

ORIGINAL ARTICLE

LCPT once-daily extended-release tacrolimus tablets versus twice-daily capsules: a pooled analysis of two phase 3 trials in important *de novo* and stable kidney transplant recipient subgroups

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SUMMARY

African-American and elderly kidney transplant recipients (KTR) have increased risk for poor clinical outcomes post-transplant. Management of immunosuppression may be challenging in these patients and contribute to worse outcomes. A novel once-daily formulation of tacrolimus (LCPT) has demonstrated noninferiority, similar safety, improved bioavailability, a consistent concentration time profile, and less peak and peak-trough fluctuations vs. tacrolimus twice-daily (Tac BID). This pooled analysis of two phase 3 randomized, controlled trials, including 861 (LCPT $N = 428$; Tac BID $N = 433$; 38% of patients were stable KTR, and 62% were *de novo* KTR) patients, examined the efficacy of LCPT in KTR subgroups (blacks, females, and age ≥ 65). Overall, treatment failure [death, graft failure, centrally read biopsy-proven acute rejection (BPAR), or lost to follow-up] at 12 months was as follows: LCPT: 11.9%, BID Tac: 13.4% [-1.48% (-5.95% , 2.99%)]. BPAR rates were as follows: LCPT: 8.2%, Tac BID: 9.5% [-1.29% (-5.14% , 2.55%)]. Numerically, fewer treatment failure events with LCPT were found in the majority of subgroups, with significantly less treatment failure associated with LCPT among black KTR [-13.82% (-27.22% , -0.31%)] and KTR ≥ 65 [-13.46% (-25.27% , -0.78%)]. This pooled analysis suggests numerically lower efficacy failure rates associated with LCPT among high-risk subgroups, in particular black KTR and KTR ≥ 65 years old.

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Key words

efficacy, extended-release, immunosuppression, kidney transplantation, tacrolimus

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Introduction

Disparities in clinical outcomes following kidney transplantation among patient subgroups have long been reported [1]. African-American race is associated with a

higher risk for acute rejection [2,3] and graft loss; [3] some data suggest an increased risk for graft loss [4,5] and mortality in older kidney transplant recipients [4,5] and females have been shown to have a greater risk for mortality following kidney transplantation than men

[6]. The reason for disparities in clinical outcomes is multifactorial and includes both immunological (e.g., biology, immunity, genetics, metabolism, pharmacology) and nonimmunological factors (e.g., comorbidities; time on dialysis; donor, organ, and recipient characteristics; socioeconomic status, medication adherence, access to care) [1].

LCPT is a novel, once-daily, extended-release, tablet formulation of tacrolimus [Envarsus[®] XR; Envarsus in Europe, (LCP-Tacro), Veloxis Pharmaceuticals, Hørsholm, Denmark] that has been developed using MeltDose[®] drug delivery technology. MeltDose results in a decreased particle size [7] that improves pharmacokinetic (PK) properties compared to the commonly used tacrolimus twice-daily capsules (Prograf[®], Astellas Pharma US, Inc.). For example, as a result of increased bioavailability and broader absorption in the GI tract, compared to tacrolimus twice-daily, LCPT is associated with an approximately 20% lower dose (30% in non-blacks and 15% in blacks/African-Americans) [8,9] requirement to achieve similar tacrolimus trough levels; LCPT also results in lower peak and less peak-to-trough fluctuation compared to tacrolimus twice-daily [10–12].

Clinically, LCPT has shown noninferior efficacy and similar safety as tacrolimus twice-daily following *de novo* and stable kidney transplantation [8,9].

The improved bioavailability of LCPT may be particularly beneficial in subgroups with known differences in tacrolimus metabolism. For example, lower tacrolimus bioavailability has been observed in females [13,14] and in African-American kidney transplant recipients, largely due to variations in the CYP3A5 gene expression [15] and polymorphism preponderance (CYP3A5*1 allele) [16,17], respectively. Data from a Phase 3 conversion trial demonstrated that LCPT is safe and efficacious in black kidney transplant recipients, and as a result of the improved bioavailability, black recipients benefitted from an ~15% lower dose of LCPT compared to tacrolimus twice-daily [8]. Additionally, it has been hypothesized that elderly transplant recipients are likely to have a greater degree of variability in tacrolimus PK compared to younger recipients [18]. While older recipients generally have less acute rejection as a reflection of the lack of vigor of the innate immune system due to immunosenescence [19,20], rejection episodes may be associated with greater detrimental clinical effects in older recipients [4,21].

