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Original Investigation

Novel Once-Daily Extended-Release Tacrolimus Versus Twice-Daily Tacrolimus in De Novo Kidney Transplant Recipients: Two-Year Results of Phase 3, Double-Blind, Randomized Trial

*Lionel Rostaing, MD, PhD,[1] Suphamai Bunnapradist, MD,[2] Josep M. Grinyó, MD,[3] Kazimierz Ciechanowski, MD, PhD,[4] Jason E. Denny, MD,[5] Helio Tedesco Silva Jr, MD,[6] and Klemens Budde, MD,[7] on behalf of the Envarsus Study Group**

Background: 1-year data from this trial showed the noninferiority of a novel once-daily extended-release tacrolimus (LCPT; Envarsus XR) to immediate-release tacrolimus (IR-Tac) twice daily after kidney transplantation.

Study Design: Final 24-month analysis of a 2-armed, parallel-group, randomized, double-blind, double-dummy, multicenter, phase 3 trial.

Setting & Participants: 543 de novo kidney recipients randomly assigned to LCPT (n = 268) or IR-Tac (n = 275); 507 (93.4%) completed the 24-month study.

Intervention: LCPT tablets once daily at 0.17 mg/kg/d or IR-Tac twice daily at 0.1 mg/kg/d; subsequent doses were adjusted to maintain target trough ranges (first 30 days, 6-11 ng/mL; thereafter, 4-11 ng/mL). The intervention was 24 months; the study was double blinded for the entirety.

Outcomes & Measurements: Treatment failure (death, transplant failure, biopsy-proven acute rejection, or loss to follow up) within 24 months. Safety end points included adverse events, serious adverse events, new-onset diabetes, kidney function, opportunistic infections, and malignancies. Pharmacokinetic measures included total daily dose (TDD) of study drugs and tacrolimus trough levels.

Results: 24-month treatment failure was LCPT, 23.1%; IR-Tac, 27.3% (treatment difference, −4.14% [95% CI, −11.38% to +3.17%], well below the +10% noninferiority criterion defined for the primary 12-month end point). Subgroup analyses showed fewer treatment failures for LCPT versus IR-Tac among black, older, and female recipients. Safety was similar between groups. From month 1, TDD was lower for LCPT; the difference increased over time. At month 24, mean TDD for LCPT was 24% lower than for the IR-Tac group ($P < 0.001$), but troughs were similar (means at 24 months: LCPT, 5.47 ± 0.17 ng/mL; IR-Tac, 5.8 ± 0.30 ng/mL; $P = 0.4$).

Limitations: Trial participant eligibility criteria may limit the generalizability of results to the global population of de novo kidney transplant recipients.

Conclusions: Results suggest that once-daily LCPT in de novo kidney transplantation has comparable efficacy and safety profile to that of IR-Tac. Lower TDD reflects LCPT's improved bioavailability and absorption.

INDEX WORDS: Immunosuppression; tacrolimus; kidney transplantation; extended-release; formulation; bioavailability; efficacy; treatment failure; safety; biopsy-proven acute rejection; Envarsus; pill burden; transplant recipient; end-stage renal disease (ESRD); randomized controlled trial (RCT).

Tacrolimus is overwhelmingly used as an immunosuppressant in kidney transplantation, both early posttransplantation and as part of long-term maintenance regimens.[1] While highly effective in preventing acute transplant rejection, tacrolimus has several limitations, including a narrow therapeutic window (necessitating drug monitoring and individual dose titration[2]), interindividual variation in absorption, and low bioavailability (17% ± 10%) of the currently widely used immediate-release tacrolimus

From the [1]University Hospital Toulouse-Rangueil, Toulouse, France; [2]David Geffen School of Medicine at UCLA, Los Angeles, CA; [3]Hospital Universitari de Bellvitge, Catalunya, Spain; [4]Pomeranian Medical University, Szczecin, Poland; [5]Henry Ford Hospital, Detroit, MI; [6]Hospital do Rim e Hipertensao, Sao Paulo, Brazil; and [7]Department of Nephrology, Charité Universitätsmedizin, Berlin, Germany.

[*]A list of the members of the Envarsus Study Group appears in the Acknowledgements.

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Address correspondence to Lionel Rostaing, MD, PhD, DNTO, CHU Rangueil, TSA 50032, 1 avenue Jean Poulhes, 31400 Toulouse Cédex 9, France. E-mail: rostaing.l@chu-toulouse.fr

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(IR-Tac) twice-daily capsule formulation (Prograf; Astellas Pharma US, Inc).[3] In addition, both the IR-Tac formulation and another extended-release once-daily tacrolimus formulation (Advagraf/Astagraf XL; Astellas Pharma US, Inc) are associated with similar peak concentrations[4]; unwanted tacrolimus-associated neurologic adverse events (AEs) have been noted to happen or be most pronounced at peak serum tacrolimus blood concentrations.[5-7] Additionally, the twice-daily formulation adds further pill burden to a patient population already encumbered with taking many long-term medications. Multiple daily drug dosing is associated with increased risk for nonadherence[8-10]; this may result in acute rejection[11] and, in severe cases, transplant failure.[12]

