

Switching Study of Kidney Transplant Patients with Tremor to LCP-Tacrolimus (STRATO): an open-label, multicenter, prospective phase 3b study

Langone A, Steinberg SM, Gedaly R, Chan LK, Shah T, Sethi KD, Nigro V, Morgan JC. Switching Study of Kidney Transplant Patients with Tremor to LCP-Tacrolimus (STRATO): an open-label, multicenter, prospective phase 3b study.

Abstract: Tremor is a common side effect of tacrolimus correlated with peak-dose drug concentration. LCPT, a novel, once-daily, extended-release formulation of tacrolimus, has a reduced C_{max} with comparable AUC exposure, requiring a ~30% dose reduction vs. immediate-release tacrolimus. In this phase 3b study, kidney transplant recipients (KTR) on a stable dose of tacrolimus and with a reported clinically significant tremor were offered a switch to LCPT. Tremor pre- and seven d post-conversion was evaluated by independent, blinded movement disorder neurologists using the Fahn–Tolosa–Marin (FTM) scale and by an accelerometry device; patients completed the QUEST (quality of life in essential tremor) and the Patient Global Impression of Change. There were 38 patients in the mITT population. A statistically and clinically significant improvement in tremor (FTM score, amplitude as measured by the accelerometry device and QOL [p-values < 0.05]) resulted post-conversion. Change in QUEST was significantly ($p = 0.006$) correlated ($R = 0.44$) with change in FTM; 78.9% of patients reported an improvement after switching to LCPT ($p < 0.0005$). To our knowledge this is the first trial in KTR that utilizes a sophisticated and reproducible measurement of tremor. Results suggest LCPT is associated with clinically meaningful improvement of hand tremor and may be an alternative management approach in lieu of further dose reduction of immediate-release tacrolimus for patients experiencing tremor.

Anthony Langone^a, Steven M. Steinberg^b, Roberto Gedaly^c, Laurence K. Chan^d, Tariq Shah^e, Kapil D. Sethi^f, Vincenza Nigro^g and John C. Morgan^f on behalf of STRATO Investigators

^aVanderbilt University Medical Center, Nashville, TN, ^bCalifornia Institute of Renal Research, San Diego, CA, ^cUniversity of Kentucky Medical Center, Lexington, KY, ^dUniversity of Colorado Denver, Aurora, CO, ^eTransplant Research Institute, Los Angeles, CA, ^fGeorgia Regents University, Augusta, GA, and ^gVeloxis Pharmaceuticals, Edison, NJ, USA

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Corresponding author: Anthony J. Langone, MD, Vanderbilt University Medical Center, 1161 21st Ave., So., S-3223 MCN, Nashville, TN 37232, USA.
Tel.: 615-322-6976; fax: 615-343-8216;
e-mail: anthony.langone@vanderbilt.edu

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Tacrolimus twice-daily capsules (Prograf[®]; Astellas Pharma US, Inc., Northbrook, IL, USA) is the most widely used calcineurin inhibitor in contemporary kidney transplantation, due to its effectiveness in preventing acute rejection (1, 2). However, tacrolimus possesses a narrow therapeutic index that requires individual dose titration to achieve

satisfactory efficacy while minimizing dose-related toxicities (3). One of the most common tacrolimus-induced side effects is tremor, occurring in 34%–54% of kidney transplant recipients (4, 5). Other neurologic side effects reported with tacrolimus include headaches, insomnia, nightmares, vertigo, dysesthesia, photophobia, and

mood disturbances, as well as more severe manifestations such as akinetic mutism, seizures, cortical blindness, focal deficits, psychosis, encephalopathy, and reduced cognitive ability (5–8). The exact mechanism by which tacrolimus induces neurological adverse events (AEs) remains unknown; however, it has been observed that many symptoms occur or are most pronounced at peak serum tacrolimus blood concentrations and symptoms generally improve when the tacrolimus dose is reduced or when tacrolimus is withdrawn (6, 9, 10). Tremor is associated with a significant decrease in the quality of life (QOL) of transplant patients (11, 12). Furthermore, side effects of immunosuppressant drugs are associated with non-adherence to medication regimens in transplant patients (11, 13, 14).

