LCP-Tacro or TacNo:
Can the benefits of once-a-day keep the cost at bay?
Novel prolonged-release, once-daily tacrolimus versus traditional twice-daily tacrolimus in renal transplantation

Elisabeth Kincaide, PharmD
PGY1 Pharmacy Resident
University Health System
Division of Pharmacotherapy, The University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center
The University of Texas Health Science Center San Antonio

March 31, 2017

Learning Objectives:
1. Convert different oral formulations of tacrolimus
2. Summarize the current literature for LCP-Tacro
3. Identify criteria for use of LCP-Tacro
LCP-Tacro or TacNo:
Can the benefits of once-a-day keep the cost at bay?
Novel prolonged-release, once-daily tacrolimus versus traditional twice-daily tacrolimus in renal transplantation

Elisabeth Kincaide, PharmD
PGY1 University Health System Resident
March 31, 2017
University Health System and McDermott Building

Learning Objectives:
At the completion of this activity, the participant will be able to:

1. Convert different oral formulations of tacrolimus.
2. Summarize the current literature for LCP-Tacro.
3. Identify criteria for use of LCP-Tacro.

Assessment Questions:

1. In Caucasian renal transplant recipients, the following conversion of IR-Tac to LCP-Tacro should be utilized:
   a. 1 : 0.25
   b. 1 : 0.50
   c. 1 : 0.70
   d. 1 : 0.90

2. In clinical trials when compared to IR-Tac, LCP-Tacro showed:
   a. Superiority
   b. Non-inferiority
   c. Similar safety
   d. A and C
   e. B and C

3. LCP-Tacro may be beneficial to recommend for patients experiencing which of following adverse events?
   a. Nephrotoxicity
   b. Tremor
   c. Nausea
   d. Alopecia

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Faculty (Speaker) Disclosure: Elisabeth Kincaide has indicated she has no relevant financial relationships to disclose relative to the content of her presentation
IMMUNOSUPPRESSION THERAPY

I. Renal transplantation provides the greatest potential in improvement of quality-of-life in patients with end-stage kidney disease\(^1\)

II. Immunosuppression therapy
   a. Essential in preventing allograft rejection

III. Standard of care\(^1\)

IV. Calcineurin Inhibitors (CNIs)\(^1-3\)
   a. Backbone of immunosuppression therapy
   b. Used immediately and long-term in the majority of renal transplantation
   c. Lifelong administration required to prevent organ rejection
   d. Cyclosporine
      i. “Cyclosporine era”
      ii. Greatly improved graft survival
      iii. Fell out of favor with the approval of tacrolimus (FK506, Prograf®)
   e. Tacrolimus
      i. KDIGO guidelines suggest that tacrolimus be used as the first-line CNI agent
      ii. Approximately 90% of U.S. adult kidney transplant recipients were reported to receive tacrolimus as part of their initial maintenance immunosuppressive medication regimen

TACROLIMUS

I. Mechanism of action\(^4-6\)
   a. Inhibits T-lymphocyte activation, by binding to intracellular protein, FKBP-12 and thereby complexes with calcineurin dependent proteins inhibiting calcineurin phosphatase activity
   b. Prevents transcription of IL-2, resulting in impaired lymphocyte function and replication

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[Figure 1: Immunosuppression Medication Therapy]

[Figure 2: OPTN/SRTR 2012 Annual Report in Adult Renal Transplant Patients]

[Figure 3: Tacrolimus Mechanism of Action]
II. Adverse events\textsuperscript{1,4,7–9}
   a. Alopecia
   b. Electrolyte abnormalities: hyperkalemia, hypomagnesaemia
   c. Gastrointestinal disturbances: diarrhea, nausea
   d. Hyperlipidemia
   e. Hypertension
   f. Nephrotoxicity
   g. Neurotoxicity: headache, peripheral neuropathy, tremors, seizure
   h. Post-transplant diabetes mellitus