The medication LCP-Tacro (LCPT; Envarsus XR; Veloxis Pharmaceuticals) is an extended-release tablet formulation of tacrolimus with once-daily dosing that has been developed using a proprietary MeltDose drug delivery technology (Veloxis Pharmaceuticals), distinguishing LCPT from other once-daily extended-release tacrolimus products (eg, Astagraf XL). The MeltDose technology decreases a drug's particle size to the smallest possible units as single molecules (ie, a "solid solution").[13] Drug particle size critically affects drug dissolution and absorption; if particle size is smaller, the surface area of the drug increases and the drug will be dissolved more quickly, resulting in better absorption.[14] Results of the MeltDose technology are increased absorption and bioavailability associated with LCPT tablets compared with other extended-release and IR tacrolimus formulations currently available. Phase 1 and phase 2 trials confirmed that LCPT enables broader absorption throughout the gastrointestinal tract and sustains consistent tacrolimus concentrations.[15] In addition, LCPT showed a lack of diurnal variability[16] common with other formulations.[3,17]

Phase 2 trials of de novo and stable kidney[18,19] and liver recipients[20,21] showed a steadier and more consistent concentration-time profile over 24 hours, with reduced peak and peak-to-trough fluctuations for LCPT compared to IR-Tac, increased bioavailability of ~30%, and comparable efficacy and safety profiles. A robust correlation between the area under the curve at 24 hours and the minimum concentration was also shown, indicating that therapeutic drug monitoring of minimum concentration as a measure of tacrolimus exposure can be applied to LCPT. A phase 3 conversion trial showed that LCPT had noninferior efficacy and comparable safety profile to IR-Tac, with lower doses (~20% lower than IR-Tac overall and 30% lower in white patients) of LCPT.[22]

Previously, the 12-month primary efficacy and safety outcomes were reported from this phase 3 double-blind double-dummy trial of de novo kidney transplant recipients randomly assigned to LCPT or IR-Tac.[23] Here, the prespecified blinded efficacy and safety outcomes at 24 months' follow-up are reported from this same phase 3 trial. Efficacy was also analyzed within patient subgroups (ie, females, blacks, and recipients aged ≥ 65 years) in order to explore the consistency of results, or lack thereof, within specific patient populations.

METHODS

Study Overview

This was a 2-armed, parallel group, prospective, randomized, double-blind, double-dummy, multicenter, 24-month, phase 3 trial. The study design has been previously reported.[23] Both the 1- and the 2-year analyses were a priori planned as explicitly stated in the study protocol. The primary endpoint was based on the 1-year analysis and the 2-year analysis was the final analysis designed to assess long-term efficacy and safety outcomes; patients and investigators stayed blinded for the full 24 months. In brief, adult de novo recipients of a living or deceased donor kidney transplant were randomly assigned to receive LCPT tablets once daily on a starting dose of 0.17 mg/kg/d or IR-Tac twice-daily (Prograf) capsules at 0.1 mg/kg/d. Subsequent doses of each study drug were adjusted to maintain whole-blood trough concentrations within the target range of 6 to 11 ng/mL for the first 30 days, then 4 to 11 ng/mL for the rest of the study. All patients also received a matching double-dummy placebo to maintain the blind. All patients also received mycophenolate mofetil (1 g twice daily) or mycophenolic acid (720 mg twice daily), an interleukin 2 receptor antagonist, and corticosteroids per local practice.

Key study exclusion criteria were as follows: receipt of an organ transplant other than kidney; panel-reactive antibody > 30%; body mass index < 18 or >40 kg/m^2; receipt of sirolimus, everolimus, azathioprine, or cyclophosphamide within 3 months before enrollment; and abnormal laboratory values.

Health authority, ethics committee, and institutional review board approval were obtained at each participating center, and informed consent was obtained from all patients. The study was undertaken in accordance with the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Harmonized Tripartite Guidelines for Good Clinical Practice and conformed to the Declaration of Helsinki.

Study End Points

Efficacy

The incidence of treatment failures (any of the following: death, transplant failure, biopsy-proven acute rejection [BPAR; Banff grade ≥ 1A, using Banff 2007 criteria; based on centrally read biopsies], or loss to follow-up) within 24 months after randomization was compared between LCPT and IR-Tac for the overall sample and also stratified by the following subgroups: age (<65 and ≥65 years), race (black or nonblack), and sex (male or female).

The incidence of each individual event (death, transplant failure, BPAR, or loss to follow-up) within 24 months after the randomization date was also assessed. Efficacy results are reported for the overall 24-month study period and separately for the 0- to 12-month and 13- to 24-month periods.

Safety

Safety end points at 24 months included the following: incidence of AEs, serious AEs (SAEs), and discontinuations due to AEs; incidence of predefined potentially clinically significant laboratory values; new-onset diabetes after transplantation

(NODAT); incidence of posttransplantation lymphoproliferative disorder; mean change from baseline (day 30) in estimated glomerular filtration rate (MDRD7 [Modification of Diet in Renal Disease] Study equation); change in clinical laboratory values and vital signs; incidence of opportunistic infections; and any malignancy or BK virus diseases. As prespecified in the study protocol, NODAT analysis was restricted to patients without diabetes at baseline and patients with no medical history of diabetes, baseline fasting plasma glucose level < 126 mg/dL, no prior use of a hypoglycemic agent for diabetes conditions, no prior use of insulin for diabetes conditions, or hemoglobin A_{1c} level $< 6.5\%$ before transplantation. Patients meeting the at-risk definition were considered to have NODAT if they met any of the following 4 criteria: fasting plasma glucose level ≥ 126 mg/dL, hemoglobin A_{1c} level $\geq 6.5\%$ 90 days or later after randomization, new-onset oral hypoglycemic agent use, or new-onset insulin use for more than 30 days. In general, AEs and infections were spontaneously reported by the investigator and then mapped to MedDRA (Medical Dictionary for Regulatory Activities) preferred terms.

