceutics Classification System [BCS] Class II compounds) (12). Drug particle size is a crucial aspect affecting drug dissolution and absorption. The smaller the particle size, the greater the surface area of the drug and the faster the drug will be dissolved resulting in better absorption. MeltDose® is a clinically validated formulation technology that is able to decrease a drug's particle size to a molecular level; the particles are broken down into the smallest possible units as single molecules or what is referred to as a ''solid solution'' (13). This occurs by heating the active pharmaceutical ingredient (i.e. tacrolimus), to create a ''MELT'' solution. Using a patented nozzle, the atomization of the drug occurs and is sprayed on an inert particulate carrier. The drug and carrier solidifies in a state of ''solid solution'' that results in a granulate. The granulate is then compressed into tablets where the dissolution profile and particle size remain stable. Phase I and Phase II trials confirmed that LCPT enables broader absorption in the gastro-intestinal tract and sustains consistent tacrolimus concentrations (14), even in patients that may be poor absorbers or rapid metabolizers (data on file). In addition, LCPT showed similar pharmacokinetics (PK) regardless if administered in the morning or evening (15).

Clinically, Phase II trials of *de novo* and stable renal (16,17) and liver recipients (18,19) showed a steadier and more consistent concentration time profile over 24 h, reduced peak and peak-to-trough fluctuations for LCPT compared to Prograf®, with an increased bioavailability of approximately 30%, few treatment failures and a good safety profile. The greater bioavailability of LCPT allows for once-daily dosing and enables a lower drug dose to achieve similar systemic exposure and trough levels as twice-daily tacrolimus. A robust correlation between area under the curve $(AUC)_{24}$ and minimum concentration (C_{min}) with LCPT was also shown, indicating that therapeutic drug monitoring of C_{min} as a measure of tacrolimus exposure can be applied to LCPT. Furthermore, in a Phase III conversion trial, LCPT showed noninferior efficacy and similar safety to twice-daily tacrolimus, with lower doses (~30% less) of LCPT (20). That study also demonstrated that LCPT is safe and efficacious in the traditionally higher risk black kidney transplant recipients, whom also benefited from lower doses of LCPT (~15% less) compared to twice-daily tacrolimus.

The primary objective of the present study was to evaluate the efficacy and safety of LCPT tablets compared to twice-daily tacrolimus capsules for prevention of acute allograft rejection in the first 12 months posttransplant in adult *de novo* renal transplant recipients in a randomized, double-blind, double-dummy study.

Methods

Study design and conduct

This was a two-armed, parallel group, prospective, randomized, double-blind, double-dummy, multicenter, Phase III trial (ClinicalTrials.gov: NCT01187953). *De novo* kidney transplant recipients were randomly assigned to study treatment in a 1:1 ratio, using a fixed-block randomization scheme via an interactive, automated system. Randomization was stratified by site and recipient race (black vs. nonblack). The randomization scheme was generated before the initiation of the study by an independent statistician/programmer who was not a member of the study team. The duration for the entire study was 24 months. However, the primary end point was efficacy and safety at 12 months. The 12-month data are currently available and reported here.

Health Authority, Ethics Committee and Institutional Review Board approval was obtained at each participating center and informed consent was obtained from all patients. The study was undertaken in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice and conformed to the Declaration of Helsinki.

Patient population

Eligible patients were adult (≥18 years) *de novo* recipients of a living or deceased donor kidney transplant (except for donation after cardiac death). Major exclusion criteria included: recipients of another organ or a bone marrow transplant; patients with a panel reactive antibody (PRA) >30%; patients with a BMI <18 kg/m^2 or >40 kg/m^2; patients who received or expected to receive sirolimus, everolimus, azathioprine or cyclophosphamide within 3 months before enrollment; or patients with laboratory variables that were abnormal (outside laboratory reference range) and clinically relevant, as judged by the investigator.

Study drug dosing

Patients were randomly assigned to receive LCPT tablets, once daily, orally; provided in 0.75, 1.0 and 4.0 mg dosage strengths or tacrolimus (Prograf®) capsules twice-daily, orally; provided in 0.5, 1 and 5 mg dosage strengths. All patients also received matching double-dummy placebo to maintain the blind. LCPT was started at 0.17 mg/kg/day given as a single morning dose. PK data from a Phase II study in *de novo* kidney transplant patients demonstrated that a starting dose of 0.17 mg/kg/day is an appropriate starting dose for LCPT. According to product labeling, tacrolimus twice-daily was started at a total daily dose (TDD) of 0.1 mg/kg/day, given as two equally divided doses 12 h apart (one in the morning before noon and one in the evening) (5). The sites were recommended to not do any dose adjustments during the first 48 h after the initial dose. Subsequent doses of each study drug were adjusted to maintain trough concentrations of tacrolimus in whole blood within the target range of 6–11 ng/mL for the first 30 days, then 4–11 ng/mL for the remainder of the study.

All patients also received mycophenolate mofetil (MMF; 2 g/day) and an IL-2 receptor antagonist (Simulect®, basiliximab; Novartis Pharmaceuticals, East Hanover, NJ) based on product labeling, and corticosteroids per local practice.

Study end points

Primary efficacy: The primary efficacy endpoint was the incidence of treatment failures within 12 months after the randomization date. Treatment failure was a composite end point that included any of the following events: death, graft failure, biopsy-proven acute rejection (BPAR) (Banff Grade $\geq$1A, using Banff 2007 criteria; based on biopsy reading from a blinded central pathologist), or lost to follow-up.

Secondary efficacy: The incidence of each event (death, graft failure, BPAR and death or graft failure) within 12 months after the randomization date was secondary efficacy end points.

Safety: The safety end points at the 12-month visit included: incidence of adverse events (AEs), serious AEs (SAEs) and discontinuations due to AEs; incidence of predefined potentially clinically significant laboratory values; new-onset diabetes mellitus (NODM); incidence of posttransplant lymphoproliferation disorder; mean change from baseline (Day 30) in estimated creatinine clearance by using the estimated GFR (eGFR; MDRD7 formula) at Months 3, 6 and 12; change in clinical laboratories and vital signs at each time point; incidence of 12-lead electrocardiograms (ECGs) clinical findings at each time point; mean change from baseline (Day 30) in hemoglobin A1c (HbA1c) at Days 90, 180 and 360; incidence of opportunistic infections, including cytomegalovirus; and, any malignancy or BK virus diseases. Mean dose of study drug and mean tacrolimus whole blood trough level (collected at each postrandomization scheduled and unscheduled visit) were also *a priori* safety outcomes; these results are reported under the results section ''immunosuppression.'' A Central Laboratory used validated methods for assessing tacrolimus levels in human whole blood using high-performance liquid chromatography and triple stage quadrupole tandem mass spectrometry. Dose adjustments to maintain tacrolimus whole blood trough levels were based on local laboratory determinations. As prespecified in the study protocol, the analysis of NODM was restricted to patients without diabetes at baseline and to patients with no medical history of diabetes, a baseline fasting plasma glucose $<$126 mg/dL, no prior use of hypoglycemic agent for diabetes conditions, no prior use of insulin for diabetes conditions, or a HbA1c $<$6.5% before transplant.

