

# Evaluation of Flexible Tacrolimus Drug Concentration Monitoring Approach in Patients Receiving Extended-Release Once-Daily Tacrolimus Tablets

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## Abstract

The majority of United States kidney transplant patients are treated with tacrolimus, a drug effective in preventing graft rejection, but with a narrow therapeutic range, necessitating close monitoring to avoid increased risks of transplant rejection or toxicity if the tacrolimus concentration is too low or too high, respectively. The trough drug concentration tests are time sensitive; patients treated on a twice-daily basis have blood draws exactly 12 hours after their previous dose. The schedule's rigidity causes problems for both patients and health care providers. Novel once-daily tacrolimus formulations such as LCPT (an extended-release tablet by Veloxis Pharmaceuticals, Inc., Cary, North Carolina) have allowed for blood draws on a once-daily basis; however, even that schedule can be restrictive. Results from tests taken either before or after that 24-hour target time may be discarded, or worse, may lead to inappropriate dose changes. Data from ASTCOFF, a phase 3B pharmacokinetic clinical trial (NCT02339246), demonstrated that the unique pharmacokinetic curve of LCPT may allow for a therapeutic monitoring window that extends for 3 hours before or after the 24-hour monitoring target. Furthermore, important tools to help clinicians interpret these levels, such as formulas to estimate the 24-hour trough level if an alternative monitoring time is used, were constructed from these data. These study results give treating clinicians access to data that allow them to safely use and monitor LCPT in their patients and expand the body of evidence surrounding differentiation and practical application of the novel LCPT tacrolimus formulation.

## Keywords

pharmacokinetics and drug metabolism, renal disease, transplantation (TRP), tacrolimus, monitoring, calcineurin inhibitor, daily

Tacrolimus is the cornerstone immunosuppressant for kidney transplant patients, with more than 90% of newly transplanted patients receiving the drug following transplantation.<sup>1</sup> Tacrolimus is effective in preventing graft rejection<sup>2</sup>; however, it has a narrow therapeutic range and requires close monitoring to ensure that both supra- and subtherapeutic concentrations are avoided.<sup>1,2</sup> Trough concentrations below the therapeutic range are associated with increased risk of rejection,<sup>3–5</sup> whereas blood concentrations above the therapeutic range increase the risk of toxicity.<sup>6–8</sup>

The majority of patients in the United States are treated with twice-daily immediate-release tacrolimus capsules (IR-Tac: Prograf; Astellas Pharma US, Inc., Northbrook, Illinois), which are administered every 12 hours. As a result, routine monitoring of tacrolimus trough concentrations is necessary to customize each patient's dose and obtain the optimal drug exposure.<sup>9</sup> It is common that tacrolimus monitoring in the first 3 months take place daily to weekly. Among patients who are considered stable and are further posttransplant, monitoring frequency typically decreases.

Monitoring tacrolimus at the anticipated time of its lowest, or trough, concentration is the standard for evaluation of tacrolimus exposure, as this trough time correlates well with overall 24-hour tacrolimus

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exposure.<sup>10,11</sup> Tacrolimus concentrations drawn at other times, for example, too long before or after a trough, may be uninterpretable and could result in unwarranted dosage adjustments, ultimately leading to unintentional under- or overdosing for the patient and placing him or her at risk for the consequences of such deviation from target exposure. The most common practice for transplant centers is to check the tacrolimus trough concentration before a patient's morning dose of IR-Tac. This standardization of practice to accommodate laboratory work can result in many patients presenting for their blood draws at or around the same time and can create logistical challenges for providers and patients alike.