Statistical Analysis

Sample Size Determination

Sample size determination was based on the 12-month primary end point. Based on an expected treatment failure rate of 15% at 1 year, 270 patients per group were required to have 90% power to reject the null hypothesis that LCPT was inferior to IR-Tac based on a 2-sided 95% confidence interval (CI) upper bound and a 10% noninferiority margin.

The study design and vigorous 10% noninferiority margin used for the 12-month analysis were decided upon in pretrial collaboration with the US Food and Drug Administration. Subgroup analyses were prespecified in the Statistical Analysis Plan for the study for the 12-month outcomes; the same subgroup analyses were performed at 24 months for consistency check of the 12- and 24-month data.

Analysis Method

The total daily dose (TDD) the day before a trough sample recorded in the case report forms was used to compute the ratio of trough value to dose for each trough sample for each patient. The ratio was then tabulated by treatment group and time point; differences in ratios between groups at each time point were evaluated by 1-way analysis of variance with main effect of treatment.

Treatment failure within 24 months was assessed using a 2-sided 95% CI for the difference (LCPT minus IR-Tac) in treatment failure rates between treatment groups. The incidence of clinically suspected and treated acute rejection episodes and the incidence of BPAR episodes was compared between treatment groups using Fisher exact test and 2-sided 95% CI for the difference. The 2-sided 95% CIs for the differences were calculated using the Newcombe-Wilson score method. In addition, the association between treatment and severity grade of the first BPAR episode was assessed using Cochran-Mantel-Haenszel test for general association.

Differences between treatment groups in time-to-event distributions were evaluated using log-rank tests, displayed as Kaplan-Meier curves. Baseline characteristics and treatment-emergent AEs were tabulated by treatment. Change from baseline in lipid levels was compared using an analysis of covariance model with main effect of treatment and baseline as covariates.

RESULTS

Study Overview

The study was initiated on October 13, 2010. All randomly assigned participants completed the 24-month visit by March 26, 2014, at 68 sites (United States, n = 31; Latin America, n = 13; Europe, n = 15; and Asia Pacific, n = 9).

Patient Disposition and Baseline Characteristics

A total of 543 patients were randomly assigned to the study drug (intention-to-treat population; LCPT, n = 268; IR-Tac, n = 275). Overall, 507 (93.4%) patients completed the 24-month study period and 394 (72.6%) completed the 24-month study on study drug (LCPT, n = 195; IR-Tac, n = 199; Fig 1).

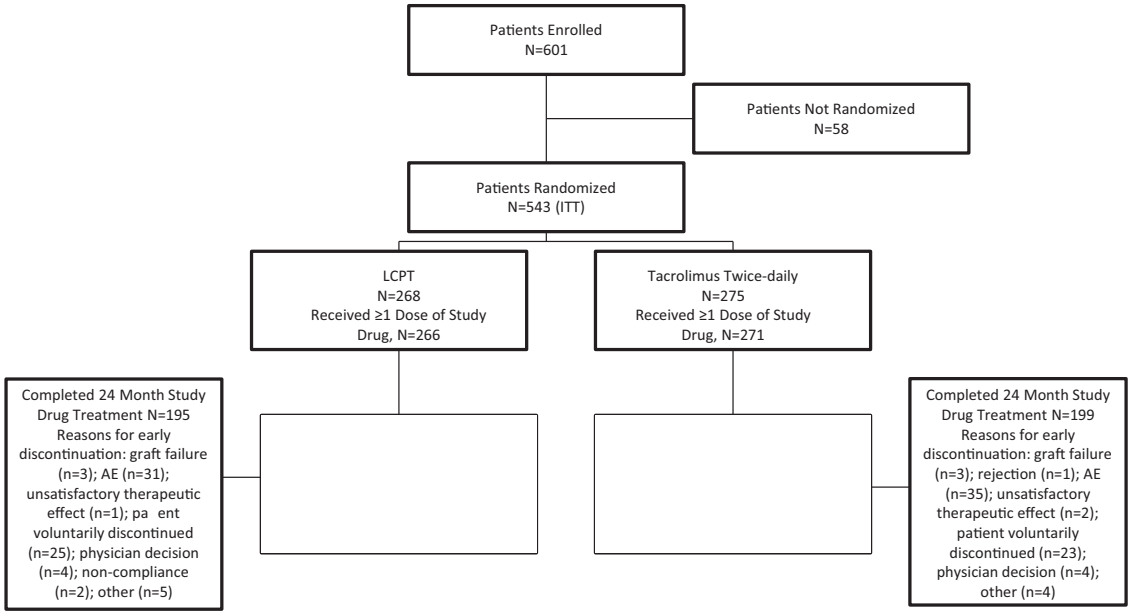

Figure 1. Patient disposition. Abbreviations: AE, adverse event; LCPT, extended-release tacrolimus, once daily.

Demographic characteristics were similar between treatment groups. The patient population was predominately white (76.8%) and male (65.4%); mean age was 45.8 years (Table 1).

Immunosuppression

As a result of the higher starting dose for LCPT, initial TDDs were higher in patients in the LCPT group versus the IR-Tac group. From months 1 through 12, TDDs were lower in the LCPT group, and the difference between groups increased over time. At month 3, TDD for the LCPT group was ~14% lower, and by month 12, ~20% lower. At month 24, mean TDD for the LCPT group was 24.4% lower than that for the IR-Tac group (3.4 ± 0.15 [standard error] and 4.5 ± 0.22 mg, respectively; $P < 0.001$; Fig 2).