III. Oral formulations of tacrolimus\textsuperscript{7,10–12}
   a. Immediate-release tacrolimus: dosed twice daily
      i. Prograf \textsuperscript{®} capsules
   b. Extended-release tacrolimus: dosed once daily
      i. Envarsus XR\textsuperscript{®} tablets
      ii. Astagraf XL\textsuperscript{™} capsules
   c. Oral formulations are not interchangeable

d. Astagraf XL\textsuperscript{™} limitations\textsuperscript{13–17}
   i. Studies in stable KTR showed a 5 – 15\% reduction in total drug exposure
   ii. Studies in de novo KTR found a 30 – 40\% reduction in AUC\textsubscript{24} with significantly higher doses required to maintain a therapeutic C\textsubscript{min}
   iii. Phase III RCTs found higher rates of acute rejection in KTR

IV. Pharmacokinetics of oral tacrolimus\textsuperscript{4,18}

<table>
<thead>
<tr>
<th>Table 1: Tacrolimus Pharmacokinetic Properties</th>
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</thead>
<tbody>
<tr>
<td>Absorption</td>
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<tr>
<td>Distribution</td>
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<td></td>
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<tr>
<td>Metabolism</td>
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<tr>
<td>Excretion</td>
</tr>
</tbody>
</table>
V. Pharmacokinetic comparison of oral tacrolimus formulations

Table 2: A steady-state head-to-head PK comparison of all FK-506 (tacrolimus) formulations (ASTCOFF)

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluate the pharmacokinetic profile of IR-Tac, ER-Tac, and LCP-Tacro in stable renal transplant patients to develop conversion recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomized, open-label, two-sequence, single center, three-period crossover study</td>
</tr>
</tbody>
</table>
| Intervention | • Dose conversion of 1 : 1 : 0.80 for IR-Tac : ER-Tac : LCP-Tac, no dose titrations were permitted  
• 24-hour PK collections were obtained at the end of each 1-week period |
| Outcomes | Primary: Evaluate the PK profile of LCP-Tacro compared to ER-Tac and IR-Tac to generate clinical conversion recommendations  
Secondary: Evaluate daily trough levels of each formulation during the 7-day crossover periods  
Evaluate labeled conversion factors |
| Results | Baseline Characteristics n = 30 (15/group) included in the PK analysis: median (IQ range) TDD = 6 (4 – 8) mg for IR-Tac and ER-Tac vs. 4.8 (3.3 – 6.3) mg for LCP-Tacro |
| Endpoints | **Primary Efficacy** | LCP-Tacro vs. IR-Tac | LCP-Tacro vs. ER-Tac |
|           | AUC_{0-24} (h*ng/mL): | RGM*: 117% (107.9, 127), p = 0.002 | RGM*: 125.7% (114.1, 138.5), p < 0.001 |
|           | Fluctuation (%): | LSM: -29% (-48.4, -9.6), p = 0.004 | LSM: -35.3% (-53.4, -17.3), p < 0.001 |
|           | T_{max} (h): | 3 (1.6, 4.4), p < 0.001 | 3 (1.9, 4), p < 0.001 |
| Bioavailability | LCP-Tacro had ~50% greater bioavailability compared to IR-Tac and ER-Tac, p < 0.001 |
| **Secondary Efficacy** | Result |
| Tacrolimus trough concentrations (ng/mL), d 4 – 6 | LCP-Tacro vs. IR-Tac, NS  
LCP-Tacro vs. ER-Tac (p = 0.021)  
ER-Tac and IR-Tac (p = 0.036) |
| Dose Normalization: | IR-Tac to LCP-Tacro: -30%  
IR-Tac to ER-Tac: +8%  
ER-Tac to LCP-Tacro: -36% |
| C_{max} (ng/mL): | C_{max} ~17% lower for LCP-Tacro compared to IR-Tac and ER-Tac, RGM: 82% (p = 0.002 and 0.006, respectively)  
C_{min} ~6% lower for LCP-Tacro compared with IR-Tac |
| AUC_{0-24}: IR-Tac \rightarrow LCP-Tacro RGM = 102% (90% CI 94% - 111%), p = 0.627 |

Author's Conclusion | Oral formulations of tacrolimus are not interchangeable  
30% TDD reduction is recommended for IR-Tac \rightarrow LCP-Tacro  
36% TDD reduction for ER-Tac \rightarrow LCP-Tacro  
8% TDD increase from IR-Tac \rightarrow ER-Tac |
| Critiquer's Conclusion | In Caucasian renal transplant patients converting between IR-Tac \rightarrow LCP-Tacro, a dose conversion factor of 1 : 0.70 should be utilized based on the dose normalization of -30%. |