LCP-Tacro tablets (Envarsus XR™; Veloxis Pharmaceuticals, Hørsholm, Denmark) is an extended-release formulation of tacrolimus designed for once-daily administration. LCP-Tacro is associated with consistent tacrolimus exposure (AUC) at an approximately 30% lower dose compared to twice-daily, immediate-release tacrolimus (15). Tacrolimus peak (C_{max}), the C_{max}/C_{min} ratio, and percent fluctuation and swing are significantly lower for LCP-Tacro vs. twice-daily tacrolimus, and T_{max} is significantly prolonged (15). There is a robust correlation between LCP-Tacro tacrolimus exposure and trough levels, with AUC_{24} and C_{min} correlation coefficients after seven and 14 d of therapy of ≥ 0.86 (15). A hallmark difference between LCP-Tacro and other forms of once- and twice-daily tacrolimus products is the unique, proprietary MeltDose® drug delivery technology (Veloxis Pharmaceuticals), which reduces tacrolimus's particle size to a molecular level (16). The decreased surface area of the drug particles results in complete absorption and increased bioavailability. Studies in *de novo* and stable renal (15) and liver recipients (17–20) have shown that the bioavailability of tacrolimus is 20%–30% higher for LCP-Tacro compared to traditional twice-daily tacrolimus capsules. The increased bioavailability of LCP-Tacro allows for lower doses of LCP-Tacro (approximately 30%; 15% for black patients) compared to tacrolimus twice-daily capsules, with non-inferior efficacy and similar safety between the two formulations (18, 21, 22).

This study's primary objective was to determine the change in tremor severity after switching from tacrolimus twice-daily capsules to LCP-Tacro once-daily tablets, in stable kidney transplant recipients experiencing clinically significant pre-conversion tremors.

Materials and methods

Patient population

Eligible patients were adult (≥ 18 yr) recipients of a living or deceased donor kidney transplant who had received their kidney transplant between one month and five yr prior to screening and were on a stable dose of oral twice-daily tacrolimus capsules for at least seven consecutive days at targeted trough levels. A clinically significant tremor was either initially observed by a health care provider or appraised by patient complaint. A formal examination needed to display amplitude postural or action tremor (finger to nose) characterized by a score of at least two (moderate in intensity) on any of the four upper extremity (UE) postural or action and intention assessments of the Fahn–Tolosa–Marin (FTM) tremor rating scale. Patients who had a history of tremor prior to transplantation or with a family history of tremor were excluded from enrollment.

Other exclusionary criteria included: recipients of any extra-renal organ except for bone marrow transplant; an estimated glomerular filtration rate (eGFR) (based on MDRD7) < 30 mL/min at screening; receiving treatment with an investigational agent within three months prior to screening; unstable dosing and concomitant use of medications known to affect the metabolism of or affect the pharmacokinetic (PK) profile of tacrolimus; a diagnosis of parkinsonism, or tremor from any cause other than tacrolimus including medications known to induce tremors or dopamine blocking agents within the past six months; patients who were taking unstable dosing of drugs known to reduce tremor; and patients who had a rejection episode within three months of screening.

Study design and conduct

This was a 2-sequence, open-label, prospective phase 3b, multicenter, clinical study. Stable kidney transplant patients with tremor were converted from twice-daily tacrolimus to once-daily LCP-Tacro (Fig. 1).

Following the screening (day 0) and enrollment visits (day 1), scheduled study visits were conducted on day 7 and day 14. Subjects were assessed and videotaped two h after tacrolimus dosing. On days 1 through 7, patients continued their pre-study twice-daily tacrolimus regimen to prove stability in dosing and tacrolimus trough levels. On day 8, patients were switched to once-daily LCP-Tacro for a total of seven d. For safety assurance, all patients who received at least a single dose of LCP-Tacro received either a follow-

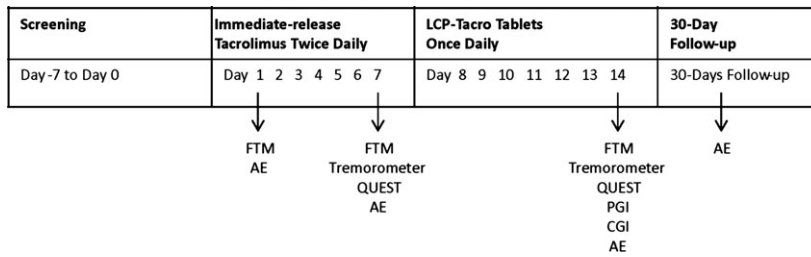


Fig. 1. Study design. AE, adverse event; FTM, Fahn–Tolosa–Marin rating scale; CGI, clinician global impression of change; PGI, patient global impression of change; QUEST, quality of life in essential tremor scale.

up telephone call or study visit 30 d after their last dose.

Patients who completed the two-wk study period were offered to participate in the extension phase of the study and continue treatment with LCP-Tacro for an additional two yr. Patients who declined participation in the extension phase returned to their prior tacrolimus regimen.

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.