Statistical analysis

Sample size determination: Based on an expected treatment failure rate of 15% at 1 year, 270 patients per group would be required to have 90% power to reject the null hypothesis that LCPT was inferior to tacrolimus twice-daily based on a two-sided 95% confidence interval (CI) and a 0.10 noninferiority margin.

The study design and vigorous 10% noninferiority margin was decided upon in pretrial collaboration with the US Food and Drug Administration (FDA).

Analysis method: The noninferiority of LCPT to tacrolimus twice-daily with respect to treatment failure within 12 months was assessed using a two-sided 95% CI based on the difference (LCPT minus tacrolimus twice-daily) in treatment failure rates between the treatment groups at 12 months. The 95% confidence limits for the difference in treatment failure rates were calculated using the Newcombe–Wilson score method. If the upper bound of the 95% CI for the difference in treatment failure rates was less than 0.10, then LCPT was considered noninferior to tacrolimus twice-daily.

The incidence of clinically suspected and treated acute rejection episodes, and the incidence of BPAR episodes, was compared between treatment groups using a Fisher exact test. A two-sided 95% CI for the difference was constructed using the Newcombe–Wilson score method. In addition, the association between treatment and severity grade of the first episode of BPAR was assessed using the Cochran Mantel Haenszel test for general association.

Differences between treatment groups in time-to-event distributions were evaluated using log rank tests. Baseline characteristics and treatment emergent AEs were tabulated by treatment.

Results

The study was initiated on October 13, 2010; all randomized subjects completed 12-month visit by March 20, 2013 at 68 sites (n = 31 US, n = 13 Latin America, n = 15 Europe, n = 9 Asia Pacific).

Patient disposition and baseline characteristics

A total of 601 patients entered the study, of which 58 were screen failures and 543 patients were randomly assigned to the study drug (intent-to-treat [ITT] population; LCPT: n = 268; tacrolimus twice-daily: n = 275); two patients in the LCPT group and four patients in the tacrolimus twice-daily group were randomly assigned but not dosed. Overall, 425 patients completed the 12-month treatment period (LCPT, n = 206; tacrolimus twice-daily, n = 219) (Figure 1).

Demographic characteristics were similar between the treatment groups. The patient population was predominately white (77%) and male (65%); mean age was 45.8 years (Table 1).

Immunosuppression

The mean duration of study drug exposure was similar in both treatment groups (333.5 and 334.5 days in the LCPT and twice-daily tacrolimus groups, respectively). The majority of patients in both groups received study drug for at least 331 days (78.4% and 80.0% of the LCPT and twice-daily tacrolimus groups, respectively).

Tacrolimus dose and trough level

In the first week of dosing, TDDs were higher in the patients in the LCPT group compared with the tacrolimus twice-daily group, and were similar in both treatment groups from Day 10 through Week 3. From Week 3 onward, TDDs were lower for the LCPT group and the difference between the two groups increased over time. TDDs were 6.9% and 18.3% lower in the LCPT versus tacrolimus twice-daily group at 30 days and 12 months, respectively. The cumulative dose over the entire study period was 14.3% lower in the LCPT group as a result (LCPT: 1659.5 mg; tacrolimus twice-daily: 1935.8 mg).

Following the initial study drug dose, 36.6% of patients in the LCPT group and 18.5% of patients in the tacrolimus twice-daily group were within the target tacrolimus trough range of