*Appendix A
VI. Drug interactions and metabolism\textsuperscript{1,18,20}

a. Substrate for CYP3A4 and p-glycoprotein (p-gp)

b. CYP3A4 inhibitors
   i. Increase tacrolimus levels
   ii. Risk of serious adverse reactions

c. CYP3A4 inducers
   i. Decrease tacrolimus levels
   ii. Risk of rejection

d. Pre-systolic metabolism of tacrolimus by gastrointestinal CYP3A isoenzymes and removal by p-gp is extensive

<table>
<thead>
<tr>
<th>Table 3: CYP3A Isoenzymes</th>
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<tbody>
<tr>
<td><strong>CYP3A4</strong></td>
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</table>
| • Accounts for ~30 – 40% total CYP content in the liver and small intestine
| • Inter- and intra-individual variability |
| **CYP3A5**                |
| • Main isoform in the stomach and esophagus |
| • High expressors have a much higher CYP3A liver content |
| • Polymorphic |
| • Wild type CYP3A5* require the highest tacrolimus dosage requirements |
| **CYP3A7**                |
| • Negligible effects in the adult liver |
| **CYP3A43**               |
| • Detected in liver, kidney, prostate, and pancreas |
| • Considerably lower liver expression compared to CYP3A4 |

e. A Study of Extended Release Tacrolimus in African-Americans (ASERTAA)\textsuperscript{21}
   i. Prospective, randomized, open-label, two sequence, three-period crossover study; n = 46 patients
   ii. Baseline: 100% African American; 76% carriers of the CYP3A5*1 allele
   iii. $C_{\text{max}}/C_{\text{min}}$ ratio, % fluctuation, and % swing were significantly lower and $T_{\text{max}}$ significantly higher for LCP-Tacro compared to IR-Tac (p < 0.0001)
   iv. LCP-Tacro showed similar exposure in both CYP3A5 expressors and non-expressors
   v. LCP-Tacro was less impacted by CYP3A5 genotype (Figure 5)
   vi. Homozygous CYP3A5*1 expressors in the IR-Tac group required the highest doses, across all groups
   vii. IR-Tac $\rightarrow$ LCP-Tacro 1 : 0.85 resulted in higher AUC (RGM 112.6%)
   viii. African Americans: 1 : 0.80 – 0.85 dose conversion factor for IR-Tac $\rightarrow$ LCP-Tacro

Figure 5: Mean Plasma Concentration by Time, Expressor, and Drug Group (Adapted from ASERTAA)\textsuperscript{21}
I. MeltDose® proprietary drug delivery technology\textsuperscript{22-26}
   a. Decreased conventional drug size of 10 \textmu m to < 0.1 \textmu m diameter (Figure 6)
   b. Particles broken down into a solid solution
   c. Melt solution is sprayed onto an inert matrix
   d. Optimized pharmacokinetics
      i. Flatter and smoother pharmacokinetic profile
      ii. More controlled, steady drug dissolution
   e. Radiolabeled LCP-Tacro administered after a 10-hour overnight fast (Figure 8)
      i. Initial disintegration occurs in the stomach and/or proximal small bowel
      ii. Complete disintegration occurs in the distal bowel and colon

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{meltdose_technology.png}
\caption{MeltDose® Drug Delivery Technology Compared to Conventional/Nanocrystal Technologies}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{meltdose_pharmacokinetics.png}
\caption{MeltDose® Improved Pharmacokinetics}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{meltdose_radiolabeled.png}
\caption{Radiolabeled LCP-Tacro (Adapted from Philosophe et al.)\textsuperscript{26}}
\end{figure}

\section*{CLINICAL CONTROVERSY}

I. Is LCP-Tacro as effective and safe compared to IR-Tac?
II. Can certain populations benefit from LCP-Tacro versus IR-Tac?
III. What cost barriers must a patient overcome to obtain LCP-Tacro?
LITERATURE REVIEW

I. LCP-Tacro clinical trials27-31

MELT Trial
12-month efficacy

Bunnapradist et al.
Subgroup efficacy

Budde et al.
12-month efficacy

Rostaing et al.
24-month efficacy

STRATO
Safety

Figure 9: LCP-Tacro Phase III and IIIb Efficacy and Safety Clinical Trials in Renal Transplantation

CLINICAL QUESTION: Is LCP-Tacro as effective and safe compared to IR-Tac?