Tacrolimus trough levels were notably higher in the LCPT group compared with the IR-Tac group in the first 2 weeks after dosing; thereafter, trough levels in the 2 groups were similar (Fig 2). Although a greater proportion of LCPT (67%) versus IR-Tac (25%) patients had tacrolimus trough levels ≥ 6 ng/mL by day 2,[23] the majority of patients in both treatment groups were within the post–30-day target range of 4 to 11 ng/mL from month 1.5 through month 24 (71.5%-84.5% for LCPT and 78.3%-87.0% for IR-Tac).

Table 1. Patient Demographics and Baseline Characteristics

	LCPT (n = 268)	IR-Tac (n = 275)
Age, y	44.8 ± 13.29	46.9 ± 14.26
Sex		
Male	174 (64.9)	181 (65.8)
Female	94 (35.1)	94 (34.2)
Race		
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	11 (4.1)	11 (4.0)
Donor type		
Living	135 (50.4)	129 (46.9)
Deceased	133 (49.6)	145 (52.7)
Missing	0 (0.0)	1 (0.4)
PRA, %	1.5 ± 5.10	1.5 ± 5.98
PRA < 5%	243 (90.7)	253 (92.0)
Diabetes at time of transplantation	50 (18.7)	56 (20.4)
Time from transplantation to first study drug dose, h	34.15 ± 8.9	34.38 ± 9.7

Note: Values for categorical variables are given as number (percentage); for continuous variables, as mean ± standard deviation.

Abbreviations and definitions: IR-Tac, immediate-release tacrolimus, twice-daily; LCPT, extended-release tacrolimus, once daily; PRA, panel-reactive antibody.

Analysis of trough to dose ratio demonstrated an increasing ratio for LCPT throughout the 24 months (Fig 3); this reflected the improved absorption provided by the MeltDose formulation. This is apparent over time as the dose decreases but the trough level remains stable and similar to that of IR-Tac. Absorption (ie, bioavailability) per milligram was significantly higher in the LCPT group versus the IR-Tac group by month 12 (means for LCPT and IR-Tac of 2.3 ± 0.11 and 1.6 ± 0.07, respectively; $P < 0.001$) and month 24 (means for LCPT and IR-Tac of 2.2 ± 0.11 and 1.68 ± 0.07, respectively; $P < 0.001$).

Efficacy End Point

Treatment failure at 24 months was 23.1% for patients in the LCPT group and 27.3% for patients in the IR-Tac group. The treatment difference was −4.14% (95% CI, −11.38% to +3.17%), well below the noninferiority margin of 10% that was used for the 12-month primary efficacy end point. No statistically significant difference was observed between the LCPT and IR-Tac groups for the incidence of all-cause mortality ($P = 0.8$), transplant failure ($P = 0.5$), BPAR ($P = 0.8$), or loss to follow-up ($P = 0.4$; Table 2).

No statistically significant difference was observed between the 2 treatment groups in time-to-event distribution during the 24-month study period by log-rank test: treatment failure ($P = 0.3$) and first episode of BPAR ($P = 0.7$). Overall patient survival was 95.9% versus 95.2% ($P = 0.7$), and transplant survival was 95.8% versus 94.4% ($P = 0.4$) for LCPT and IR-Tac, respectively. Both drug groups had more treatment failures in the first versus second 12 months of the study. In both study years, LCPT had fewer treatment failures; a larger difference between groups was seen between study years 1 and 2 compared to the first 12 months (Table 2; Fig 4).

There were no statistically significant differences between the 2 treatment groups in incidence of patients with clinically suspected and treated rejections, number of BPAR episodes, or severity of the first BPAR episode (Table 3). There were more acute rejection episodes in the first year compared to the second study year in both groups (Tables 2 and 3).

Subgroup analyses showed that the LCPT group had fewer treatment failures compared to the IR-Tac group in females, blacks, and recipients 65 years or older (Fig 5).

Safety

Treatment-Emergent AEs

Mean numbers of AEs per patient during the study were 14.3 and 14.4 for the LCPT and IR-Tac groups, respectively. The incidence of AEs was similar between the 2 treatment groups (Table 4). AEs reported

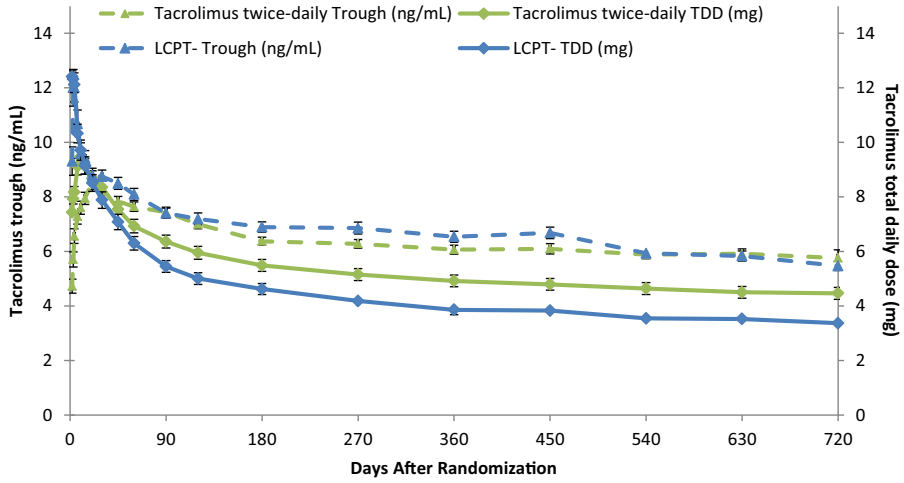

Figure 2. Mean (± standard error) tacrolimus trough levels and tacrolimus daily dose over the 24-month study period. Abbreviations: LCPT, extended-release tacrolimus, once daily; TDD, total daily dose.

in the second year tended to follow the same pattern as in the first study year; however, AEs tended to be fewer for the second year of the study compared to the first 12 months (percentages of patients with ≥1 AE in the first vs second year were 98% vs 74% and 99% vs 70% for the LCPT and IR-Tac groups, respectively).