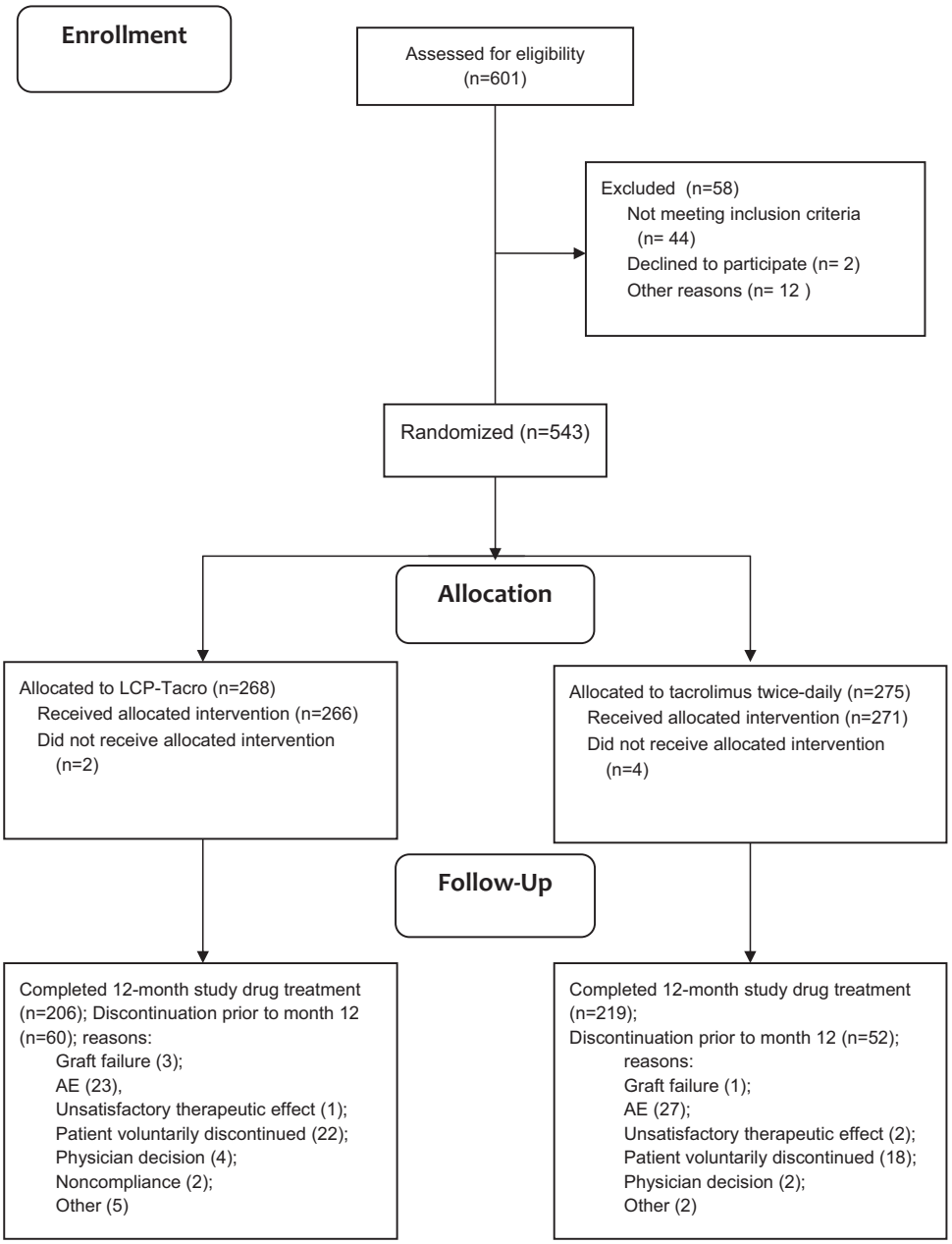

Figure 1: Patient disposition.

6–11 ng/mL; the majority of tacrolimus twice-daily patients (74.7%) had trough levels less than 6 ng/mL compared with 33.5% in the LCPT group; and 29.9% of patients in the LCPT group and 6.7% of patients in the tacrolimus twice-daily group had levels greater than 11 ng/mL. Tacrolimus trough levels were notably higher in the LCPT group compared with the tacrolimus twice-daily group in the first 2 weeks after dosing; thereafter, trough levels in the two groups were similar through Month 12 (Figure 2).

The analysis of trough/dose ratio demonstrated (Figure 3) from Day 2 through Month 12, an increasing trough/dose ratio; reflecting the improved absorption provided by the MeltDose® formulation. The difference between LCPT and tacrolimus twice-daily was statistically significant (p 0.02) at all time points, except Week 3. This is apparent over time as the dose decreases but the trough level remains stable and similar to that of tacrolimus twice-daily. At Month 12, the mean TDD was 4.09 mg for LCPT and 5.01 mg for tacrolimus

Table 1: Patient demographics and baseline characteristics—modified intent-to-treat set

	LCP-Tacro (N = 268)	Tacrolimus twice-daily (N = 275)
Age (years), mean (SD)	44.8 (13.29)	46.9 (14.26)
Sex, n (%)		
Male	174 (64.9)	181 (65.8)
Female	94 (35.1)	94 (34.2)
Race, n (%)		
White	203 (75.7)	214 (77.8)
Black	10 (3.7)	15 (5.5)
Asian	10 (3.7)	10 (3.6)
Other	45 (16.8)	36 (13.1)
Previous transplant, n (%)	11 (4.1)	11 (4.0)
Donor type, n (%)		
Living	135 (50.4)	129 (46.9)
Deceased	133 (49.6)	145 (52.7)
Missing	0	1 (0.4)
PRA (%), mean (SD)	1.5 (5.10)	1.5 (5.98)
PRA <5%, n (%)	243 (90.7)	253 (92.0)
Diabetes at the time of transplant, n (%)	50 (18.7)	56 (20.4)
Time from transplant to first study drug dose (h), mean (SD)	34.15 (8.9)	34.38 (9.7)

PRA, panel reactive antibody.

twice-daily; the mean trough level was 6.50 ng/mL for both groups. The absorption (i.e. bioavailability) per mg was higher in LCPT group than in the tacrolimus twice-daily group ($p < 0.0001$).

Primary efficacy end point

The overall incidence of treatment failure was 18.3% for patients in the LCPT group and 19.6% for patients in the tacrolimus twice-daily group. The treatment difference (95% CI) was −1.35% (−7.94% to +5.27%), well below the noninferiority margin of 10%. No statistically significant difference was observed between the LCPT and tacrolimus twice-daily treatment groups for the incidence of all-cause mortality ($p > 0.999$), graft failure ($p = 0.821$), BPAR ($p = 0.900$), or lost to follow-up ($p > 0.999$) (Table 2).

Secondary efficacy end points

No statistically significant treatment differences were observed in the occurrences of treatment failure, graft failure, BPAR or lost to follow-up when analyzed by categorical time of occurrence ($p = 0.124$). Although, within the first 3 months posttransplant, treatment failure was numerically lower for LCPT: 10% versus twice-daily tacrolimus: 14% ($p = 0.195$) (Table 2).

No statistically significant difference was observed between the two treatment groups in time-to-event distribution during the first 12 months by log-rank test: treatment failure (Figure 2) ($p = 0.632$) and first episode of BPAR ($p = 0.852$). Overall patient survival was 97.0% versus

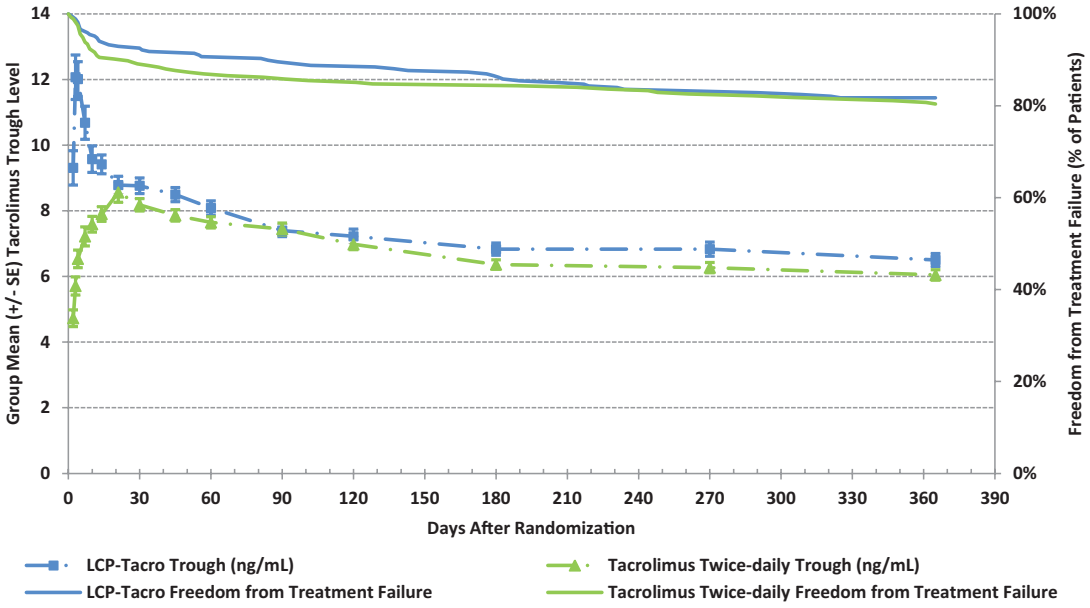

Figure 2: Mean tacrolimus trough levels and Kaplan–Meier freedom from treatment failure over the study period, LCP-Tacro versus tacrolimus twice-daily.