Envarsus XR (Veloxis Pharmaceuticals, Inc., Cary, North Carolina) is a once-daily extended-release tacrolimus tablet formulation (LCPT; formerly LifeCycle Pharma-Tacrolimus) that is produced using MeltDose technology (US patent 7,217,431), a proprietary drug-delivery technology. MeltDose is designed to increase the bioavailability of drugs with low water solubility. The MeltDose process enhances the absorption of drug substances by the creation of a solid dispersion, or a solid solution, of the drug substance through a physical process called "controlled agglomeration." Extended-release products release their medication in a controlled manner at a predetermined rate, duration, and location in the gastrointestinal tract to achieve and maintain optimum therapeutic blood concentrations of a drug. Prior randomized trials in renal transplant recipients comparing LCPT with IR-Tac have shown that LCPT has greater bioavailability, a steadier and more consistent concentration–time profile over 24 hours, and reduced peak-to-trough fluctuations and swing compared with IR-Tac. In addition, LCPT has demonstrated comparable efficacy<sup>12–15</sup> and improved tolerability,<sup>16</sup> plus robust area under the concentration–time curve (AUC)/minimum whole-blood concentration ( $C_{\min}$ ) correlations.

Based on the novel technology used in LCPT, we hypothesized that the tacrolimus trough measurement window could be extended for LCPT because of the flatter pharmacokinetic curve and slow-tailing effect, which was reported in previous studies.<sup>17–19</sup>

The objective of this analysis was to assess the correlation between overall 24-hour tacrolimus exposure, AUC<sub>0–24</sub> (area under the concentration–time curve over 24 hours), and each of 3 times ( $C_{21}$ ,  $C_{24}$ , and  $C_{27}$ ; concentration at 21, 24, and at 27 hours, respectively) to evaluate the potential clinical utility of nonstandard tacrolimus concentration monitoring and to help transplant care providers interpret these concentrations. Second, this evaluation sought to more clearly describe the slow tailing effect of LCPT as it nears the end of its 24-hour dosing interval.

## Methods

Data from the ASTCOFF study (Clinical Trial NCT02339246), "A Steady-state Head-to-Head Pharmacokinetic Comparison Of all FK-506 (Tacrolimus) Formulations," were used. ASTCOFF was a phase 3B study conducted at a single center and was the first pharmacokinetic (PK) study to directly compare IR-Tac, ER-Tac, and LCPT. Tremblay et al.<sup>18</sup> reported on the study methodology and primary results; more in-depth information on PK comparisons among tacrolimus formulations can be found in that publication. The ASTCOFF study was sponsored by Veloxis Pharmaceuticals, Inc.

The University of Cincinnati Institutional Review Board approved the study protocol (IRB# 2014–7906). Informed consent was obtained for all participants; the study's inclusion criteria included patient willingness to give written informed consent and to comply with study visits and restrictions.

PK data from 30 LCPT-treated kidney transplant patients participating in this open-label, randomized, 2-sequence, 3-period crossover trial were used. For a detailed overview of the study design, please refer to the original publication by Tremblay et al.<sup>18</sup> In brief, eligible patients on stable IR-Tac doses were randomized in a 1:1 fashion to 1 of 2 treatment sequences: (1) continue IR-Tac for 7 days, switch to LCPT, then switch to once-daily extended-release tacrolimus capsule (ER-Tac: Astagraf XL; Astellas Pharma US, Inc., Northbrook, Illinois); (2) continue IR-Tac for 7 days; switch to ER-Tac, then switch to LCPT. All patients received each drug for 7 days, and a conversion factor of 1:1:0.80 for IR-Tac:ER-Tac:LCPT was used. This conversion factor was based on the Food and Drug Administration labeling for converting patients from IR-Tac to LCPT. Because no Food and Drug Administration-labeled recommendation is available for conversion to ER-Tac, the literature and recommendations from ex-US labeling were reviewed. No immunosuppressant dose titrations (tacrolimus, mycophenolate, or prednisone, if present) were allowed during the 3-week study period. Twenty-four-hour steady-state PK was obtained at the end of each 1-week dosing period for each of the 3 products. Blood samples for tacrolimus concentrations were drawn as follows: predose concentration ( $C_0$ ), then 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, 18, 21, 24, and 27 hours after administration of tacrolimus. This article presents the results for treatment under LCPT, as the 27-hour blood draw was not included for IR-Tac or ER-Tac, only for LCPT.