I. MELT trial27
   a. Phase III noninferiority trial in stable KTR; n = 324
   b. Primary efficacy endpoint: proportion of patients with efficacy failures defined as death, graft failure, locally read biopsy-proven acute rejection (BPAR), or loss to follow-up
   c. Results
      i. Noninferior with similar safety
         1. 2.5% (n = 4) in both groups, -4.21% to 4.21% (9% noninferiority margin)
      ii. Mean daily dose of LCP-Tacro was significantly lower than preconversion IR-Tac
      iii. Black KTR benefited from a ~15% lower TDD from IR-Tac to LCP-Tacro

II. Budde et al.28
   a. Phase III RCT trial examining efficacy and safety in de novo KTR; n = 543
   b. Primary efficacy endpoint: proportion of patients with efficacy failures
   c. Results
      i. Noninferior with similar safety
         1. -1.35% treatment difference, -7.94 to 5.27% (10% noninferiority margin)

III. Rostaing et al.29
   a. Two year outcomes of Budde et al.; n = 507 (93% participants from Budde et al.)
   b. Results
      i. Noninferior with similar safety
         1. -4.14%, -11.38 to 3.17% (10% noninferiority margin)
      ii. Subgroup analysis: numerically fewer treatment failures for LCP-Tacro in black, older (≥ 65 years old), and female participants
      iii. Difference in TDD increased over time
         1. TDD was approximately 24% lower with LCP-Tacro at 24 months
**Clinical Question:** Can certain populations benefit from LCP-Tacro versus IR-Tac?\textsuperscript{30,31}

I. Bunnapradis and colleagues performed a pooled analysis to investigate a benefit in subgroups

<table>
<thead>
<tr>
<th>Table 4: Pooled analysis of two phase III trials in de novo and stable kidney transplant recipient subgroups\textsuperscript{30}</th>
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<tbody>
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<td><strong>Objective</strong></td>
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<td><strong>Methods</strong></td>
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<td><strong>Patient Population</strong></td>
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KINCAIDE 9
### Subgroup Analyses

<table>
<thead>
<tr>
<th>Subgroup Analyses</th>
<th>LCP-Tacro n = 44</th>
<th>IR-Tac n = 49</th>
<th>Differences (95% CI)</th>
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<tbody>
<tr>
<td><strong>African American:</strong> treatment failure</td>
<td></td>
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<tr>
<td>Overall, n (%)</td>
<td>2 (4.7%)</td>
<td>9 (18.5%)</td>
<td>-13.82% (-27.22%, -0.31%); p = 0.0541</td>
</tr>
<tr>
<td>BPAR</td>
<td>1 (2%)</td>
<td>6 (12%)</td>
<td>-10% (-22%, 3%)</td>
</tr>
<tr>
<td>Graft loss</td>
<td>0</td>
<td>1 (2%)</td>
<td>-2% (-11%, 6%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (2%)</td>
<td>0</td>
<td>-2% (-5%, 12%)</td>
</tr>
<tr>
<td>Lost to FUP</td>
<td>0</td>
<td>2 (4%)</td>
<td>-4% (-14%, 4%)</td>
</tr>
<tr>
<td><strong>≥ 65 years old:</strong> treatment failure</td>
<td>LCP-Tacro n = 32</td>
<td>IR-Tac n = 52</td>
<td>Differences (95% CI)</td>
</tr>
<tr>
<td>Overall, n (%)</td>
<td>0</td>
<td>7 (13.55%)</td>
<td>-13.46% (-25.27%, -0.78%); p = 0.0407</td>
</tr>
<tr>
<td>BPAR</td>
<td>0</td>
<td>4 (8%)</td>
<td>-8% (-18%, 4%)</td>
</tr>
<tr>
<td>Graft loss</td>
<td>0</td>
<td>1 (2%)</td>
<td>-2% (-10%, 9%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>3 (6%)</td>
<td>-6% (-16%, 6%)</td>
</tr>
<tr>
<td>Lost to FUP</td>
<td>0</td>
<td>1 (2%)</td>
<td>-2% (-10%, 9%)</td>
</tr>
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</table>