Subgroup analyses can play an important role in determining if there is potential heterogeneity of treatment effect among distinct patient groups, and can be useful if there are practical questions about how to dose

based on patient characteristics, and/or if there are questions about benefits of therapy in specific groups of patients [22]. Post hoc subgroup analyses from a randomized double-dummy trial in *de novo* kidney transplant recipients showed numerically less treatment failures among black, older, and female recipients treated with LCPT compared to tacrolimus twice-daily [23]. Pooling efficacy data from separate studies provides a larger database for exploring comparative efficacy overall and in subgroups. Clinically speaking, even though the risk of graft loss (and other events defining treatment failure) may be higher immediately after a transplant in *de novo* patients than in the stable patients, the relative risk associated with different tacrolimus formulations (administered in the therapeutic range) is not expected to differ in the *de novo* and stable patient. This clinical rationale for pooling the study was supported by the fact that while the 12-month treatment failure rates were different in the individual studies (18–19% in *de novo* vs. 2–4% in stable recipients), the relative difference between the treatment groups was consistent (–1.14% in *de novo* vs. –1.85% in stable patients). To increase the power, for the present analysis, data from the *de novo* trial were pooled with data from a trial in stable kidney transplant recipients randomized to switch from tacrolimus twice-daily to LCPT, or to remain on tacrolimus twice-daily. The primary objective of this study was to evaluate the results of the pooled efficacy analysis of LCPT in preventing allograft rejection of kidney transplant recipients, as well as an overall assessment of its treatment effectiveness in subgroups. Specifically efficacy and safety of LCPT tablets compared to tacrolimus twice-daily capsules was assessed in black kidney transplant recipients, recipient's ≥ 65 years of age, and females and is reported here.

Methods

Study design and conduct

This was a pooled analysis of data from 2 two-arm, parallel group, prospective, randomized, multicenter, Phase 3 clinical trials (studies 3001 and 3002). Study 3001 was an open label trial (ClinicalTrials.gov: NCT00817206) in stable kidney transplant patients [8]. Following a 7-day run-in period during which patients continued on their existing dose of tacrolimus twice-daily capsules, patients were randomized 1:1 to receive a reduced dose of LCPT tablets once-daily or to continue on tacrolimus twice-daily capsules (Prograf, Astellas Pharma) for 12 months. Study 3002 was a double-blind, double-dummy trial

(ClinicalTrials.gov: NCT01187953) in which *de novo* kidney transplant recipients were randomly assigned to LCPT tablets once-daily or tacrolimus twice-daily capsules [9].

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

Patient population

Eligible patients for study 3001 were stable adult (≥ 18 years) male and female recipients of a living or deceased donor kidney transplant between 3 months and 5 years (average of 2 years) before screening, on a stable dose of tacrolimus twice-daily capsules with tacrolimus trough levels within the predefined therapeutic range of 4–15 ng/ml. Eligible patients in study 3002 were adult *de novo* recipients of a living or deceased donor kidney transplant (except for donation after cardiac death). Major exclusion criteria in both studies included recipients of another organ or a bone marrow transplant; patients who received 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

In the conversion study (3001), due to higher bioavailability offered by LCPT, initial dosing of LCPT was 0.7 times the total daily dose of tacrolimus twice-daily being taken by the patient before conversion. Because black patients typically require higher doses of tacrolimus to achieve comparable blood concentrations to Caucasians [24], black patients were converted using a 0.85 conversion multiplier. All subsequent study drug dose adjustments were based on clinical assessment of the patient and maintenance of target tacrolimus whole blood trough levels within the predefined range of 4–15 ng/ml.

In the *de novo* study (3002), LCPT was started at 0.17 mg/kg/day once-daily and tacrolimus twice-daily was started at a total daily dose of 0.1 mg/kg/day. Subsequent doses of each study drug were adjusted to maintain trough concentrations of tacrolimus in whole blood within the target range of 6 to 11 ng/ml for the

first 30 days, then 4 to 11 ng/ml for the remainder of the study. Patients in the *de novo* study 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.

Efficacy endpoints

The incidence of treatment failures within 12 months after the randomization date was the primary efficacy endpoint in both studies. Treatment failure was a composite endpoint 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. In this pooled analysis, treatment failure was compared overall and stratified by sex (male; female), age (< 65 years; ≥ 65 years), and race (black; nonblack).