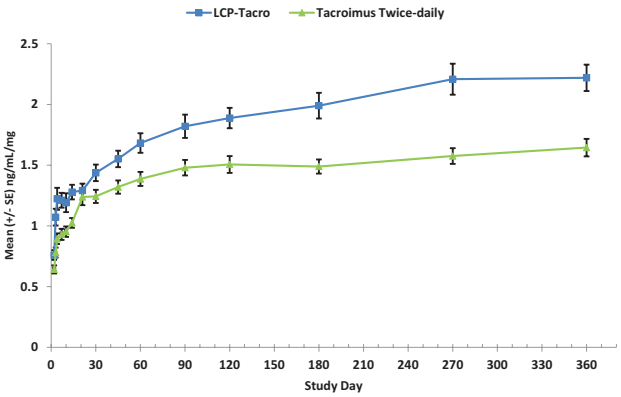

Figure 3: Tacrolimus trough level (ng/mL) achieved per total daily dose (mg) (modified intent-to-treat set).

97.1% (p = 0.982); graft survival was 96.6% versus 96.0% (p = 0.684); and graft and patient survival combined was 94.4% versus 93.5% (p = 0.625), for LCPT and tacrolimus twice-daily, respectively, during this period.

There was no statistically significant difference between the two treatment groups in the incidence of patients with clinically suspected and treated rejections (LCPT: 13.8%; twice-daily tacrolimus: 15.6%, p = 0.628), the number of BPAR episodes (p > 0.999), or the severity of the first BPAR episode (p = 0.984) (Table 3).

Safety

Treatment emergent AEs: Overall, 6,342 treatment emergent AEs were reported (Table 4), and the mean number of AEs experienced per patient during the study was 11.7 events in both treatment groups. The incidence of AEs was similar between the two treatment groups: 260 (97.0%) patients in the LCPT group and 269 (97.8%) patients in the tacrolimus twice-daily. The most frequently reported AEs (reported in 20% or more of patients overall) were: diarrhea (32.0%), anemia (27.4%), urinary tract infection (UTI) (24.5%), hypertension (22.8%) and constipation (21.4%).

Overall, the majority of patients experienced at least one mild (88.8% vs. 90.5%) or moderate (75.7% vs. 80.0%) AE. Sixty-three (23.5%) patients in the LCPT group and 77 (28.0%) patients in the tacrolimus twice-daily group experienced at least one severe event.

The majority of events (>80%) were not suspected to be related to study drug. However, more than half of all patients experienced at least one event suspected to be related to study drug: 165 (61.6%) patients in the LCPT group and 150 (54.5%) patients in the tacrolimus twice-daily group.

The proportion of patients who experienced AEs resulting in discontinuation from study drug and/or withdrawal from the study was similar in the treatment groups (12.3% in LCPT; 12.4% in twice-daily tacrolimus).

Treatment emergent SAEs: More than half of all patients experienced at least one treatment-emergent serious adverse event (SAE): 143 (53.4%) patients in the LCPT group and 162 (58.9%) patients in the tacrolimus twice-daily group. SAEs experienced by more than 5% of patients in any treatment group (LCPT vs. tacrolimus

Table 2: Primary and secondary efficacy results, LCP-Tacro versus tacrolimus twice-daily—intent-to-treat set

	LCP-Tacro (n = 268)	Tacrolimus twice-daily (n = 275)	
Primary end point (treatment failure within 12 months), n (%)	49 (18.3)	54 (19.6)	
Treatment difference (95% CI)[1]		−1.35% (−7.94%, +5.27%)	
Secondary end points	LCP-Tacro	Tacrolimus twice-daily	p-Value[2] (treatment difference; 95% CI[1])
Individual efficacy components at 12 months			
Death, n (%)	8 (3.0)	8 (2.9)	>0.999 (0.08%; −3.02%, 3.21%)
Graft failure, n (%)	9 (3.4)	11 (4.0)	0.821 (−0.64%; −4.05%, 2.75%)
Lost to follow-up, n (%)	4 (1.5)	5 (1.8)	>0.999 (−0.33%; −2.86%, 2.18%)
BPAR, n (%)	35 (13.1)	37 (13.5)	0.900 (−0.39%; −6.14%, 5.38%)
End points at 3 months			
Treatment failure, n (%)	28 (10.4)	39 (14.2)	0.195 (−3.73%; −9.31%, 1.85%)
Death, n (%)	0 (0)	5 (1.8)	0.062 (−1.82%; −4.18%, −0.06%)
Graft failure, n (%)	6 (2.2)	7 (2.5)	>0.999 (−0.31%; −3.19%, 2.57%)
BPAR, n (%)	22 (8.2)	26 (9.5)	0.652 (−1.25%; −6.12%, 3.63%)

The prespecified noninferiority margin was 10%.
BPAR, biopsy-proven acute rejection; CI, confidence interval.
[1]Two-sided 95% CIs were calculated using Newcombe–Wilson score intervals. For the primary efficacy end point (12-month treatment failure rate), the difference between groups was assessed via a noninferiority approach with a noninferiority margin of 10%.
[2]The p-value was based on a two-sided Fisher exact test to evaluate the difference between treatment groups in the incidence of events defining treatment failure (death, graft failure, BPAR and lost to follow-up).