### Secondary Safety

<table>
<thead>
<tr>
<th></th>
<th>LCP-Tacro</th>
<th>IR-Tac</th>
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</thead>
<tbody>
<tr>
<td>≥ TEAEs</td>
<td>92.3%</td>
<td>92.8%</td>
</tr>
<tr>
<td>African American</td>
<td>90.9%</td>
<td>98%</td>
</tr>
<tr>
<td>≥ 65</td>
<td>87.5%</td>
<td>92.3%</td>
</tr>
</tbody>
</table>

- SAEs were similar; numerically less in the African American subgroup (29.5% vs. 38.8%)
- Common (>15%) TEAEs: diarrhea, urinary tract infection, peripheral edema, hypertension, and constipation

### Author’s Conclusion

Numerically lower efficacy failure rates are associated with LCP-Tacro use in high-risk patients, particularly black KTR and patients ≥ 65 years of age

### Reviewer’s Critique

#### Strengths/ Limitations

**Strengths:**
- Internal validity: majority white male, age 45 – 50 years old, centrally-read BPAR
- External validity: pooled analysis with stable and de novo KTR, multicenter, U.S., Europe, Latin America, and Asian Pacific
- Selection: randomization, prospective
- Measurement: both studies had the same efficacy endpoint and duration

**Limitations:**
- Publication bias funding: Veloxis Pharmaceuticals Inc
- Low internal validity: different baseline characteristics: de novo vs. stable KTR
- Budde et al. dosing: LCP-Tacro was started at a 70% higher initial dose for de novo KTR vs. IR-Tac
- Basiliximab used as induction agent in all patients in Budde et al.
- P-value not specified by investigators

#### Bunnapradist et al. Conclusion

Efficacy benefits were seen in black and elderly subgroups. There was no significant difference in gender. The notion that de novo KTR achieves quicker troughs with LCP-Tacro is convoluted by higher initial doses in the LCP-Tacro group vs. IR-Tac. When assessing treatment failure, BPAR carried the weight for the African American population which may be due to higher initial LCP-Tacro dosing and the use of basiliximab in the data pooled from Budde et al. The elderly subgroup analysis of treatment failure was widespread across the subgroups of the composite endpoint; this may be explained by greater variability in CYP metabolism in elderly patients or by confounders/baseline characteristics that were not reported and/or assessed.
II. **STRATO**

a. Tremor is reported in approximately 40% of renal transplant recipients.

**Table 5: Switching Study of Kidney Transplant Patients with Tremor to LCP-Tacro (STRATO)**

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluate the change in tremor severity after switching from twice-daily tacrolimus to once-daily LCP-Tacro in patients experiencing clinically significant tremor</th>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Two-sequence, open-label, multicenter, prospective phase IIIb exploratory study</td>
</tr>
</tbody>
</table>
| **Patient Population** | **Inclusion**
- > 18 yr old
- KTR of living or deceased donor
- Received transplant 1 month – 5 years prior to screening
- Stable dose of IR-Tac for ≥ 7 consecutive days
- Reported clinically significant tremor |
| | **Exclusion**
- History of tremor prior to transplantation
- Family history of tremor
- Extra-renal organ recipients
- eGFR < 30mL/min
- Treatment of investigational agent within 3 months prior to screening
- Unstable dosing
- Concomitant medications known to affect metabolism or PK profile of tacrolimus
- Diagnosis of Parkinsonism
- Tremor from any cause other than tacrolimus
- Patients taking unstable dosing of drugs known to reduce tremor
- Rejection episode within three months of screening |
| **Intervention** | Subjects were converted from twice-daily tacrolimus to LCP-Tacro
- Conversion factor: 0.7 for non-African American and 0.85 for African American patients
- Goal trough: 3 – 12 ng/mL
- Tremor pre- and seven d post-conversion was evaluated
- Tremor evaluation methods: FTM tremor rating scale, accelerometry device, QUEST, PGI, and CGI (Appendix B)
- Subjects videotaped 2 h post tacrolimus dosing and evaluated by blinded neurologists |
| **Outcomes** | **Primary Efficacy:** mean absolute change from baseline (d 7) in the total FTM score seven days after LCP-Tacro conversion (d 14) |
| | **Secondary Efficacy:**
- FTM score: % change overall
- FTM: subscale scores
- Tremorometer™ measured three positions: (i) posture; (ii) movement; (iii) load
- QUEST, PGI, and CGI |
| | **Secondary Safety:**
- Reported AEs for IR-Tac and LCP-Tacro
- Serious AEs for IR-Tac and LCP-Tacro
- Physical examinations
- Lab assessments |
**Statistics**
- Efficacy analysis utilized the mITT and safety analysis included all patients enrolled
- Primary efficacy analysis used paired t-test (0.05 significance level) with a 95% CI
- Secondary analyses: % change of FTM overall score at baseline to day 14; correlation between FTM subscale scores/overall score and CGI scores; tremorometer descriptive summary; CGI descriptive summaries; one-sample binomial test with 95% CI to evaluate LCP-Tacro improvement on CGI and PGI; QUEST five components and overall summary of quality of life was summarized by presentation of change
- Spearman’s correlation was utilized to examine the relationship between tacrolimus trough and tremor
- Safety endpoints were analyzed through descriptive summaries