Safety

The safety endpoints evaluated in the pooled data included the incidence of adverse events (AEs) and serious AEs (SAEs).

Statistical analysis

All subjects who were randomized and received study medication were included in the analysis. The proportion of patients with treatment failure at 12 months was compared between LCPT and tacrolimus twice-daily (overall and within each stratified by subgroup) using a 2-sided Fisher's exact test and 95% confidence interval (CI) for the difference in proportions (LCPT minus tacrolimus twice-daily). The 2-sided 95% CI for the difference in proportions was calculated using the Newcombe–Wilson score method. Mantel–Haenszel (MH) methods were also used to evaluate the treatment difference, with stratification by study [25]. Differences between study-adjusted MH risk estimates yielded similar results. To simplify the presentation, pooled results are presented in this paper without stratification by study. Preliminary tests of treatment-by-study interaction (Breslow–Day test for homogeneity of the odds ratios) revealed no significant heterogeneity, thereby justifying the pooling of studies [26].

Baseline characteristics and treatment emergent AEs (TEAE) were tabulated by treatment for the pooled studies.

Results

Patient baseline characteristics

In total, 861 patients were included in the two studies (LCPT, $N = 428$; tacrolimus twice-daily, $N = 433$); 38% of patients were stable kidney transplant recipients, and 62% were *de novo* kidney transplant recipients. Treatment groups were comparable with respect to pretreatment demographics and prognostic factors (Table 1). In particular, stable patients who converted to LCPT had similar baseline renal function compared to those maintained on tacrolimus.

Efficacy

At 12 months, the overall incidence of treatment failure was similar in the two treatment groups, occurring in 11.9% of patients in the LCPT group and 13.4% in the tacrolimus twice-daily group (treatment difference of -1.48% , 95% CI: -5.95% , 2.99%) (Table 2). As expected, the risk of treatment failure was higher in *de novo* than stable transplant recipients. However, the relative effects of LCPT and tacrolimus (size and direction of the treatment difference) were consistent for the two populations, providing a clinical rationale for combining studies.

The subgroup analyses showed that, for the majority of subgroups analyzed, LCPT had numerically fewer treatment failures; (Fig. 1) particularly, the differences in black kidney transplant recipients [LCPT: 4.6%, tacrolimus twice-daily: 18.4%; treatment difference: -13.82% (95% CI: -27.22% , -0.31%)] (Table 3) and in kidney transplant recipient's ≥ 65 years old [LCPT: 0; tacrolimus twice-daily: 13.5%; treatment difference: -13.46% (95% CI: -25.27% , -0.78%)] (Table 4) significantly favored the LCPT group.

The mean trough levels tended to be similar between treatments in both subgroups, age ≥ 65 and black recipients, with the exception of Week 1 (which was driven by higher starting doses in the *de novo* LCPT group).

Safety

Treatment emergent adverse events

The proportion of LCPT versus tacrolimus twice-daily patients with ≥ 1 TEAE was similar overall (LCPT: 92.3%; tacrolimus twice-daily: 92.8%), and among female patients (LCPT: 94.9%; tacrolimus twice-daily: 94.2%); TEAE tended to be lower for LCPT among black patients (LCPT: 90.9%; tacrolimus twice-daily: 98.0%), and those

≥ 65 years (LCPT: 87.5%; tacrolimus twice-daily: 92.3%). The proportion of patients with ≥ 1 SAE was similar for LCPT (41.8%) vs. tacrolimus twice-daily (43.4%) overall and among subgroups (≥ 65 , 46.9% vs. 48.1%; females, 44.9% vs. 46.8%; for LCPT versus tacrolimus twice-daily, respectively) with the exception of the black patient subgroup that experienced numerically less SAEs in the LCPT group (29.5%) vs. the tacrolimus twice-daily group (38.8%). Adverse events occurring in more than 15% of patients were as follows: diarrhea (24.3% vs. 24.7%; urinary tract infection 18.7% vs. 20.8%; anemia 17.3% vs. 18.5%; hypertension 15.9% vs. 16.6%; constipation 13.1% vs. 15.9%; and edema peripheral 12.4% vs. 15.5%, for LCPT versus tacrolimus twice-daily, respectively).