Materials

Tremor was evaluated by independent, blinded movement disorder neurologists applying the FTM tremor rating scale to videotaped examinations obtained pre- and seven d post-conversion. If the FTM scores differed significantly between the two neurologists, a third neurologist was enlisted to adjudicate the disparate scores for the ratings in question. The FTM score is derived from 21 elements within three subscales: (i) tremor location/severity rating – four elements on upper limb postural and action tremor severity based on tremor amplitude; (ii) specific motor tasks/functions of writing, pouring liquids and drawing (nine elements); and (iii) subject-reported functional disabilities resulting from tremor (i.e., eating, dressing, drinking, writing; eight elements). Each subscale and the overall score is converted to a 0–100 scale (higher = worse) (23, 24).

To provide a quantitative measure of tremor, a Tremorometer™ (FlexAble Systems; Fountain Hills, AZ, USA) was utilized. A Tremorometer™ is an accelerometry device that measures frequency and amplitude of tremor. Subjects were studied in three positions while wearing the tremorometer device on each hand: posture-holding (posture), with movement on finger to nose (move) and with a 135 gram weight in the hand studied (load). Typically tacrolimus-induced tremor is in the 7–8 Hz range (25).

Lastly, the patients made self-assessments by completing the Quality of Life in Essential Tremor (QUEST) scale (26) and Patient Global Impression of Change (PGI). Physicians completed the Clinical Global Impression of Improvement (CGI) scale. The PGI and CGI are 7-point scales assessing tremor change ranging from most improved to the most significant worsening of symptoms.

Training and blinding procedures

Staff from participating centers who were responsible for enrolling patients into the study and conducting study visits underwent a formal training and certification process. The video-taped FTM instrument administration was sent to independent neurologists in a blinded fashion (i.e., neurologists were not able to differentiate whether the FTM instrument was taken on day 7 or day 14).

Study drug dosing

Following screening, the two-wk treatment period consisted of one wk of twice-daily tacrolimus (days 1 through 7) with conversion to once-daily LCP-Tacro based on a conversion factor from twice-daily tacrolimus to LCP-Tacro of 0.7 for non-black patients and 0.85 for black patients. The goal was to maintain tacrolimus trough levels between 3 and 12 ng/mL.

Patients were maintained on LCP-Tacro for one wk (days 8 through 14). All patients continued their pre-conversion antimetabolite and prednisone without dosage changes.

Study endpoints

Primary efficacy. The primary efficacy endpoint was mean change from baseline in the total FTM score seven d after LCP-Tacro conversion.

Secondary efficacy. The secondary efficacy endpoints were percent change in FTM overall and subscale tremor scores from baseline to seven d after LCP-Tacro conversion, FTM subscale scores, tremorometer measurements, PGI, QUEST, and CGI scores.

Safety. The safety evaluation included reporting AEs and serious adverse events (SAEs), performing physical examinations and obtaining laboratory assessments.

Statistical analyses

The efficacy analyses were conducted using the modified intent-to-treat (mITT) analysis set which included all patients who received at least one investigational treatment (i.e., LCP-Tacro) and had evaluable baseline (pre-conversion) and post-conversion FTM scores. The safety analysis set included all patients who were enrolled in the study.

The primary efficacy analysis was based on evaluating mean change (i.e., absolute change) from baseline (day 7, pre-conversion) on FTM overall score to day 14 (post-conversion) using paired *t*-test (at 0.05 significance level). A 95% confidence interval (CI) was constructed for the mean change from baseline.

The secondary efficacy analyses included evaluating percent change from baseline on FTM overall score to day 14; the correlation between FTM subscale scores/overall score and CGI scales; descriptive summary of tremorometer measurements by treatment phases; descriptive summary of CGI for each score with additional categorized presentation (favorable and unfavorable categories); one-sample binomial test with 95% CI to evaluate LCP-Tacro improvement on CGI scale; improvement in PGI was treated similarly as for CGI scale; summarized presentation of change from baseline in five components of the QUEST questionnaire (Physical, Psychosocial, Communication, Hobbies/Leisure, and Work/Finance) as well as the summary index to evaluate overall patient quality of life with tremor.

Spearman’s correlation was used to examine the relationship between tacrolimus trough and tremor. Analyses of Safety included descriptive summary of AEs, SAEs, and other safety endpoints.

Results

The study took place from 20 December 2011 to 18 April 2013 at 12 US sites.

Patient disposition and baseline characteristics

Forty-four patients were included in the ITT/safety population and 40 (90.9%) completed the study period. Four (9.1%) patients withdrew prematurely from the treatment period. No patients withdrew from study due to an AE. Of the 40 patients

Table 1. Patient demographics and baseline characteristics – ITT and mITT population

	ITT population twice-daily tacrolimus → LCP-Tacro (N = 44)	mITT population twice-daily tacrolimus → LCP-Tacro (N = 38)
Age (yr), mean (SD)	47.8 (13.68)	48.3 (13.73)
Sex		
Male	34 (77.3)	29 (76.3)
Female	10 (22.7)	9 (23.7)
Race		
White	34 (77.3)	31 (81.6)
Black	6 (13.6)	4 (10.5)
Asian	1 (2.3)	0
Other	3 (6.8)	3 (7.9)
Mean (SD) months from current kidney transplant to enrollment	16.85 (14.45)	15.63 (13.72)
Donor type, n (%)		
Living	15 (34.1)	14 (36.8)
Deceased	29 (65.9)	24 (63.2)

ITT, intent-to-treat; mITT, modified intent-to-treat.

who completed the study period, 38 (86.4%) patients were evaluable for efficacy evaluation and were included in the mITT population.