Table 3: Severity of the first episode of BPAR and incidence of clinically suspected and treated acute rejection episodes within 12 months after randomization

Parameter	LCP-Tacro (N = 268)	Tacrolimus twice-daily (N = 275)	LCP-Tacro—Tacrolimus twice-daily (95% CI)[1]	p-Value
Number (%) of patients with ≥1 clinically suspected and treated rejections	37 (13.8)	43 (15.6)	−1.83% (−7.81%, 4.18%)	0.628[2]
Patients with 1 episode	33 (12.3)	37 (13.5)		
Patients with 2 episodes	3 (1.1)	6 (2.2)		
Patients with 3 episodes	1 (0.4)	0		
Patients with ≥4 episodes	0	0		
Patients with ≥1 BPAR episode, n (%)	38 (14.2)	40 (14.5)	−0.37% (−6.30%, 5.59%)	>0.999[2]
Patients with 1 episode	29 (10.8)	32 (11.6)		
Patients with 2 episodes	6 (2.2)	6 (2.2)		
Patients with 3 episodes	2 (0.7)	2 (0.7)		
Patients with ≥4 episodes	1 (0.4)	0		
Severity of first BPAR episode (Banff criteria), n (%)				
Mild	30 (11.2)	31 (11.3)		0.984[3]
Moderate	7 (2.6)	8 (2.9)		
Severe	1 (0.4)	1 (0.4)		

BPAR, biopsy-proven acute rejection. Mild is acute T cell–mediated rejection Grade IA or IB; moderate is acute T cell–mediated rejection Grade IIA or Grade IIB; and severe is acute T cell-mediated rejection Grade III utilizing Banff 2007 criteria. BPAR events were based on the central biopsy reading. Events occurring prior to or on Study Day 404 or March 20, 2013, whichever is earlier, are included.
[1]The two-sided Newcombe–Wilson score CIs are presented.
[2]p-Value from two-sided Fisher exact test.
[3]p-Value from Cochran–Mantel–Haenszel test for general association.

twice-daily) were UTI (9.3% vs. 6.9%), kidney transplant rejection (5.2% vs. 8.0%) and complications of transplanted kidney (most of which were delayed graft function [DGF], 3.0% vs. 6.5%).

There were 16 deaths: 8 (3.0%) patients in the LCPT group and 8 (2.9%) patients in the tacrolimus twice-daily group. Causes of death in the LCPT group were cardiopulmonary failure (2), sepsis (1), respiratory distress due to bacterial sepsis (1), acute myocardial infarction (1), lymphoma (1) or unknown (2). Causes of death for patients in the tacrolimus twice-daily group were cardiac failure due to pneumonia (1), sepsis (4), cardio-respiratory arrest (1) and pneumonia (2). None of the fatal SAEs in the LCPT group were suspected of being related to study drug. Three fatal SAEs in the tacrolimus twice-daily group were suspected to be related

Table 4: Summary of adverse events (AEs), LCP-Tacro versus tacrolimus twice-daily

	LCP-Tacro (N = 268)	Tacrolimus twice-daily (N = 275)	p-Value[1]
Number of AEs	3,128	3,214	
Number of AEs suspected of being related to study drug	417	465	
Number (%) of patients with at least one AE	260 (97.0)	269 (97.8)	0.598
AEs occurring in ≥20% of patients, n (%)			
Anemia	70 (26.1)	79 (28.7)	0.503
Diarrhea	82 (30.6)	92 (33.5)	0.520
Constipation	49 (18.3)	67 (24.4)	0.094
Urinary tract infection	66 (24.6)	67 (24.4)	>0.999
Hypertension	62 (23.1)	62 (22.5)	0.919
Delayed graft function, n (%)	19 (7.1)	30 (10.9)	0.135
Malignancies, n (%)	4 (1.5)	3 (1.1)	0.722
Number (%) of patients with at least one serious AE (SAE)	143 (53.4)	162 (58.9)	0.196
Infections (any opportunistic), n (%)	92 (34.3)	84 (30.5)	0.360
Cytomegalovirus infection, n (%)	31 (11.6)	25 (9.1)	0.398
BK virus infection, n (%)	24 (9.0)	26 (9.5)	0.883
Number of SAEs	389	415	

[1]p-Value from two-sided Fisher exact test.

to study drug (cardiac failure due to pneumonia, and the two sepsis cases).

Potentially clinically significant laboratory values and renal function: No statistically significant difference was observed between treatment groups in the incidence of predefined potentially clinically significant laboratory measures.

The laboratory result most commonly reported as an AE was anemia (27.4% of patients overall), followed by hypophosphatemia (14.4%), leukopenia (13.6%), hyperkalemia (12.9%), blood creatinine increased (12.7%), hypokalemia (12.0%), hypomagnesemia (11.8%) and hyperglycemia (11.4%). These events occurred in both treatment groups, and the majority were mild or moderate in severity and were not suspected to be related to study drug.

Hematology, chemistry, hepatic profile, urinalysis, vital signs, physical examination and spot protein:creatinine results showed that mean change from baseline for these parameters was minimal for both tacrolimus formulations, and the results were similar for both treatment groups.

Despite higher starting dose and tacrolimus trough levels for LCPT versus tacrolimus twice-daily in the early posttransplant period, mean eGFR (Figure 4) and change from baseline were similar between the groups. Although LCPT was associated with a higher exposure, LCPT was not associated with higher incidence of DGF, in fact the incidence of DGF, as assessed via a *post hoc* analysis of AEs of interest, trended in favor of LCPT (LCPT: n = 19 vs. tacrolimus twice-daily: n = 30, p = 0.135).

Fasting lipid profiles showed that mean cholesterol values, were similar. Interestingly, the triglycerides in the LCPT group tended to be on average approximately 20 mg/dL lower than those in the tacrolimus twice-daily group (p = 0.0578) (Table 5).

There was no evidence of PR interval, QRS complex or QT interval prolongation and no significant change from baseline for ECG parameters in either treatment group.

Within 12 months after randomization, 18 of 88 at-risk patients (20.5%) and 11 of 74 at risk patients (14.9%) in the LCPT and tacrolimus twice-daily treatment groups, respectively, had developed NODM. The difference was not statistically significant (p = 0.414). Change from baseline in HbA1c was similar for both treatment groups at Months 3, 6 and 12. However, for patients with diabetes at the time of transplant, the mean HbA1c was slightly higher at baseline for the LCPT group (7.02 [1.45]) compared with the tacrolimus twice-daily group (6.85 [1.04]) and mean (standard error) change from baseline was higher at Months 3 (LCPT: 0.66 [0.34]; tacrolimus twice-daily: 0.60 [0.21]; p = 0.3036), 6 (LCPT: 1.37 [0.37]; tacrolimus twice-daily: 0.85 [0.24]; p = 0.0696) and 12 (LCPT: 1.27 [0.41]); tacrolimus twice-daily: 1.06 [0.23]; p = 0.1506).