**Baseline Characteristics**
- n = 44 ITT/safety population; 40 completed the study; 4 withdrew
- n = 38/40 included into the mITT analysis/efficacy evaluation
- ITT:
  - 77.3% male; 77.3% white; 50.5 yr median age; mean (SD) months from current kidney transplant to enrollment: 16.85 months; 11/44 (25%) had previous KTs
- mITT
  - 6.7 ng/mL tacrolimus trough on d 1; 6.4 ng/mL d 7; 6.1 ng/mL d 14

**Endpoints**

<table>
<thead>
<tr>
<th></th>
<th>Primary Efficacy</th>
<th>Result</th>
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<tbody>
<tr>
<td>FTM score: absolute change</td>
<td>-5.35 ([7.50]; p &lt; 0.0001)</td>
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<table>
<thead>
<tr>
<th></th>
<th>Secondary Efficacy</th>
<th>Result</th>
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<tbody>
<tr>
<td>FTM score: % change overall</td>
<td>-15.59% (32; p = 0.005)</td>
<td></td>
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</table>

**FTM subscales:**
- tremor location/severity (part A)
  - -3.62 (11.95; p = 0.07)
  - -5.18% (58.23; p = 0.59)
- specific motor tasks/function rating (part B)
  - -3.29 (8.17; p = 0.02)
  - -8.61% (24.96; p = 0.04)
- functional disabilities (part C)
  - -9.13 (10.30; p < 0.0001)
  - -36.48% (38.01; p < 0.0001)

**Tremorometer measurements:**
- Posture
  - -21.58 mg (58.34); p = 0.03
  - NS
- Movement and load
  - NS

**QUEST:**
- Overall
  - -7.04; p < 0.0001; -39.08%; p < 0.0001
  - -11.91; p < 0.0001; -31.08%; p < 0.0001
- Physical
  - -7.02; p < 0.0001; -39.10%; p < 0.0001
  - -6.61; p = 0.02; -53.06%; p = 0.0005
  - NS
- Psychosocial
  - NS
- Work/finance
  - NS
- Communication; hobbies/leisure
  - NS

**Change in QUEST correlated with change in FTM total score and FTM part C**
- p = 0.006
  - p < 0.0001

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<tr>
<th></th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGI</td>
<td>78.9% reported improvement; p &lt; 0.0005</td>
</tr>
<tr>
<td>CGI</td>
<td>86.6% reported improvement; p &lt; 0.0001</td>
</tr>
</tbody>
</table>

**Secondary Safety**

<table>
<thead>
<tr>
<th></th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs IR-Tac</td>
<td>10 (22.7%) pts with ≥ 1 AE</td>
</tr>
<tr>
<td></td>
<td>2 (4.5%) were drug-related</td>
</tr>
<tr>
<td>AEs LCP-Tacro</td>
<td>8 (19.5%) pts with ≥ 1 AE</td>
</tr>
<tr>
<td></td>
<td>1 (2.4%) was drug-related</td>
</tr>
<tr>
<td>SAEs IR-Tac</td>
<td>1 (2.3%), cellulitis at incision site</td>
</tr>
</tbody>
</table>
Author’s Conclusion