In the ITT population, the majority of patients were male (77.3%) and white (77.3%), with a median age of 50.5 yr. The mean (SD) tacrolimus trough on day 1 for the mITT population was 6.70 (1.83) ng/mL. The mean time from kidney transplantation to study enrollment was 16.85 months. Eleven of 44 (25.0%) patients had a previous kidney transplant (Table 1). All demographics and baseline characteristics were similar in the mITT population.

Primary efficacy endpoint

After the switch from twice-daily tacrolimus and completion of treatment with LCP-Tacro for one wk, the mean (SD) absolute change (improvement) in FTM total tremor score (TTS) from baseline (day 7) was –5.35 ([7.50]; *p* < 0.0001) on day 14 (Table 2 and Fig. 2).

Secondary efficacy endpoints

Fahn–Tolosa–Marin. After the switch from twice-daily tacrolimus and completion of treatment with LCP-Tacro for one wk, there was a significant reduction (improvement) in the mean (SD) percent change FTM TTS (–15.59% (32.00; *p* = 0.005).

FTM category – visit	FTM scores (N = 38)		
	Original value	Absolute change	Percent (%) change
Total score – day 7			
Mean (SD)	25.30 (9.472)		
Total score – day 14			
Mean (SD)	19.96 (7.613)	–5.35 (7.501)	–15.59 (32.004)
95% CI (p-value) ^a		–7.81, –2.88 (<0.0001)	–26.11, –5.07 (0.0048)
Part A: tremor location/severity rating – day 7			
Mean (SD)	26.32 (13.409)		
Part A: tremor location/severity rating – day 14			
Mean (SD)	22.70 (11.107)	–3.62 (11.950)	–5.18 (58.229)
95% CI (p-value) ^a		–7.55, 0.31 (0.0699)	–24.59, 14.24 (0.5920)
Part B: specific motor tasks/function rating – day 7			
Mean (SD)	26.90 (10.213)		
Part B: specific motor tasks/function rating – day 14			
Mean (SD)	23.61 (8.008)	–3.29 (8.165)	–8.61 (24.963)
95% CI (p-value) ^a		–5.97, –0.61 (0.0177)	–16.82, –0.40 (0.0402)
Part C: functional disabilities resulting from tremor – day 7			
Mean (SD)	22.70 (13.071)		
Part C: functional disabilities resulting from tremor – day 14			
Mean (SD)	13.57 (9.701)	–9.13 (10.285)	–36.48 (38.005)
95% CI (p-value) ^a		–12.51, –5.75 (<0.0001)	–49.34, –23.62 (<0.0001)

FTM, Fahn–Tolosa–Marin; mITT, modified intent-to-treat.

^aAsymptotic 95% confidence interval for the mean absolute changes and p-value for paired *t*-test (absolute change); asymptotic 95% confidence interval for the mean % changes and p-value using one-sample *t*-test (percent change).

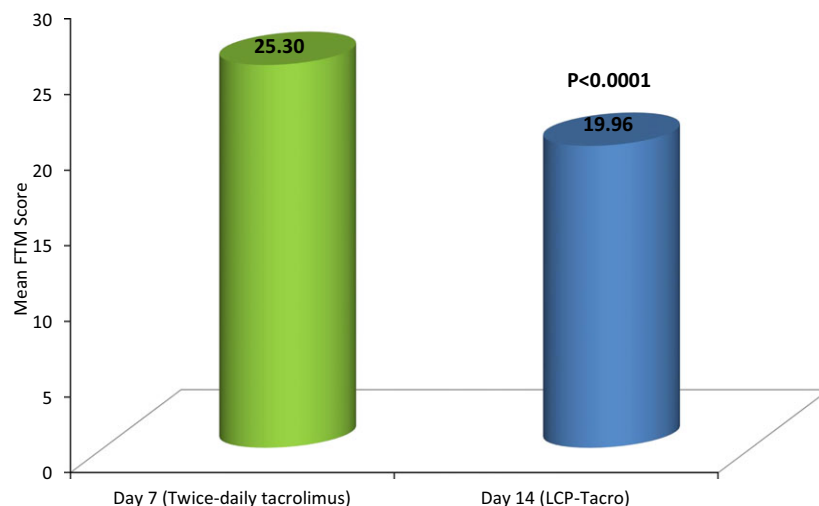


Fig. 2. Fahn–Tolosa–Marin (FTM) score reduction (improvement) after conversion to LCP-Tacro in patients experiencing severe hand tremors.