Discussion

The results reported here are from the first 12 months of a Phase III trial examining the efficacy and safety of once-daily LCPT MeltDose® tablets versus twice-daily tacrolimus capsules in *de novo* renal transplant patients. This double-blind, double-dummy, randomized study in 543 *de novo* kidney transplant recipients demonstrated that once-daily LCPT was noninferior to twice-daily tacrolimus

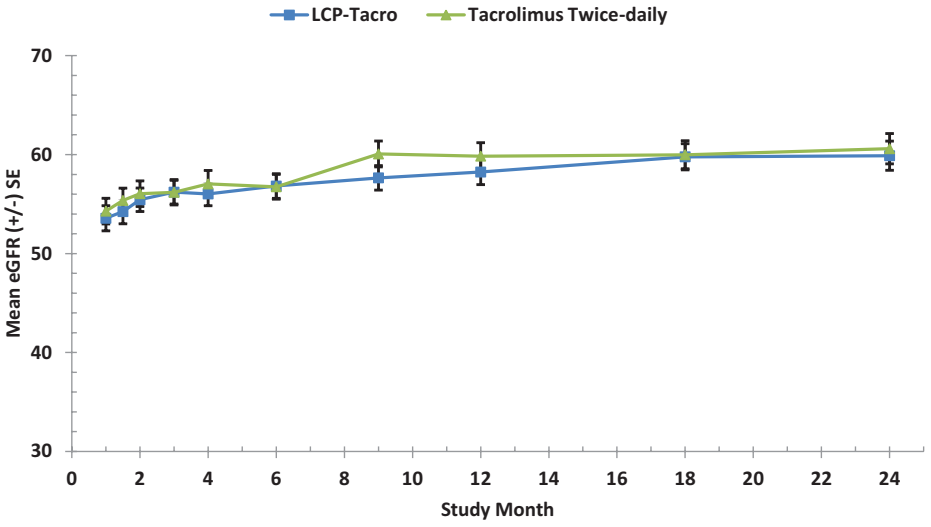

Figure 4: Renal function over the study period.

Table 5: Analysis of metabolic parameters

	Baseline		12 Months	
	LCP-Tacro	Tacrolimus twice-daily	LCP-Tacro	Tacrolimus twice-daily
HDL cholesterol (mg/dL)				
Median (range)	40.0 (14–97)	38.0 (14–103)	53.0 (21–119)	50.0 (15–136)
Change from baseline, mean (SE)			12.7 (1.14)	13.2 (0.87)
p-Value[1]				0.8473
LDL cholesterol (mg/dL)				
Median (range)	84.0 (20–314)	80.0 (20–214)	103.0 (23–230)	105.0 (3–257)
Change from baseline, mean (SE)			19.2 (2.71)	23.0 (2.77)
p-Value[1]				0.2528
Total cholesterol (mg/dL)				
Median (range)	149.0 (57–454)	140.0 (77–313)	184.0 (94–360)	185.0 (89–370)
Change from baseline, mean (SE)			36.0 (3.19)	41.9 (3.14)
p-Value[1]				0.1936
Triglyceride (mg/dL)				
Median (range)	84.0 (20–440)	86.0 (22–782)	132.0 (42–448)	148.0 (41–1856)
Change from baseline, mean (SE)			57.2 (5.09)	74.9 (9.19)
p-Value[1]				0.0578
HbA1c				
Median (range)	5.40 (4.0–11.4)	5.40 (4.3–10.4)	5.50 (4.4–12.6)	5.70 (4.6–14.6)
Change from baseline, mean (SE)			0.42 (0.08)	0.47 (0.06)
p-Value[1]				0.6124

HbA1c, hemoglobin A1c.
[1]p-Value from analysis of covariance controlling for baseline value.

capsules, with similar safety and requires lower doses to achieve similar trough levels compared with twice-daily tacrolimus.

Kaplan–Meier analyses showed comparable efficacy throughout the 12-month study period. Within the first 3 months after transplant, when patients are at the greatest risk of rejection, the treatment failure rates were numerically, though not statistically significantly ($p = 0.195$), lower for LCPT compared to tacrolimus twice-daily. Target tacrolimus trough levels were more rapidly achieved in the LCPT group and it is possible that the rapid achievement of therapeutic tacrolimus blood trough levels may offer greater protection from treatment failure. Most importantly, this study provides evidence that targeted trough levels are achieved immediately posttransplant on Day 1. This is clearly different from the modified-release version of tacrolimus currently approved by the European Medicines Evaluation Agency/FDA (Advagraf/Astagraf), which have found that initial tacrolimus exposure is lower for once-daily, prolonged release tacrolimus formulations versus tacrolimus twice-daily capsules (21–23). The KDIGO clinical practice guideline for the care of kidney transplant recipients specifically states that the earlier that therapeutic blood levels of a calcineurin inhibitor (CNI) can be attained, the more effective the CNI will be in preventing acute rejection (3). Furthermore, the incidence of DGF and eGFR were similar between the groups throughout the study, even in the first 3 months, indicating that achieving rapid therapeutic tacrolimus trough levels with LCPT was not associated with obvious negative nephrotoxic effects.

The incidence of treatment emergent AEs and the incidence of predefined potentially clinically significant laboratory measures were similar between both tacrolimus formulations. Specifically, renal function was similar between the two groups at 12 months, as were the incidences of malignancy, infections and NODM during this period.

The study results demonstrated that during long-term outpatient therapy, LCPT patients required a daily dose that was approximately 14% lower than patients receiving tacrolimus twice-daily, reflecting the improved absorption provided by the MeltDose® drug delivery technology. In fact, the absorption (i.e. bioavailability) per mg was significantly higher in the LCPT group than in the tacrolimus twice-daily group. This result is consistent with data from Phase II studies, which showed that LCPT is associated with an increase in bioavailability (16,17), and a Phase III conversion study in which the required total daily LCPT dose was about 30% lower than preconversion tacrolimus twice-daily dose, while drug levels were stable (20).

In addition to the potential for a lower tacrolimus dose with LCPT, LCPT tablets have an advantageous once-a-day dosing. Multiple daily dosing can contribute to lack of adherence (7–9,24), and posttransplant drug regimens are often associated with high pill burden. Importantly, lack of adherence is common in transplant recipients (25–27), and a recently published paper reported nonadherence to be a major contributor to graft failure (28) and one of the barriers to improving long-term kidney transplant

outcomes. In this double-dummy trial, all patients were assigned to twice-daily dosing, so as not to break the blind. Thus, we are unable to examine in this trial whether adherence is improved for LCPT compared to twice-daily tacrolimus.