- LCP-Tacro is associated with clinically meaningful improvement of hand tremor
- LCP-Tacro may be an alternative to dose reductions of IR-Tac in patients experiencing tremor (moderate intensity defined by FTM)

Reviewer’s Critique

Strengths:
- Measurement: 12 U.S. sites, two-sequence design
- Selection: appropriate inclusion and exclusion criteria
- Independent, blinded movement neurologists
- Staff underwent certification and formal training
- Objective criteria used to measure tremor

Limitations:
- Measurement: open-label
- Short duration: LCP-Tacro steady state is approximately 8 days
- Interpret PGI and CGI with caution, 55% in each group only reported as “a little better”
- PK measurements were limited to trough, $C_{\text{max}}$ would have been useful in correlation with tremor severity

STRATO Conclusion

STRATO is the first clinical trial showing a safety benefit when using LCP-Tacro vs. IR-Tac. Risk vs. benefit must be weighed in interpreting these findings, taking into consideration the benefits of reducing polypharmacy (i.e. addition of medications to control tremor). The short duration of the study did not allow LCP-Tacro to reach steady state (~8 days); therefore, the benefit of reduced tremor may be overestimated in this current study. Tremor assessments were done at IR-Tac peak (2 h), not LCP-Tacro peak (4 h), which may confound the results. Decision to utilize LCP-Tacro in patients with tremor on IR-Tac must be highly individualized. LCP-Tacro may help with tremor that is affecting posture, task/motor function, functional disabilities, and/or quality of life.

**CLINICAL QUESTION:** What cost barriers must a patient overcome to obtain LCP-Tacro?

I. Cost analysis

| Table 6: AWP Comparative Pricing of Immediate Release Tacrolimus Formulations & LCP-Tacro |
|-----------------------------------------------|------------------|------------------|------------------|
| **IR-Tac (Prograf®)** | **Generic** | **LCP-Tacro (Envarsus XR®)** |
| Strength (mg) | | | |
| 0.5 | 1 | 5 | 0.5 | 1 | 5 | 0.75 | 1 | 4 |
| AWP ($/pill) | | | |
| 3.29 | 6.58 | 32.88 | 2.23 | 4.45 | 22.30 | 4.33 | 5.73 | 23 |
| Example (day) | | | |
| $39.48/3 mg bid | $26.7/3 mg bid | $23/4 mg day |

Disclaimer: pricing represents average whole sale price (AWP) and should be used for benchmarking purposes only

| Table 7: Comparative Pricing of Various Benchmarking and Purchasing Methods of IR-Tac Formulations & LCP-Tacro |
|---------------------------------------------------------------|------------------|------------------|------------------|
| **IR-Tac (Prograf®)** | **Generic IR-Tac** | **LCP-Tacro (Envarsus XR®)** |
| AWP | $\ldots$ | $\ldots$ | $\ldots$ |
| WAC | $\ldots$ | $\ldots$ | $\ldots$ |
| GPO | $\ldots$ | $\ldots$ | $\ldots$ |
| 340B | $\ldots$ | $\ldots$ | $\ldots$ |
II. Insurance
   a. Medicare part B
   b. Texas Medicaid
   c. Private insurance payers
   d. Barriers
      i. Highly dependent on PBM and drug tier formulary lists (many list LCP-Tacro as tier 4–5 or as non-preferred)
      ii. Prior authorization with clinical evidence from patient medical records often required
      iii. If denied: transplant center may appeal and/or patients may apply for assistance

III. Veloxis assistance programs for LCP-Tacro
   a. Patient assistance program (PAP)
      i. Out-of-pocket savings for commercially-insured patients
      ii. $0 Co-pay Cards
      iii. Typically covers one year’s supply, approximately $5K annual cap
      iv. Family of four cannot exceed approximately $190K gross income to qualify
   b. Veloxis transplant support (VTS) program
      i. 7-day discharge pack
      ii. 21-day starter pack
      iii. 30-day bridging supply

CONCLUSION

I. Summary
   a. Efficacy: noninferior
   b. Safety: similar safety, decreased tremor
   c. Availability: assistance programs available, federal and commercial insurance drug formulary tiers, increased cost compared to generic formulation of IR-Tac