For the subscale of tremor location/severity (Part A), the mean (SD) absolute change in total score from baseline was -3.62 (11.95, $p = 0.07$) on day 14 and the corresponding percent change was -5.18% (58.23, $p = 0.59$). For specific motor tasks (Part B), the mean (SD) absolute change in total score from baseline was -3.29 (8.17; $P = 0.02$) on day 14 and the corresponding percent change was -8.61% (24.96; $p = 0.04$). For functional disabilities resulting from tremor (Part C), the mean (SD) absolute change in total score from baseline was -9.13 (10.30; $p < 0.0001$) on day 14 and the corre-

sponding percent change was -36.48% (38.01; $p < 0.0001$) (Table 2 and Fig. 3).

Tremorometer. Table 3 and Fig. 4 summarizes absolute change at day 14 from original values in tremorometer measures by frequency and amplitude score for the dominant hand. Thirty-six patients had a mean (SD) absolute improvement (-21.58 milli-g [58.34]) in measured amplitude for posture position of the dominant hand that was statistically significant ($p = 0.03$). There was no change in tremor frequency (~ 8 Hz)

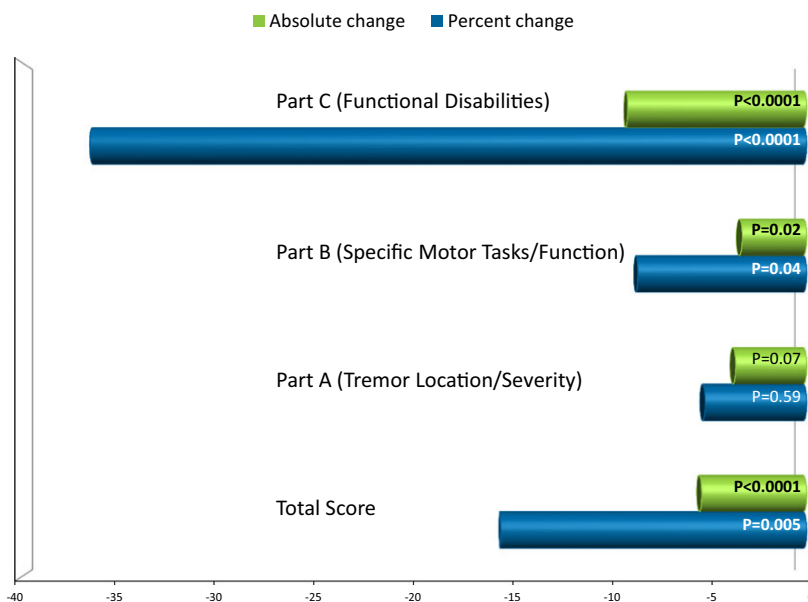


Fig. 3. Absolute and percent change (improvement) in Fahn-Tolosa-Marin (FTM) score and subscale scores at day 14.

Table 3. Summary of tremorometer measurements (dominant hand, absolute change): mITT population

Visit/Position	Posture		Load		Move	
	Original value ^a	Absolute change	Original value ^a	Absolute change	Original value ^a	Absolute change
Frequency – day 7						
N	36		36		35	
Mean (SD)	8.48 (0.97)		8.32 (1.12)		7.96 (1.59)	
Frequency – day 14						
N	37	36	38	36	37	34
Mean (SD)	8.58 (1.10)	0.06 (0.77)	8.42 (1.28)	0.08 (0.88)	7.92 (1.55)	-0.06 (2.00)
95% CI (p-value) ^b		-0.20, 0.32 (0.63)		-0.21, 0.38 (0.57)		-0.76, 0.64 (0.87)
Amplitude – day 7						
N	36		36		35	
Mean (SD)	52.53 (63.02)		40.86 (38.37)		150.37 (71.97)	
Amplitude – day 14						
N	37	36	38	36	37	34
Mean (SD)	30.54 (17.11)	-21.58 (58.34)	30.18 (23.15)	-9.83 (32.50)	135.57 (75.29)	-18.56 (89.61)
95% CI (p-value) ^b		-41.32, -1.84 (0.03)		-20.83, 1.16 (0.08)		-49.83, 12.71 (0.24)

mITT, modified intent-to-treat.

^aFrequency, amplitude, spread, and tremor score value of zero (0) are set to missing for the summary.