As with all clinical trials, these results and the generalizeability of these results to the general population of *de novo* renal kidney recipients, are limited by the fact that patients in a trial must meet eligibility criteria to participate and might not necessarily be representative of the global population of *de novo* renal kidney recipients. Additionally, trial participants are in a highly controlled environment, and the behavior of the patients (i.e. dose adherence and return for clinical follow-up) and of the treating clinicians may differ outside of the trial conditions, affecting clinical outcomes. Strengths of this trial include the fact that it was double-blind with a titratable drug.

The MeltDose® technology that improves bioavailability, together with extended drug release has resulted in a novel once-daily dosing version of tacrolimus. The results presented here confirm the benefit a lower dose to achieve target trough levels. This trial provides evidence that LCPT is an efficacious alternative to currently available twice-daily tacrolimus in *de novo* kidney transplantation.

Acknowledgments

Envarsus study group: *USA*: Denny, Jason E., Henry Ford Health System, Detroit, MI; Kulkarni, Sanjay, Yale University, New Haven, CT; Hricik, Donald, University Hospitals Case Medical Center, Cleveland, OH; Bresnahan, Barbara A., Medical College of Wisconsin, Milwaukee, WI; Bunnapradist, Suphamai, University of California Los Angeles Medical Center, Los Angeles, CA; El-Sabrout, Rafik A., Westchester Medical Center, Valhalla, NY; Chan, Laurence K., University of Colorado, Denver, CO; Ciancio, Gaetano, University of Miami, Miami, FL; El-Ghoroury, Mohamed A., St. Clair Specialty Physicians, Detroit, MI; Goldstein, Michael J., Mount Sinai Medical Center, New York, NY; Gaston, Robert S., Univ. of Alabama at Birmingham, Birmingham, AL; Gohh, Reginald Y., Rhode Island Hospital, Providence, RI; Killackey, Mary T., Tulane University Medical Center, New Orleans, LA; King, Anne, Virginia Commonwealth University, Richmond, VA; Knight, Richard J., The Methodist Hospital, Houston, TX; Kore, Arputharaj H., Loma Linda University Health Care, Loma Linda, CA; Sudan, Debra L., Duke University Medical Center, Durham, NC; Chapochnick Friedmann, Javier, Montefiore Medical Center, Bronx, NY; Mulgaonkar, Shamkant P., Saint Barnabas Medical Center, Livingston, NJ; Nolan, Charles, University of Texas, San Antonio, TX; Pankewycz, Oleh G., Erie County Medical Center, Buffalo, NY; Pirsch, John D., University of Wisconsin, Madison, WI; Schaefer, Heidi M., Vanderbilt University Medical Center, Nashville, TN; Steinberg, Steven M., California Institute of Renal Research, San Diego, CA; Gelb, Bruce E., New York University Medical Center, New York, NY; True, Karin A., University of North Carolina at Chapel Hill, Chapel Hill, NC; West-Thielke, Patricia M., University of Illinois at Chicago, Chicago, IL; Waybill, Mary M., Central Pennsylvania Transplant Foundation, Harrisburg, PA; Wolf, Joshua H., Piedmont Healthcare Research Institute, Atlanta, GA; Ketel, Beverley L., Renal Care Associates, Peoria, IL; Harland, Robert C., East Carolina University, Greenville, NC; Shihab, Fuad S., University of Utah, Salt Lake City, UT. *France*: Cassuto, Elisabeth, Hôpital l'Archet Nice; Le Meur, Yannick, Hôpital de La Cavale Blanche, Brest; Rostaing, Lionel, Hôpital de Rangueil, Toulouse; Mariat, Christophe, Association SRT, Saint-Etienne. *Spain*: Grinyó, Josep Maria, Hospital Universitari De Bellvitge, Cataluña; Puig, Jose, Hospital del Mar, Barcelona; Seron, Daniel, Hospital Vall D'Hebron Barcelona. *Italy*: Tisone, Giuseppe, Fondazione PTV Policlinico, Roma. *Poland*: Ciechanowski, Kazimierz, Samodzielny Publiczny Szpital Kliniczny, Szczecin; Foroncewicz, Bartosz, Szpital Kliniczny Dzieciatka Jezus, Warszawa; Wlodarczyk, Zbigniew, Szpital Uniwersytecki im. Dr A.Jurasza, Bydgoszcz. *Germany*: Budde, Klemens, Charitè Campus Mitte, Berlin; Witzke, Oliver, Universitätsklinikum Essen, Essen. *Mexico*: Mondragon, Guillermo A., Instituto Mexicano de Transplantes, Cuernavaca, Morelos; Mancilla Urrea, Eduardo, Instituto Nacional de Cardiologia ''Dr. Ignacio Chavez,'' Mexico City; Alberu Gomez, Josefina, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City; Reyes Acevedo, Rafael, Centenario Hospital Miguel Hidalgo, Aguascalientes. *Argentina*: Rial, Maria del Carmen, Instituto de Nefrología, Buenos Aires; Novoa, Pablo A., Hospital Cordoba, Cordoba. *Brazil*: Silva Junior, Helio T., Hospital do Rim e Hipertensão, São Paulo; Garcia, Valter D., Irmandade Santa Casa de Misericórdia de Porto Alegre, Rio Grande do Sul; Carvalho, Deise D., Hospital Geral de Bonsucesso, Rio de Janeiro; Santamaria Saber, Luciana T., Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto; Contieri, Fabiana L., Hospital Universitário Evangélico de Curitiba, Curitiba; Bastos, Marcos G., Fundacao IMEPEN, Juiz de Fora; Manfro, Roberto C., Hospital de Clínicas de Porto Alegre, Rio Grande do Sul. *Australia*: Kanellis, John, Monash Medical Centre, Clayton Vic; Eris, Josette, Royal Prince Alfred Hospital, Camperdown NSW; O'Connell, Philip, Westmead Hospital, Westmead, NSW; Hughes, Peter, Royal Melbourne Hospital, Parkville, Vic; Russ, Graeme, Royal Adelaide Hospital, Adelaide. *New Zealand*: Pidgeon, Grant B., Wellington Hospital, Wellington; Dittmer, Ian D., Auckland City Hospital, Grafton Auckland. *Singapore*: Kee, Terence, Singapore General Hospital; Vathsala, Anantharaman, National University of Singapore. *Serbia*: Naumovic, Radomir, Clinical Center of Serbia, Belgrade; Mitic, Igor, Clinical Centre of Vojvodina, Novi Sad. Central reader: Parmjeet Randhawa, University of Pittsburgh Medical Center. Portions of these data were presented at the 2013 European Society for Organ Transplantation (ESOT) in Vienna, Austria, the 2013 American Transplant Congress (ATC) in Seattle, WA and 2014 World Transplant Congress (WTC) in San Francisco, CA. This study was funded by Veloxis Pharmaceuticals. Kristin Kistler, PhD, from Evidera provided medical writing support.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Klemens Budde received research funds and/or honoraria from AiCuris, Astellas, Bristol-Myers Squibb, Hexal, Effimune Pharma, Novartis, Pfizer, Roche, Siemens, Chiesi, Fresenius, Alexion and Veloxis Pharma. Suphamai Bunnapradist participated in clinical trials with Veloxis as a principal investigator in the last 12 months. Kazimierz Ciechanowski participated in clinical trials with Veloxis as a principal investigator. H. Tedesco Silva participated in this clinical trial with Veloxis as a principal investigator and has received honoraria from Novartis and Pfizer. Dr. Silva's institution has received research grants from Novartis, BMS, Pfizer, Roche, Teraclone. Lionel Rostaing has been on the ad board and provided consultancy to Veloxis. Josep M. Grinyo and Jason E. Denny have nothing to disclose.