The majority of patients had at least 1 mild (LCPT, 92.2%; IR-Tac, 93.8%) or moderate (LCPT, 82.8%; IR-Tac, 84.7%) AE. Eighty (29.9%) patients in the LCPT group and 95 (34.5%) in the IR-Tac group had at least 1 severe event.

The majority of events (>80%) were not suspected to be related to study drug. However, 64.9% of patients in the LCPT group and 59.3% of patients in the IR-Tac group had at least 1 event suspected to be related to the study drug.

The proportion of patients who had AEs resulting in discontinuation from study drug and/or withdrawal from the study was similar in the treatment groups (0-12 months: 8.6% in LCPT, 9.8% in IR-Tac; 0-24 months: 11.6% in LCPT, 12.7% in IR-Tac).

Treatment-Emergent SAEs

In the LCPT and IR-Tac groups, 61.9% and 67.3% of patients, respectively, had treatment-emergent SAEs. The frequency of SAEs tended to be fewer for the second year versus the first 12 months (percentages

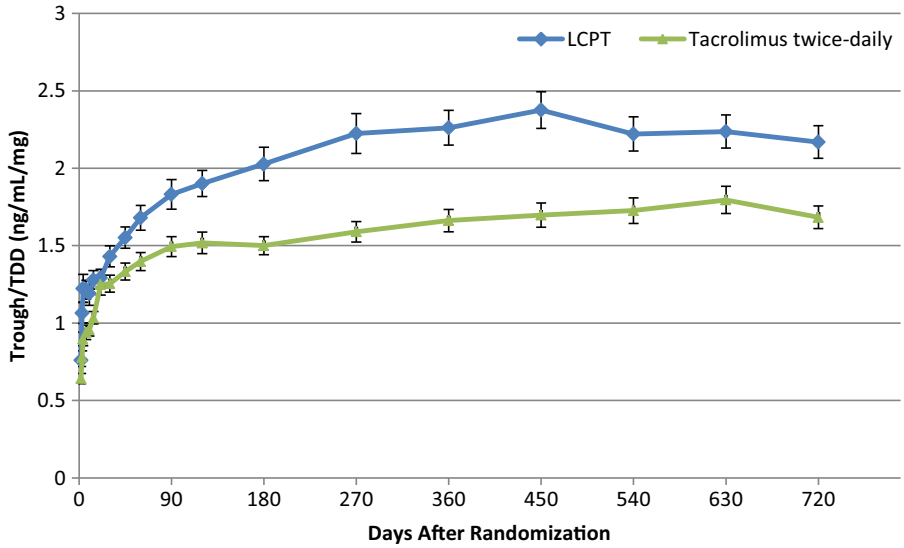

Figure 3. Mean (± standard error) tacrolimus trough level (ng/mL) achieved per total daily dose (TDD; mg). Abbreviation: LCPT, extended-release tacrolimus, once daily.

Table 2. Efficacy Results During the First and Second 12 Months and Over the 24-Month Study Period

	LCPT (n = 268)	IR-Tac (n = 275)	Treatment Difference (95% CI)[a]
Treatment failure			
0-12 mo	49 (18.3)	54 (19.6)	−1.35% (−7.94% to 5.27%)
13-24 mo[b]	13 (5.1)	21 (8.0)	−2.94% (−7.38% to 1.42%)
0-24 mo	62 (23.1)	75 (27.3)	−4.14% (−11.38% to 3.17%)
Death			
0-12 mo	8 (3.0)	8 (2.9)	0.08% (−3.02% to 3.21%)
13-24 mo[b]	3 (1.2)	5 (1.9)	−0.74% (−3.33% to 1.73%)
0-24 mo	11 (4.1)	13 (4.7)	−0.62% (−4.29% to 3.03%)
Transplant failure			
0-12 mo	9 (3.4)	11 (4.0)	−0.64% (−4.05% to 2.75%)
13-24 mo[b]	2 (0.78)	4 (1.5)	−0.75% (−3.15% to 1.48%)
0-24 mo	11 (4.1)	15 (5.5)	−1.35% (−5.15% to 2.40%)
Loss to follow-up			
0-12 mo	4 (1.5)	5 (1.8)	−0.33% (−2.86% to 2.18%)
13-24 mo[b]	0 (0.0)	3 (1.2)	NA
0-24 mo	4 (1.5)	8 (2.9)	−1.42% (−4.29% to 1.27%)
BPAR			
0-12 mo	35 (13.1)	37 (13.5)	−0.39% (−6.14% to 5.38%)
13-24 mo[b]	11 (4.3)	13 (5.0)	−0.66% (−4.50% to 3.16%)
0-24 mo	46 (17.2)	50 (18.2)	−1.02% (−7.44% to 5.43%)

Note: Unless otherwise indicated, values are given as number (percentage). The prespecified noninferiority margin was 10%.

Abbreviations: BPAR, biopsy-proven acute rejection; CI, confidence interval; IR-Tac, immediate-release tacrolimus, twice-daily; LCPT, extended-release tacrolimus, once daily; NA, not applicable.