^bAsymptotic 95% confidence interval for the mean change and p-value using one-sample t-test.

post-conversion in any position ($p > 0.50$) or amplitude with loading ($p = 0.08$) the hand with a 135 gram weight.

Quality of life. There was a significant ($p < 0.0001$) improvement in the QUEST QOL summary score at day 14. The mean (SD) absolute change from baseline was -7.04 (9.41), and the corresponding mean percent change was -39.08% (39.43). Change in the QUEST score was driven by the change in the physical (mean absolute and percent change from baseline: -11.91 , $p < 0.0001$; -31.80% , $p < 0.0001$), psychosocial (-7.02 ,

$p < 0.0001$; -39.10% , $p < 0.0001$), and work/finance (-6.61 , $p = 0.02$; -53.06% , $p = 0.0005$) subscales. Mean absolute and percent change from baseline in the other subscales were communication, -3.07 ($p = 0.19$), -33.46% ($p = 0.07$); and, hobbies/leisure: -6.58 ($p = 0.15$), -29.10% ($p = 0.23$) (Fig. 5).

Change in QUEST score was significantly ($p = 0.006$) correlated (Pearson coefficient $R = 0.44$) with change in FTM total score; change in QUEST and change in Part C were also significantly ($p < 0.0001$) correlated (Pearson coefficient $R = 0.68$). Most notable, change in physical,

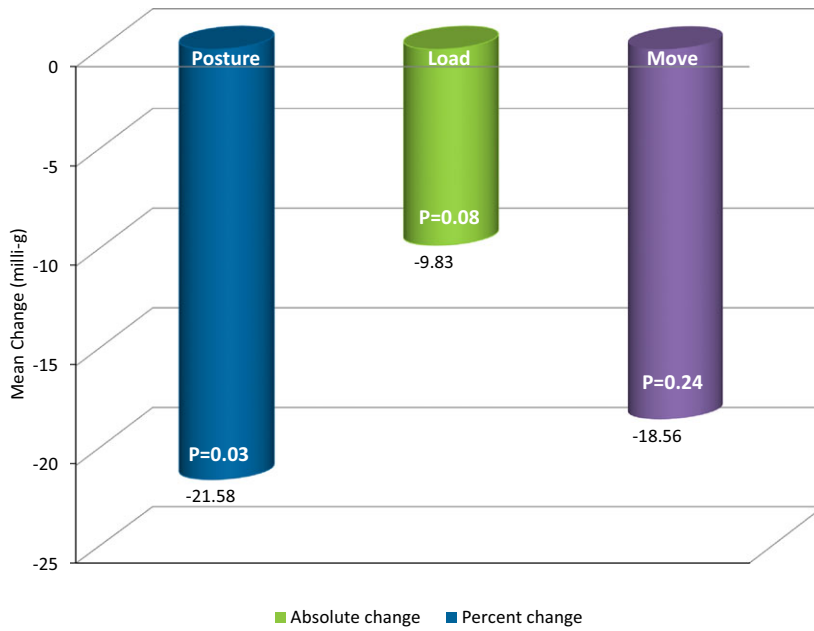


Fig. 4. Absolute change from baseline (improvement) in tremorometer amplitude indicators.

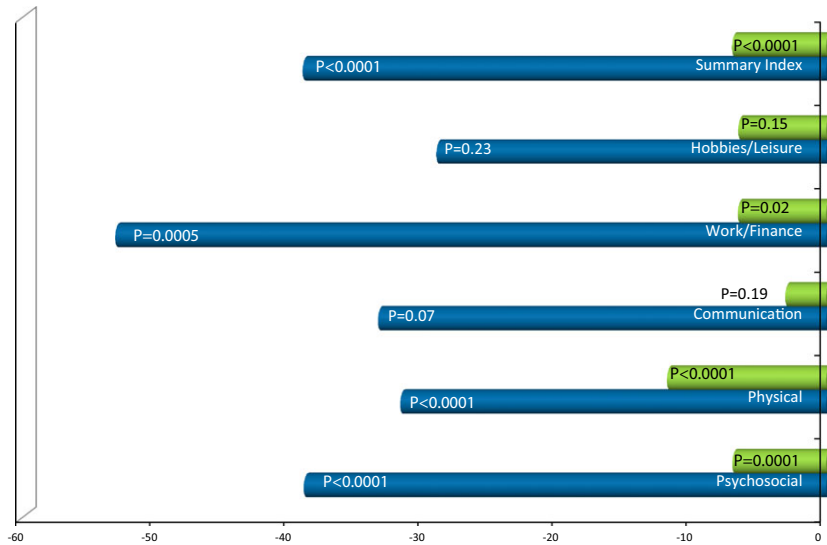


Fig. 5. Absolute and percent change (improvement) in QUEST score and subscale scores at day 14.