References

1. Webster AC, Taylor RRS, Chapman JR, Craig JC. Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients. Cochrane Database Syst Rev 2005; Art. No.: CD003961. DOI:10.1002/14651858.CD003961.pub2
2. Organ Procurement and Transplantation Network. *(OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2012 Annual Data Report*. Rockville, MD: Department of Health and Human Services; Health Resources and Services Administration; 2014.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009; 9(Suppl 3): S1–S157.
4. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM181006.pdf. Accessed February 2, 2014.
5. *Prograf Prescribing Information*. Northbrook, IL: Astellas Pharma US, Inc; 2013.
6. Borra LC, Roodnat JI, Kal JA, Mathot RA, Weimar W, van Gelder T. High within-patient variability in the clearance of tacrolimus is a risk factor for poor long-term outcome after kidney transplantation. Nephrol Dial Transplant 2010; 25: 2757–2763.
7. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 1990; 150: 1881–1884.
8. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001; 23: 1296–1310.
9. Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC. Effect of medication dosing frequency on adherence in chronic diseases. Am J Manag Care 2009; 15: e22–e33.
10. Morrissey PE, Reinert S, Yango A, Gautam A, Monaco A, Gohh R. Factors contributing to acute rejection in renal transplantation: The role of noncompliance. Transplant Proc 2005; 37: 2044–2047.
11. Michelon T, Dominguez V, Losekan A, et al. Kidney graft failure due to noncompliance. Transplant Proc 1999; 31: 3031–3032.
12. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf. Accessed February 2, 2014.
13. MeltDose® Technology by the US Patent and Trademark Office, US Patent No. 7,217, 431.
14. Nigro V, Glicklich A, Weinberg J. Improved bioavailability of MELTDOSE once-daily formulation of tacrolimus (LCP-Tacro) with controlled agglomeration allows for consistent absorption over 24 hrs: A scintigraphic and pharmacokinetic evaluation. Am J Transplant 2013; 13 (Suppl 5): 339.
15. Nigro V, Glicklich A, Weinberg J. Flexible dosing of once-daily LCP-Tacro tablets: Morning vs. evening randomized crossover chronopharmacokinetic study. Paper presented at the AST/ESOT Joint Meeting, Oct. 12–14, 2012, Nice, France.
16. Alloway R, Mulgaonkar S, Ueda K, Cohen DBK. A phase 2 randomized study of the pharmacokinetics, safety and efficacy of LCP-Tacro tablets once-a-day vs Prograf capsules twice-a-day in de novo kidney transplants. Am J Transplant 2011; 11 (Suppl 2): 355.
17. Alloway RR, Mulgaonkar S, Bowers VD. A phase 2b, open-label, multi-center, prospective, randomized study to compare the pharmacokinetics and safety of LCP-Tacro™ tablets once-a-day to Prograf® capsules twice-a-day in de novo kidney transplant patients. Am J Transplant 2009; 9(Suppl 2): 414.
18. DuBay DA, Alloway RR, Alsina AE, et al. A phase 2b, open-label, multicenter, prospective, randomized study to compare the pharmacokinetics and safety of LCP-Tacro™ tablets once-a-day to Prograf® capsules twice-a-day in de novo liver transplant patients. Liver Transpl 2009; 15(Suppl 7): S134–S135.
19. Alloway RR, Eckhoff DE, Washburn WK, Teperman LW. Conversion from twice-daily tacrolimus capsules to once-daily extended-release tacrolimus (LCPT): Phase II trial of stable liver transplant recipients. Liver Transpl 2014; 20: 564–575.
20. Bunnapradist S, Ciechanowski K, West-Thielke P, et al. Conversion from twice-daily tacrolimus to once-daily extended release tacrolimus (LCPT): The phase III randomized MELT trial. Am J Transplant 2013; 13: 760–769.
21. Wlodarczyk Z, Squifflet JP, Ostrowski M, et al. Pharmacokinetics for once- versus twice-daily tacrolimus formulations in de novo kidney transplantation: A randomized, open-label trial. Am J Transplant 2009; 9: 2505–2513.
22. Krämer BK, Charpentier B, Bäckman L, et al. Tacrolimus once daily (ADVAGRAF) versus twice daily (PROGRAF) in de novo renal transplantation: A randomized phase III study. Am J Transplant 2010; 10: 2632–2643.
23. Silva HT, Yang HC, Abouljoud M, et al. One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. Am J Transplant 2007; 7: 595–608.
24. Feldman HI, Hackett M, Bilker W, Strom BL. Potential utility of electronic drug compliance monitoring in measures of adverse outcomes associated with immunosuppressive agents. Pharmacoepidemiol Drug Saf 1999; 8: 1–14.
25. Germani G, Lazzaro S, Gnoato F, et al. Nonadherent behaviors after solid organ transplantation. Transplant Proc 2011; 43: 318–323.
26. Chisholm MA. Issues of adherence to immunosuppressant therapy after solid-organ transplantation. Drugs 2002; 62: 567–575.
27. Laederach-Hofmann K, Bunzel B. Noncompliance in organ transplant recipients: A literature review. Gen Hosp Psychiatry 2000; 22: 412–424.
28. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: The dominant role of antibody-mediated rejection and nonadherence. Am J Transplant 2012; 12: 388–399.