Whole-blood concentration analyses were conducted at a central laboratory according to the principles of Good Laboratory Practice. The method used

**Table 1.** Patient Demographics and Baseline Characteristics

Parameter	All (n = 30)
Age (y), mean (SD)	48.5 (12.2)
Sex, n (%)	
Female	12 (40.0%)
Male	18 (60.0%)
Race	
Black or African American	7 (23.3%)
Native Hawaiian or Other Pacific Islander	1 (3.3%)
White	22 (73.3%)
Current transplant donor type	
Deceased	3 (10.0%)
Living	27 (90.0%)
Years since transplant to study, mean (SD)	6.1 (3.0)
Had previous transplant?	
Yes	3 (10.0%)
No	27 (90.0%)
Baseline weight (kg), mean (SD)	91.4 (15.3)
Baseline BMI (kg/m <sup>2</sup> ), mean (SD)	30.6 (4.8)
Baseline trough (ng/mL) per local laboratory, mean (SD)	6.9 (1.7)
Total daily dose (mg) while on IR-Tac and ER-Tac, mean (SD)	5.8 (2.9)
Total daily dose while on LCPT, mean (SD)	4.6 (2.3)

BMI, body mass index; SD, standard deviation.

to assess tacrolimus whole-blood concentrations was liquid chromatography–tandem mass spectrometry. In brief, tacrolimus was extracted from whole blood, separated via high-performance liquid chromatography, and detected using a TSQ Quantum tandem mass spectrometer (Thermo Fisher Scientific, Waltham, Massachusetts).

## Results

Demographics and clinical characteristics of the study sample are provided (Table 1). The patient population was predominately white (73.3%) and male (60.0%); the mean age was 48.5 years. Most subjects (90.0%) had a living donor transplant, and the mean  $\pm$  SD time from transplant was 6.1  $\pm$  3.0 years. The mean  $\pm$  SD total daily drug dose for patients was 5.8  $\pm$  2.9 mg during their weeks on IR-Tac and ER-Tac and 4.6  $\pm$  2.3 mg during the LCPT week. The protocol required this lower LCPT dose because of the formulation's higher oral bioavailability.

The 27-hour PK profile for LCPT is displayed in Supplemental Figure S1. Results for LCPT demonstrate that AUC<sub>0–24</sub> and C<sub>21</sub>, C<sub>24</sub>, and C<sub>27</sub> are highly correlated (Pearson's correlation coefficient, >0.90; *P* < .0001), with corresponding mean  $\pm$  SD concentrations of 7.2  $\pm$  2.9, 6.8  $\pm$  2.9, and 6.3  $\pm$  2.7 ng/mL for C<sub>21</sub>, C<sub>24</sub>, and C<sub>27</sub>, respectively (see Table 2 and Figure 1). Table 2 provides the formula used for interpretation of C<sub>21</sub> and C<sub>27</sub> concentrations. The predicted concentrations and the 95% ellipse for the predictions as well as the corresponding residuals for the predictions are displayed in Supplemental

**Table 2.** Trough Results 21, 24, and 27 Hours Postdose

Time	All 30 Subjects (AUC <sub>0–24</sub> mean = 213.4)	
	Mean Concentration (ng/mL) Arithmetic Mean (SD)	Pearson Linear Correlation Coefficient <sup>a</sup> Estimate (95%CI) (P)
21.0 hours postdose	7.2 (2.9)	0.91 (0.82–0.96) (< .0001)
24.0 hours postdose	6.8 (2.9)	0.91 (0.82–0.96) (< .0001)
27.0 hours postdose (n = 29)	6.3 (2.7)	0.90 (0.79–0.95) (< .0001)

AUC<sub>0–24</sub>, area under the concentration–time curve over 24 hours; C<sub>21</sub>, C<sub>24</sub>, C<sub>27</sub>, concentration at 21, 24, and 27 hours, respectively; CI, confidence interval; SD, standard deviation.