($R = 0.48$), psychosocial ($R = 0.47$), and hobbies/leisure ($R = 0.41$), p -values ≤ 0.01 , were significantly correlated with change in the functional disabilities component of the FTM.

PGI and CGI. The PGI indicated that 78.9% of patients reported an improvement of “much better” (23.7%) or “a little better” (55.3%) after switching to LCP-Tacro ($p < 0.0005$). Similarly, 86.8% of physicians on the CGI reported an improvement of “very much improved” (2.6%), “much improved” (28.9%), or minimally improved” (55.3%) ($p < 0.0001$) (Fig. 6).

Safety

Mean (SD) (ng/mL) tacrolimus trough levels were similar across all three time points: day 1: 6.70

(1.83); day 7: 6.53 (2.34); and day 14 (LCP-Tacro): 6.12 (2.64). Tacrolimus trough level was not found to be meaningfully correlated with FTM score ($r^2 = 0.07$), or with tremorometer measurements (posture, $r^2 = 0.04$; load, $r^2 = 0.03$; move, $r^2 = 0.05$). Likewise, change in tacrolimus trough was not meaningfully correlated with change in FTM score ($r^2 = 0.003$). There was a reduction in post-conversion tacrolimus dose levels. Patients enrolled were exposed to a total of 54.82 mg of twice-daily tacrolimus for a mean duration of nine d and 30.29 mg of LCP-Tacro for a mean duration of 7.4 d with only one patient requiring a dose adjustment.

During the twice-daily tacrolimus period (Week 1), there were 10 (22.7%) patients with at least one AE and two (4.5%) patients with a drug-related AE. During the LCP-Tacro administration in

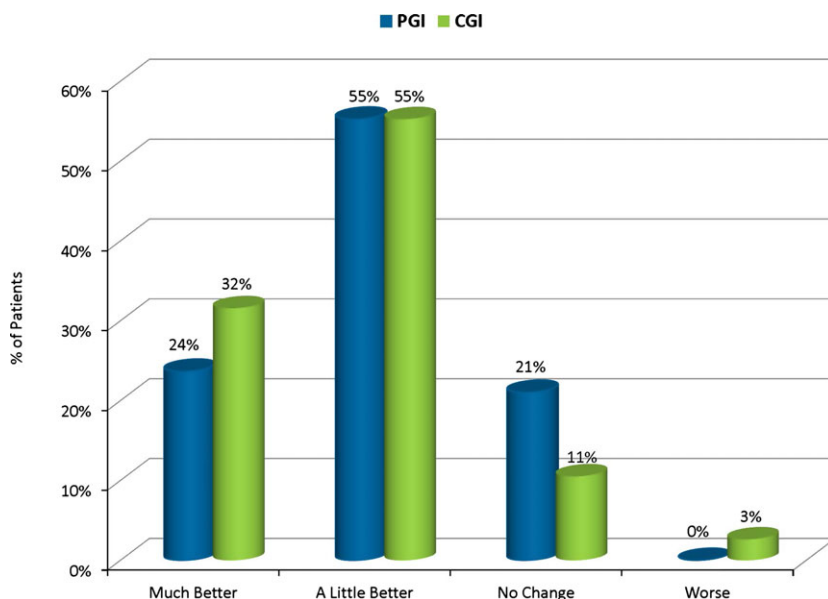


Fig. 6. CGI and PGI Scales show improvement after seven d of LCP-Tacro treatment.

Week 2, eight (19.5%) patients experienced an AE and one (2.4%) AE was drug related. All AEs were of mild or moderate severity. There were no AEs leading to drug discontinuation.

Adverse events reported in two or more patients while taking twice-daily tacrolimus included peripheral edema ($n = 3$), cardiac murmur ($n = 2$), and hyperkalemia ($n = 2$). Adverse events reported in two or more patients while taking LCP-Tacro included nausea ($n = 2$). There were no patient deaths during the study. One of 44 (2.3%) patients experienced an SAE, cellulitis at the incision site, while taking twice-daily tacrolimus. No patients in the LCP-Tacro group experienced an SAE. There were no patients with marked hematological or laboratory abnormalities, AEs causing study drug discontinuation, or events that led to an intervention.

Discussion

Tremor is the most common tacrolimus-associated side effect experienced by kidney transplant recipients (4) and may significantly affect their quality of life (11, 12). The peak serum concentration (C_{max}) of tacrolimus is associated with the highest amplitude of tremor, typically occurring two h after ingestion. Reducing tacrolimus exposure in an attempt to ameliorate tremor symptoms may increase the risk of developing an acute rejection. The PK profile of LCP-Tacro reveals a reduction in the peak-to-trough ratio and C_{max} yet prolongs the T_{max} of LCP-Tacro compared to twice-daily tacrolimus (18, 22). It was hypothesized that the lower concentration maximum experienced with LCP-Tacro may result in a reduction of tremor

severity in kidney transplant recipients previously prescribed twice-daily tacrolimus.