II. LCP-Tacro recommendations
   a. Renal transplant recipients
      i. Requiring high IR-Tac doses
         1. $0.15 mg/kg/day
      ii. Experiencing tremor without previous history of tremor prior to transplant
         1. Clinically significant tremor: moderate intensity on any of the four upper extremity assessments of the FTM tremor rating scale
         2. Tremor affecting quality of life, functional disabilities, task/motor function, and/or posture
   b. Conversion to LCP-Tacro
      i. 1:0.70 conversion factor from IR-Tac in non-African American patients
      ii. 1:0.80 – 0.85 conversion factor from IR-Tac in African American patients
   c. Additional criteria
      i. Insurance/PBM is not a barrier to obtain LCP-Tacro
      ii. If known barrier, continue therapy with IR-Tac
References:


24. Hold P, Thomassen JQ, Rasmussen SR. MeltDose® a one-step industrial process for the manufacturing of solid dispersion. 6th *World Meeting of Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology;* 7th to 10th April 2008; CCIB, Barcelona, Spain.


Table 8: Abbreviations

- AEs: adverse events
- AUC₀₋₂₄: area under the curve during 24 hours
- AUC₂₄: area under the curve at 24 hours
- BMT: bone marrow transplant
- BPAR: biopsy-proven acute rejection
- CGI: clinical global impression of improvement
- CI: confidence interval
- Cₘₐₓ: peak serum concentration
- Cₘᵢₙ: minimum blood plasma concentration
- CYP: cytochrome P
- de novo: new
- eGFR: estimated glomerular filtration rate (based on MDRD7)
- ER-Tac: extended-release tacrolimus; Astagraf XL™
- FTM: Fahn-Tolosa-Marin
- FUP: follow-up
- GPO: group purchasing organization
- IR-Tac: immediate-release tacrolimus (Prograf®, generic tacrolimus)
- KDIGO: Kidney Disease Improving Global Outcomes
- KT: kidney transplant
- KTR: kidney transplant recipients
- LCP-Taco: LCP-Tacrolimus, Envarsus XR®
- LCP: Life Cycle Pharma, former name of Veloxis Pharmaceuticals Inc
- LSM: least square means
- N: number
- NS: non-significant
- PBM: pharmacy benefits manager
- PGI: patient global impression of change
- PK: pharmacokinetics
- QUEST: quality of life in essential tremor
- RCT: randomized controlled trial
- RGM: ratio of geometric means
- SAEs: serious adverse events
- TDD: total daily dose
- TEAEs: treatment emergent adverse events
- Tₘₐₓ: the time after administration of a drug when maximum concentration is reached
- Tx: transplant
- WAC: wholesale acquisition cost

Appendix A: FDA Bioequivalence Methods

- Two products are deemed bioequivalent if the 90% confidence intervals of geometric mean generic/innovator Cₘₐₓ or AUC ratios fall within 80 – 125%
- Data must be log-transformed prior to conducting an analysis of variance (ANOVA) to obtain geometric means
- AUC is less variable than Cₘₐₓ

Appendix B: STRATO Evaluation Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Evaluator</th>
</tr>
</thead>
</table>
| Fahn-Tolosa-Marin (FTM) | Comprised of 21 elements within three subscales⁴⁶,⁴⁷  
1. Specific motor tasks/functions of writing, pouring liquids, and drawing – nine elements  
2. Subject-reported functional disabilities resulting from tremor (i.e. eating, dressing, drinking, writing, etc…) – eight elements  
3. Tremor location/severity rating – four elements on upper limb postural and action tremor severity based on tremor amplitude | Blinded movement neurologist |
| Tremorometer™ (TM)   | Accelerometry device that measures frequency and amplitude of tremor⁴⁸  
Studied in three positions:  
1. Posture  
2. Movement  
3. Load (135 g weight) | Blinded movement neurologist |
Quality of Life in Essential Tremor (QUEST)

- Self-assessment questionnaire comprised of:
  1. Communication
  2. Work and finances
  3. Hobbies and leisure
  4. Physical
  5. Psychosocial

Patient

Patient Global Impression of Change (PGI)

- 7-point scale rating tremor change from “significant worsening of symptoms” to “most improved”

Patient

Clinical Global Impression of Improvement (CGI)

Patient’s physician

Figure 10: Adapted from the Fahn, Tolosa, Marin Tremor Rating Scale (Section 11 – 13)