<sup>a</sup>Correlation between mean concentration at given time and mean AUC<sub>0–24</sub>. Equation to estimate C<sub>24</sub>: C<sub>24</sub> = C<sub>21</sub>  $\times$  (1 - 0.0190)<sup>3</sup>, where C<sub>21</sub> = 7.204. This equation gets an estimate of C<sub>24</sub> = 6.8.

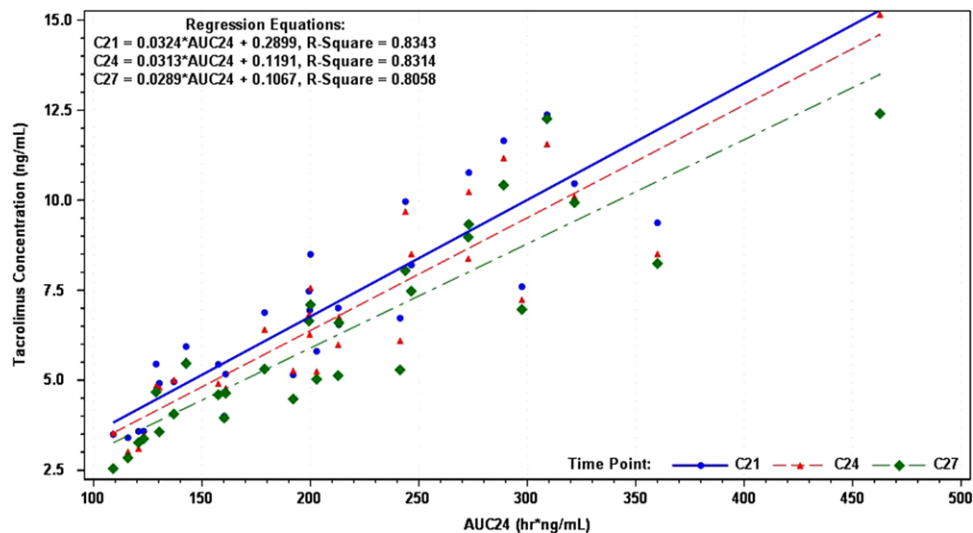
C<sub>24</sub> = C<sub>27</sub>  $\times$  (1 + 0.0261)<sup>3</sup>, where C<sub>27</sub> = 6.296. This equation gets an estimate of C<sub>24</sub> = 6.8.

Figures S2, S3, S4, and S5. The elimination rate was -1.9% per hour between C<sub>21</sub> and C<sub>24</sub>, and -2.6% per hour between C<sub>24</sub> and C<sub>27</sub>. Although individual patients will inevitably exhibit unique tacrolimus clearance, mean tacrolimus concentrations decreased by approximately 0.15 ng/mL/h between hours 21 and 27 in this study population.

## Discussion

In clinical practice, tacrolimus trough concentrations are measured to ensure the efficacy and safety of patient immunosuppression. Fortunately, multiple blood draws over the course of the dosing interval are not needed to calculate an AUC for every patient, as a 12-hour trough concentration for IR-Tac and a 24-hour trough concentration for LCPT and ER-Tac correlate well with a patient's overall exposure to tacrolimus.<sup>10,11</sup> Unfortunately, patients are still required to have blood drawn right before their next dose to monitor tacrolimus. These time-sensitive tests can lead to patients having to be in clinic for many hours, that is, arriving early to have blood drawn right before their next dose of tacrolimus and then waiting to see their transplant care provider. This can result in a backlog of patients at the transplant center because of difficulties coordinating phlebotomy, office visits with providers, and other required testing.