Discussion

LCPT is an extended-release, once-daily, tablet formulation of tacrolimus. The novel MeltDose drug delivery technology results in a tacrolimus product with improved PK parameters compared to traditional tacrolimus twice-daily capsules, namely improved bioavailability, a lower peak concentration (C_{max}), and less peak-to-trough fluctuation, while ensuring a comparable exposure. The MeltDose technology distinguishes LCPT from the other tacrolimus formulations currently on the market (i.e., Prograf, Astagraf XL [marketed as Advagraf in the EU]). Previous, post hoc subgroup analyses from a randomized double-dummy trial in *de novo* kidney transplant recipients showed numerically less treatment failures among older recipients, black recipients, and female recipients treated with LCPT compared to tacrolimus twice-daily [23]. Similar trends were evident in this pooled analysis of 861 subjects, with LCPT associated with greater efficacy among black recipients and older recipients and female recipients.

It is well-documented that African-American patients have poorer clinical outcomes following transplantation. Even after controlling for socio-economic status (SES), race/ethnicity remains a significant factor affecting graft survival [27–29]. Management of tacrolimus dosing is challenging in African-Americans due to the high prevalence of the CYP3A5*1 variant which is associated with high tacrolimus metabolism [30–32]. The absorption of LCPT distally in the GI [10] may aid to bypass some of the CYP metabolism. In this pooled analysis, African-American patients treated with LCPT had a significantly lower risk of treatment failure compared to African-American patients treated with tacrolimus twice-daily. Achieving therapeutic tacrolimus trough levels is crucial to preventing graft

Table 1. Baseline characteristics of kidney transplant recipients from two phase 3 randomized controlled trials.

	LCPT N = 428	Tacrolimus twice-daily N = 433
Age (years), mean (SD)	46.9 (12.96)	48.1 (14.05)
<65 years, n (%)	396 (92.5)	381 (88.0)
≥65 years, n (%)	32 (7.5)	52 (12.0)
Sex, n (%)		
Male	290 (67.8)	279 (64.4)
Female	138 (32.2)	154 (35.6)
Race, n (%)		
Caucasian	322 (75.2)	326 (75.3)
Black	44 (10.3)	49 (11.3)
Asian	13 (3.0)	13 (3.0)
Other	49 (11.4)	45 (10.4)
De novo transplant, n (%)	266 (62.1)	271 (62.6)
Donor type, n (%)		
Living	196 (45.8)	178 (41.1)
Deceased	232 (54.2)	255 (58.9)
PRA < 5%, n (%)	347 (81.1)	350 (80.8)
Time since transplant (years) (Stable recipients only)		
Mean (SD)	2.2 (1.37)	1.9 (1.25)
Median (range)	1.8 (0.3–5.5)	1.6 (0.3–5.0)
eGFR at conversation (MDRD7, ml/min/1.73 m ²) (Stable recipients only)		
Mean (SD)	61.5 (15.92)	60.0 (17.55)
Median (Range)	62.2 (32.7–107.7)	58.0 (23.8–109.2)
eGFR at month 12 (MDRD7, ml/min/1.73 m ²)		
Stable recipients:		
Mean (SD)	62.00 (16.96)	61.47 (18.21)
Median (Range)	62.08 (24.0–127.9)	60.34 (26.5–123.8)
De novo recipients		
Mean (SD)	58.6 (18.40)	59.8 (20.54)
Median (Range)	59.5 (8–130)	59.0 (9–122)
Diabetes at the time of transplant, n (%)		
Yes	254 (59.3)	266 (61.4)
No	174 (40.7)	167 (38.6)
BMI (kg/m ²), mean (SD),	26.9 (5.22)	27.4 (5.45)
<30 kg/m ²	311 (72.7)	307 (70.9)
≥30 kg/m ²	111 (25.9)	120 (27.7)
Missing	6 (1.4)	6 (1.4)

PRA, panel reactive antibody.

rejection; moreover, higher early tacrolimus trough levels are associated with a significant decreased risk for treatment failure, in particular, BPAR [33]. The *de novo* trial showed that LCPT was associated with a more rapid achievement of tacrolimus trough levels compared to tacrolimus twice-daily [9]. It is a reasonable hypothesis that LCPT may be associated with improved efficacy in black kidney transplant recipients due to its increased bioavailability, allowing for a quicker attainment of efficacious tacrolimus blood levels and less rejection. Preliminary results of a PK study showed that LCPT was less influenced by the genetic background in this at risk population as compared to tacrolimus twice-daily, resulting in more pre-

dictable tacrolimus blood levels despite the cytochrome status [34]. In this pooled analysis, only 1 (2%) black recipient in the LCPT group had BPAR compared to 6 (12%) in the tacrolimus twice-daily group. Unfortunately, even after pooling the two trials the relatively small number of black recipients provides limited power to detect treatment differences in the individual efficacy components. In addition to the potential benefit of improved bioavailability, the once-daily dosing may be particularly desirable in black recipients. Poor adherence to medications has been shown to be one of the most important factors predictive of graft loss [29,35], and historically, black patients have been shown to have poorer adherence to immunosuppres-