[a]Two-sided 95% CIs were calculated using Newcombe-Wilson score intervals. For the primary efficacy end point (12-month treatment failure rate), difference between groups was assessed by a noninferiority approach with a noninferiority margin of 10%.

[b]Percentage was calculated based on persons who participated in the study during this period.

of patients with ≥1 SAE in the first vs second year were 53% vs 24% and 58% vs 24%, for LCPT and IR-Tac, respectively).

Twenty-four deaths (11 in LCPT [first year, 8; second year, 3] and 13 in IR-Tac [first year, 8; second year, 5]) occurred during the study. Most causes of death were related to the cardiopulmonary system. None of the 11 fatal SAEs in the LCPT group were suspected to be related to the study drug. Three of the 13 patients who died in the IR-Tac group had events (sepsis) considered to be related to study drug.

Potentially Clinically Significant Laboratory Values and Kidney Function

No statistically significant difference was observed between treatment groups in the incidence of predefined potentially clinically significant laboratory measurements.

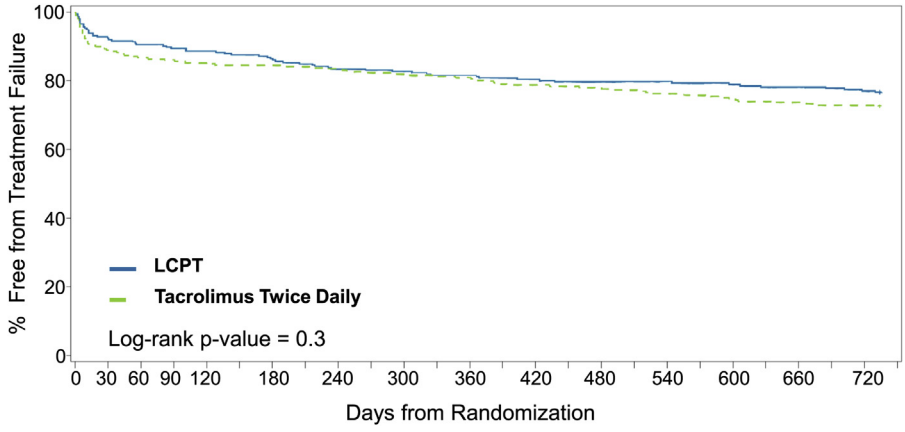

Figure 4. Kaplan-Meier analysis, proportion free of treatment failure over 24 months. Abbreviation: LCPT, extended-release tacrolimus, once daily.

Table 3. Incidence of Clinically Suspected and Treated Acute Rejection Episodes Within 24 Months After Randomization and Severity of First BPAR Episode

Parameter	LCPT (n = 268)	IR-Tac (n = 275)	LCPT − IR-Tac (95% CI)[a]	*P*
Patients with ≥1 rejection event				
0-12 mo	37 (13.8)	43 (15.6)	−1.83% (−7.81% to 4.18%)	0.6[b]
0-24 mo	46 (17.2)	48 (17.5)	−0.29% (−6.66% to 6.11%)	0.9[b]
Patients with rejections over 24-mo study				
1 episode	39 (14.6)	41 (14.9)		
2 episodes	6 (2.2)	6 (2.2)		
3 episodes	1 (0.4)	0 (0.0)		
≥4 episodes	0 (0.0)	0 (0.0)		
Severity of first BPAR episode[c]				
Mild	37 (13.8)	39 (14.2)		0.9[d]
Moderate	8 (3.0)	10 (3.6)		
Severe	1 (0.4)	1 (0.4)		
BPAR treated with polyclonal antibodies	9 (3.4)	12 (4.4)		0.6[b]

Note: Unless otherwise indicated, values are given as number (percentage).

Abbreviations: BPAR, biopsy-proven acute rejection; CI, confidence interval; IR-Tac, immediate-release tacrolimus, twice-daily; LCPT, extended-release tacrolimus, once daily.

[a]Two-sided Newcombe-Wilson score CIs are presented.

[b]*P* value from 2-sided Fisher exact test.

[c]For BPAR severity, 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 using Banff 2007 criteria. BPAR events were based on the central biopsy reading. Events occurring prior to or on study day 404 or March 18, 2013, whichever is earlier, are included.

[d]*P* value from Cochran-Mantel-Haenszel test for general association.

Laboratory results most commonly reported as an AE were anemia, hypophosphatemia, leukopenia, hyperkalemia, increased blood creatinine level, hypokalemia, hypomagnesemia, hyperglycemia, and vitamin D deficiency. Most were mild or moderate in severity and most were not suspected to be related to study drug.

Hematology, chemistry, hepatic profile, urinalysis, vital signs, physical examination, and estimated glomerular filtration rate results had minimal change from baseline for both tacrolimus formulations (Table 4).

Within 24 months after randomization, 24 of 88 (27.3%) and 12 of 74 (16.2%) at-risk patients in the LCPT and IR-Tac groups, respectively, had developed NODAT ($P = 0.1$). Change from baseline in hemoglobin A_{1c} level was similar for both treatment groups over the entire study.

DISCUSSION

The results discussed here are from the blinded 24-month follow-up of a phase 3 trial assessing the efficacy and safety of once-daily LCPT MeltDose tablets versus IR-Tac capsules in de novo kidney transplant recipients. Consistent with the 12-month results,[23] this double-blind double-dummy study in 543 recipients showed that once-daily LCPT was associated with a comparable efficacy and safety profile as IR-Tac at 24 months postrandomization. The LCPT group had fewer treatment failures compared to the IR-Tac group over the duration of the study, including early posttransplantation (ie, at 3 months), when there is the greatest risk for rejection; noninferiority was demonstrated at 12 months posttransplantation. Lower LCPT doses were able to achieve similar trough levels compared to IR-Tac.