There is a lack of published literature on the challenges of posttransplant trough measurement, and strategies to optimize timing have not been well elucidated. Dasari et al (2016) reported the timing of actual tacrolimus trough measurement blood draws compared with manufacturers' recommendations among inpatient liver transplant patients.<sup>20</sup> In that study, only 22% of measurements were taken at the recommended



**Figure 1.** AUC correlations and associated trough concentrations 21, 24, and 27 hours postdose.  $AUC_{0-24}$ , area under the concentration–time curve over 24 hours;  $C_{21}$ ,  $C_{24}$ ,  $C_{27}$ , concentration at 21, 24, and at 27 hours, respectively.

time.<sup>20</sup> Similarly, a study of inpatient kidney transplant patients deemed that only 26% of blood draws were “appropriate”; drawing blood at incorrect times was one reason there was such a low percentage of appropriate draws.<sup>21</sup>

Given this, it is not surprising that alternative monitoring strategies have been published for extended-release tacrolimus formulations. An article by van Boekel et al (2015) assessed the correlation between blood concentrations of ER-Tac taken at  $C_{32}$  and  $AUC_{0-24}$ .<sup>22</sup> The study was conducted under the premise that exposure assessed at  $C_{32}$  would be more convenient to the patient by allowing for afternoon clinic appointments. That study found good correlations between tacrolimus concentrations (drawn 24, 26, 28, 30, and 32 hours postdose) and  $AUC_{0-24}$  ( $P < .01$  for each point).<sup>22</sup>

The relevance of alternative monitoring strategies is highlighted in a recently published study by Valizadeh et al (2016).<sup>23</sup> They found that among 16 potential stressors following a kidney transplant, patients rated “travelling for check-up” as the fourth highest stressor, right after “fear of graft rejection,” “financial pressure,” and “uncertainly about future health.”<sup>23</sup> Anecdotal evidence collected by the Center for Drug Evaluation and Research (2017) suggests transplant patients experience personal burden on a routine basis with regard to scheduling, preparing for, and undergoing numerous tests, checkups, and procedures.<sup>24</sup>

Extending the window for trough concentration measurement of the LCPT tacrolimus formulation would allow greater flexibility in the timing of blood draws for tacrolimus concentrations, potentially reducing early-morning patient overload in clinics and

allowing concentrations not drawn at exactly 24 hours to be appropriately interpreted. The authors hypothesize that the flatter PK curve associated with LCPT may allow for the possible expansion of the trough measurement window. In this study, we found that blood concentrations taken at both 21 and 27 hours postdose were highly correlated with  $AUC_{0-24}$ . The high correlation coefficients found in this study were similar to those ( $>0.86$ ) found by Gaber et al (2013) in a phase 2 study of stable adult kidney transplant patients on IR-Tac who were converted to LCPT.<sup>17</sup> Further studies of alternative monitoring strategies with LCPT should focus on longer-term safety and efficacy of using such an approach. Additional analyses may also consider the use of modeling and simulation to further elucidate novel monitoring strategies for LCPT.

## Conclusions

The results reported indicate that a therapeutic drug-monitoring window of  $24 \pm 3$  hours for LCPT may be reasonable and could potentially be used with only minimal adjustment in concentration interpretation required. Extending the window for trough concentration measurement would allow for greater flexibility for the transplant clinic, thereby potentially improving the experience for patients and transplant care providers alike.

## Declaration of Conflicting Interests

Benjamin Philosophie does not report any competing interests. Nicolae Leca reports personal fees from Veloxis Pharmaceuticals (consulting, advisory board); grants and personal fees from BMS (consulting, PI

for multicenter study); grants from Quark, Novartis, and Alexion (PI for multicenter studies). Patricia M. West-Thielke reports grants and personal fees from Veloxis Pharmaceuticals (speakers' bureau, advisory board) during the conduct of the study and grants from Astellas and Alexion. Timothy Horwedel reports grants and personal fees from Veloxis Pharmaceuticals (speakers' bureau) during the conduct of the study and personal fees from Novartis Pharmaceutical Corp. and Alexion Pharmaceuticals (speakers' bureau) outside the submitted work. Christine Culkin-Gemmell reports personal fees from Veloxis Pharmaceuticals, during the conduct of the study. Daniel R. Stevens reports he received his standard salary from Veloxis Pharmaceuticals, Inc., during his work on the study and article. Kristin Kistler reports that she received her standard salary from Evidera during her work on the study and article. Evidera employees are not allowed to accept honoraria or other remuneration from clients. Veloxis Pharmaceuticals contracted with Evidera for assistance with the writing of this article.

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