The results of this phase 3b study reveal that the majority of kidney transplant patients who are experiencing tacrolimus-induced hand tremors experienced significant improvement after conversion to LCP-Tacro while maintaining comparable tacrolimus exposure. This translates into LCP-Tacro-treated kidney transplant recipients having less difficulty with numerous activities of daily living such as handwriting, eating, drinking, and dressing as well as less psychosocial embarrassment due to their tremor. Open-label studies such as this are at significant risk of being influenced by a participant placebo effect. In an attempt to reduce this possibility, the protocol was designed to “blind” the rating neurologists. In addition, the tremorometer produces objective data that are reproducible, quantitative, and cannot be falsified by a study subject without detection. One approach to ameliorating tremor is to simply reduce the immediate-release tacrolimus dose, which would lower the peak and overall exposure of the drug. In some patients, this approach might increase the rate of acute and chronic rejection, especially if their measured trough levels were at the low end of acceptable range to begin with. We did not perform a full hour by hour PK profile on each participant. Although contemplated, we expected that the performance of a full PK profile would hinder study enrollment and increase the complexity of the study likely leading to more errors than benefit.

Although the results show a statistical benefit, the question remains whether the impact is clinically significant to the patient. Three separate

(one clinician and two patient reported) questionnaires that were previously vetted as quality of life measures were administered. As all three questionnaires supported each other and were consistent with the results of the objective components of the study, we conclude that the improvements in tremor were true and meaningful to the majority of patients. Another line of evidence that supports switching to LCP-Tacro and corroborates clinician- and patient-rated meaningful improvement in tacrolimus-induced tremor comes from a comparison of our data with the essential tremor literature, where the improvements in the FTM and QUEST were similar (on a percentage basis) relative to the improvements we saw in LCP-Tacro-treated subjects in this study (27, 28).

Tremorometer results demonstrated that tacrolimus-induced tremor amplitudes were reduced across all three positions, but significantly in the posture-holding position. Many drug-induced tremors (including those caused by tacrolimus) typically represent enhanced physiological tremors that respond with a reduction of amplitude and frequency with loading (weighting) (29). The lack of reduction in tremor frequency with loading we found may indicate that the load we used with the Tremorometer was too light (only 135 g). In another study of tacrolimus- and cyclosporine-induced tremor in liver transplant recipients, a load of 500 g resulted in a reduction of tremor frequency of >1.5 Hz in the majority of patients, indicating an enhanced physiological tremor (25). As previously mentioned, tacrolimus has been implicated as a cause in every imaginable neurologic symptom from tremors to seizures. A possible future study would be to determine whether changing the PK profile of tacrolimus would influence the severity of other neurologic parameters. Certain side effects are easy to measure and quantify such as insomnia and cognitive dysfunction. In addition, these symptoms are widely reported and, similar to tremor, are likely to adversely influence affected patient's quality of life.

There were no new safety concerns with LCP-Tacro beyond those expected for Prograf/generic tacrolimus. Adverse events reported in the LCP-Tacro group were mild or moderate in severity. The reduction of dose post-conversion to LCP-Tacro yielded trough levels similar to pre-conversion tacrolimus. In addition, no correlation was found between tacrolimus trough levels and tremor.

The LCP-Tacro program has demonstrated the ability of the innovative MeltDose formulation to reduce peak and peak-to-trough fluctuation with-

out compromising efficacy. Given the narrow therapeutic window of tacrolimus, LCP-Tacro offers the unique advantage of maintaining blood levels in the therapeutic range while avoiding high peaks that may result in toxicities. The current STRATO study is the first clinical demonstration of this clinical advantage. In the STRATO study, it was demonstrated that LCP-Tacro can reduce a troubling side effect and improve quality of life over existing therapies in kidney transplant recipients for patients experiencing tremor.

It is possible that the benefit shown in the STRATO study may extend to other troubling side effects as well, including hypertension and diabetes. Further clinical study is worth undertaking to explore these additional potential significant benefits.

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Authors' contributions

Anthony Langone participated in the research design, writing of the paper, and in the performance of the research; Steven M. Steinberg participated in the writing of the paper and in the performance of the research; Roberto Gedaly participated in the writing of the paper and in the performance of the research; Laurence K. Chan participated in the writing of the paper and in the performance of the research; Tariq Shah participated in the writing of the paper and in the performance of the research; Kapil D. Sethi participated in the research design,

writing of the paper, and in the performance of the research; Vincenza Nigro participated in the research design, writing of the paper, and in the performance of the research; John C. Morgan participated in the research design, writing of the paper, and in the performance of the research.

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