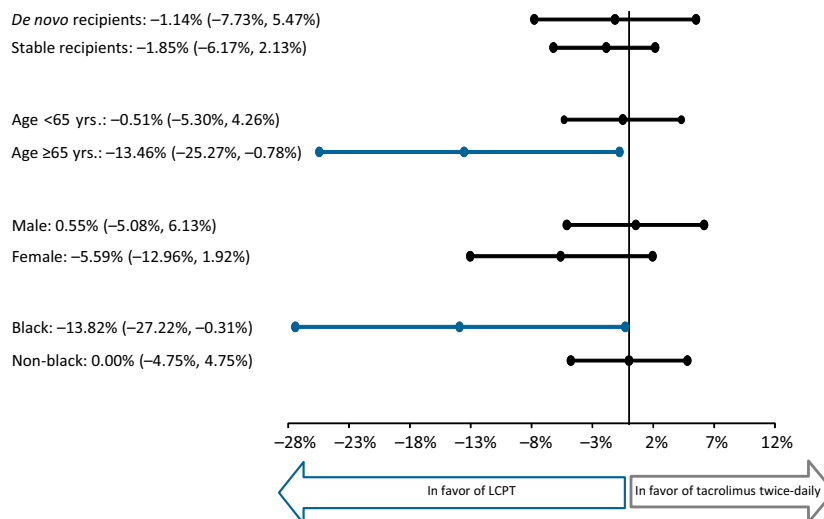
Group: Difference (95% CI)

Figure 1 Forest plot of the difference, and 95% confidence interval, between LCPT versus tacrolimus twice-daily in the standardized incidence of treatment failure at 12 months.

Table 2. Overall and individual efficacy events at 12 months from two phase 3 randomized controlled trials.

Event	LCPT <i>n</i> = 428	Tacrolimus twice-daily <i>n</i> = 433	Difference (95% CI)	<i>P</i> -value*
Treatment failure within 12 months after randomization, <i>n</i> (%)	51 (11.9)	58 (13.4)	-1.48% (-5.95%, 2.99%)	0.5396
<i>De novo</i> recipients	48/266 (18.0)	52/271 (19.2)	-1.14% (-7.73%, 5.47%)	
Stable recipients	3/162 (1.9)	6/162 (3.7)	-1.85% (-6.17%, 2.13%)	
Individual efficacy components, <i>n</i> (%)				
BPAR	35 (8.2)	41 (9.5)	-1.29% (-5.14%, 2.55%)	
Graft loss	8 (1.9)	10 (2.3)	-0.44% (-2.54%, 1.62%)	
Death	9 (2.1)	8 (1.8)	0.26% (-1.76%, 2.31%)	
Lost to follow-up	4 (0.9)	6 (1.4)	-0.45% (-2.15%, 1.18%)	

**P*-value based on Fisher's exact test (2-sided).

95% CI calculated using Newcombe-Wilson scores.

sant drug regimens [29,35–37]. High pill burden increases the risk for poor adherence. Due to the double-dummy nature of the trials, comparisons in adherence between LCPT and tacrolimus twice-daily were not possible. However, studies that have compared once versus twice-daily tacrolimus formulations have found that the once-daily formulation was associated with improved adherence [38–40].

Older-aged recipients are another important kidney transplant subgroup. As the population of the United States and the EU is steadily aging[41,42], so is the number of older-aged individuals on the waitlist for kidney transplantation [43]. While rejection is generally lower in older recipients due to immunosenescence [19,20], when rejection does occur it tends to have

more detrimental effects [21]. In addition, older recipients may be at risk for poorer clinical outcomes due to the fact that they are more likely to receive older and functionally compromised organs [44] and are more likely to have comorbidities than younger recipients. In this pooled analysis, efficacy was significantly better in older recipients treated with LCPT versus tacrolimus twice-daily; in fact, there were no treatment failures in recipients 65 years and older treated with LCPT compared to 7 (13%) in the tacrolimus twice-daily group. Data on whether older-age affects the PK of tacrolimus are mixed, with hypotheses that age-associated alterations in CYP3A and *P*-glycoprotein expression and/or activity, in addition to liver mass and body composition changes, would be expected to affect the PK of tacroli-

Table 3. Efficacy events at 12 months in black kidney transplant recipients from two phase 3 randomized controlled trials.