Post hoc subgroup analyses showed that the LCPT group had fewer treatment failures among black recipients, older recipients, and females; each of these populations has been found to have higher risk for acute rejection, transplant loss, and/or death.[24-28] Lower tacrolimus bioavailability has been observed in females[29,30] and African American kidney transplant recipients, largely due to variations in *CYP3A5* gene expression[31] and polymorphism preponderance (CYP3A5*1 allele).[32,33] The improved bioavailability of LCPT may translate into improved clinical outcomes. Although older recipients generally have less acute rejection owing to immunosenescence,[34,35] early rejection episodes may be particularly detrimental to long-term clinical outcomes in older recipients.[26,36] It has also been hypothesized that elderly transplant recipients are likely to have a greater degree of variability in tacrolimus pharmacokinetics compared with younger recipients.[37] Thus, it is reasonable to hypothesize that LCPT may be a particularly good option in older receipts due to improved pharmacokinetics and efficacy against rejection. The trends observed are consistent with a post hoc analysis performed on pooled 12-month data from de novo and stable kidney

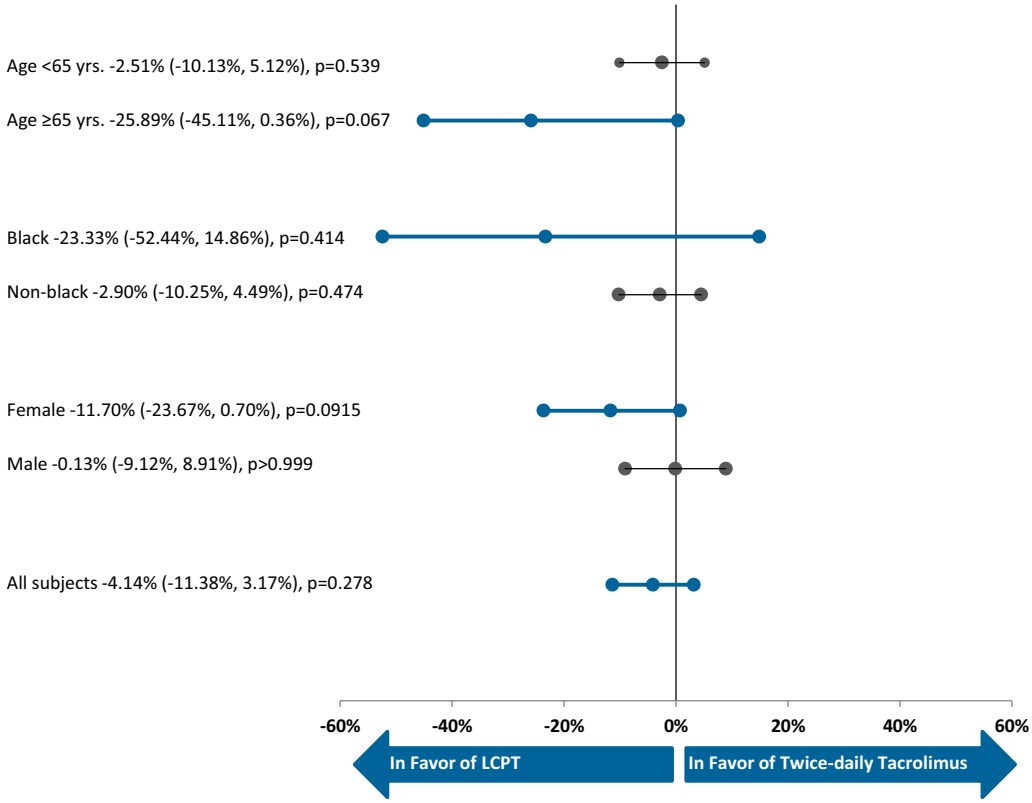

Figure 5. Forest plot of difference (95% confidence interval) in treatment failure for extended-release tacrolimus, once daily (LCPT) versus twice-daily tacrolimus by patient subgroups and overall.

transplant recipients, where significant differences in treatment failure were found in both elderly and black patients for LCPT versus IR-Tac.[38]

The incidence of treatment-emergent AEs was similar between both tacrolimus formulations. Kidney function was similar between the 2 groups throughout the 24-month study period, as were incidences of malignancy, infections, and NODAT.

During this 2-year outpatient therapy period, LCPT patients required lower doses than the IR-Tac group and the difference increased continually over time while trough levels remained similar, indicating the improved absorption by the MeltDose drug delivery technology. Absorption (ie, bioavailability) per milligram was significantly greater in the LCPT group versus the IR-Tac group. This result is consistent with data from phase 2 studies that demonstrated LCPT is associated with an increase in bioavailability[18,39] and a phase 3 conversion study in which the required TDD of LCPT was ∼20% lower than the pre-conversion IR-Tac dose, whereas drug trough levels were stable.[22]

Currently, LCPT is the only extended-release once-daily tacrolimus formulation that requires a lower tacrolimus dose to achieve similar exposure levels and demonstrates comparable efficacy to IR-Tac capsules.

There are conflicting data for the importance of tacrolimus peak concentrations. Although peak concentrations are important for cyclosporine-treated patients,[40,41] Undre et al[42] reported no association between peak concentration and rejection for tacrolimus-treated patients. Instead, overall exposure, as determined by area under the curve, is important for good rejection prophylaxis. Conversely, it has been hypothesized that peak calcineurin inhibitor levels may be associated with prevention of rejection.[40,43] However, results from the present study suggest that this is not the case because LCPT is associated with an ∼30% lower peak compared to IR-Tac, and it is the achievement of early therapeutic tacrolimus exposure that is likely more important in preventing rejection.

An advantage of LCPT tablets is their once-a-day dosing. Multiple daily dosing could contribute to lack of adherence,[8-10,44] and posttransplantation drug regimens are frequently associated with high pill burden. Transplant recipients often have lack of treatment adherence[45-47]; nonadherence is purported to be a major contributor to transplant failure[48] and a barrier to improving long-term kidney transplantation outcomes. Once-daily tacrolimus has been shown to increase adherence.[49,50] In this double-dummy trial, every patient was assigned to twice-daily dosing in

Table 4. Summary of AEs, Potentially Clinically Significant Laboratory Values, and Kidney Function

	LCPT (n = 268)	IR-Tac (n = 275)
AEs		
No. of AEs	3,842	3,965
No. of AEs suspected related to study drug	493	543
Patients with ≥1 AE	263 (98.1)	269 (97.8)
AEs occurring in ≥20% of overall patients		
Edema peripheral	50 (18.7)	66 (24.0)
Constipation	51 (19.0)	68 (24.7)
Diabetes mellitus	55 (20.5)	42 (15.3)
Tremor	59 (22.0)	51 (18.5)
Hypertension	71 (26.5)	73 (26.5)
Anemia	75 (28.0)	84 (30.5)
Urinary tract infection	81 (30.2)	80 (29.1)
Diarrhea	91 (34.0)	102 (37.1)
Malignancies		
0-12 mo	4 (1.5)	3 (1.1)
0-24 mo	8 (3.0)	8 (2.9)
Infections		
Any opportunistic[a] infection		
0-12 mo	92 (34.3)	84 (30.5)
0-24 mo	110 (41.0)	99 (36.0)
Cytomegalovirus infection		
0-12 mo	31 (11.6)	25 (9.1)
0-24 mo	33 (12.3)	29 (10.5)
BK virus infection		
0-12 mo	24 (9.0)	26 (9.5)
0-24 mo	32 (11.9)	31 (11.3)
No. of SAEs	475	519
Patients with ≥1 SAE	166 (61.9)	185 (67.3)
SAEs occurring in ≥5% of overall patients		
Urinary tract infection	9.7%	8.0%
Kidney transplant rejection	8.6%	12.0%
Complications of transplanted kidney[b]	3.0%	6.5%
Kidney function[c]		
eGFR, mL/min/1.73 m^2		
Baseline	53.9 ± 1.27	54.4 ± 1.30
Month 24	60.0 ± 1.40	60.6 ± 1.46
Change from baseline	4.1 ± 1.18	5.1 ± 1.13
Creatinine, mg/dL		
Baseline	5.59 ± 0.178	5.67 ± 0.168
Month 24	1.46 ± 0.06	1.49 ± 0.07
Change from baseline	−3.84 ± 0.19	−4.05 ± 0.19
Lipids		
HDL cholesterol, mg/dL		
Baseline	41.7 ± 0.82	40.1 ± 0.80
Month 24	56.8 ± 1.27	53.9 ± 1.20
Change from baseline	13.7 ± 1.15	14.4 ± 1.04
LDL cholesterol, mg/dL		
Baseline	86.7 ± 2.28	85.1 ± 2.11
Month 24	102.4 ± 2.01	103.3 ± 2.12
Change from baseline	15.8 ± 3.09	17.3 ± 2.67
Total cholesterol, mg/dL		
Baseline	151.2 ± 2.71	148.9 ± 2.37
Month 24	185.7 ± 2.66	186.0 ± 2.74
Change from baseline	34.0 ± 3.70	36.6 ± 3.11
Triglycerides, mg/dL		
Baseline	98.8 ± 3.55	102.7 ± 4.39
Month 24	152.6 ± 6.69	167.5 ± 6.83
Change from baseline	57.2 ± 6.54	65.1 ± 7.06

Note: Unless otherwise indicated, values are given as number (percentage) or mean ± standard error. Conversion factors for units: cholesterol in mg/dL to mmol/L, ×0.02586; creatinine in mg/dL to μmol/L, ×88.4; triglycerides in mg/dL to mmol/L, ×0.01129.

Abbreviations: AE, adverse event; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IR-Tac, immediate-release tacrolimus, twice-daily; LCPT, extended-release tacrolimus, once daily; LDL, low-density lipoprotein; SAE, serious adverse event.

[a]The opportunistic designation was assigned by the physician.

[b]Mostly delayed transplant function.

[c]Calculated as month-24 value − baseline value for each patient.

order to not break the blind. Thus, it was beyond the scope of this trial to examine whether adherence is increased for LCPT versus IR-Tac twice daily.

As for all clinical trials, these results and their generalizability are limited by the patients in a trial having to meet eligibility criteria to participate and might not necessarily be representative of the overall population of de novo kidney transplant recipients. In addition, trial participants are in a highly controlled environment and patient behavior (ie, dose adherence and return for clinical follow-up) and that of the treating clinicians might differ outside of the trial conditions, thus influencing clinical outcomes. Strengths of this trial include it being double blind with a titratable drug and blinded for 2 years.

The MeltDose technology with its improved bioavailability, along with extended drug release, has resulted in a novel once-daily dosing version of tacrolimus. Results in this report confirm the benefit of a lower dose to achieve target trough levels. This trial offers evidence that LCPT demonstrates comparable efficacy to currently available tacrolimus in de novo kidney transplantation.

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