Event	LCPT <i>n</i> = 44	Tacrolimus twice-daily <i>n</i> = 49	Difference (95% CI)	<i>P</i> -value*
Treatment failure	2 (4.65)	9 (18.47)	−13.82% (−27.22%, −0.31%)	0.0541
<i>De novo</i> recipients	2/9 (22.22)	6/15 (40.0)	−17.78% (−46.78%, 20.49%)	
Stable recipients	0/35 (0.0)	3/34 (8.82)	−8.82% (−22.96%, 2.63%)	
BPAR, <i>n</i> (%)	1 (2.37)	6 (12.24%)	−9.97% (−22.12%, 1.57%)	
Graft loss, <i>n</i> (%)	0	1 (2.0)	−2.04% (−10.69%, 6.16%)	
Death, <i>n</i> (%)	1 (2.37)	0	2.27% (−5.23%, 11.81%)	
Lost to follow-up, <i>n</i> (%)	0	2 (4.18)	−4.08% (−13.71%, 4.47%)	

**P*-value based on Fisher's exact test (2-sided).

95% CI calculated using Newcombe-Wilson scores.

Table 4. Efficacy events at 12 months in kidney transplant recipients ≥65 years old from two phase 3 randomized controlled trials.

Event	LCPT <i>n</i> = 32	Tacrolimus twice-daily <i>n</i> = 52	Difference (95% CI)	<i>P</i> -value*
Treatment failure, <i>n</i> (%)	0	7 (13.546)	−13.46% (−25.27%, −0.78%)	0.0407
<i>De novo</i> recipients	0/15 (0.0)	2/26 (7.79)	−7.69% (−24.14%, 13.44%)	
Stable recipients	0/17 (0.0)	5/26 (19.23)	−19.23% (37.88%, 2.09%)	
BPAR, <i>n</i> (%)	0	4 (7.79)	−7.69% (−18.17%, 3.99%)	
Graft loss, <i>n</i> (%)	0	1 (1.92)	−1.92% (−10.12%, 8.91%)	
Death, <i>n</i> (%)	0	3 (5.87)	−5.77% (−15.64%, 5.60%)	
Lost to follow-up, <i>n</i> (%)	0	1 (1.92)	−1.92% (−10.12%, 8.91%)	

**P*-value based on Fisher's exact test (2-sided); 95% CI calculated using Newcombe-Wilson scores.

mus [18]; some data show increased bioavailability (higher troughs despite lower tacrolimus doses) in older recipients [45] and other data show no age affects [46].

While we found a numerically lower incidence of treatment failures among female transplant recipients treated with LCPT versus tacrolimus twice-daily; the difference did not reach statistical significance, likely due to the small sample size, even with the pooling of the data. Similar to black recipients, females experience lower tacrolimus bioavailability [13–15] and thus would similarly be hypothesized to benefit from the increased bioavailability afforded by the LCPT formulation.

This pooled analysis in over 800 kidney transplant recipients provides evidence that LCPT is at least as effective as tacrolimus twice-daily in the overall target population, and is associated with improved efficacy in high-risk groups, including black and older-age recipients. The trend of improved LCPT efficacy in female recipients is suggestive but requires confirmation in a larger sample. The results of this pooled analysis provide a basis for further, hypothesis-driven, investigations of the effects of this new tacrolimus drug formulation in specific subpopulations.

Authorship

SB: interpretation of data, revising the work critically for important intellectual content. LR: interpretation of data, revising the work critically for important intellectual content. RRA: interpretation of data, revising the work critically for important intellectual content. PW-T: interpretation of data, revising the work critically for important intellectual content. JD: interpretation of data, revising the work critically for important intellectual content. SM: interpretation of data, revising the work critically for important intellectual content. KB: interpretation of data, revising the work critically for important intellectual content.

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Conflicts of interest

Suphamai Bunnapradist: grant/research support: Veloxis, BMS, Novartis, Genentech; Advisory board:

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