Dosing strategies for de novo once-daily extended release tacrolimus (LCPT) in kidney transplant recipients

NCT Number: 03713645

Date: August 21, 2018

1) Abstract of the study

Outcomes after kidney transplantation have been significantly enhanced with the advances made in immunosuppressive therapies. Tacrolimus is currently marketed as an extended-release once-daily formulation dosing option for patients, decreasing pill burden and possibly decreasing adverse effects. Some transplant recipients have been shown to have higher dosage requirements. According to the literature, this can be linked to genetic disparities in the metabolism of tacrolimus.. This potential complication, where differences on specific genes alters metabolism of tacrolimus, can increase difficulty in getting to a therapeutic drug level for immunosuppresants and is one large factor that contributes to the fact that kidney transplant survival rates differ between patients. Due to the enhanced bioavailability of Meltdose formulation once-daily extended-release tacrolimus, its de novo use in recent research and practice has been shown to expedite achievement of target tacrolimus trough concentrations. De novo use of once-daily tacrolimus formulations is understudied. Through a prospective investigational study, we aim to determine the optimal strategy for de novo dosing of once-daily extended release tacrolimus (MeltDose formulation) for kidney transplant recipients at Temple University Hospital.

2) Protocol Title

Dosing strategies for de novo once-daily extended release tacrolimus (LCPT) in kidney transplant recipients

3) Investigator(s)

Principal Investigator(s): Adam Diamond, Pharm.D. BCPS

Co-PI: Antonio Di Carlo, MD, CM, FACS, FRCSC

4) Objectives

Primary Objectives:

Identify the target dose of de novo once-daily MeltDose formulation of tacrolimus that achieves therapeutic tacrolimus trough concentrations for kidney transplant patients at Temple University Hospital

Secondary Objectives:

Identify the time to achievement of therapeutic trough concentrations for the de novo MeltDose formulation of tacrolimus

Identify if the CYP3A5 genetic allele is expressed in enrolled participants to retrospectively determine correlation betweenCYP3A5 genotype expression and other factors (e.g., time to trough, tacrolimus dosing, patient outcomes, demographics) in kidney transplant patients

5) Rationale and Significance

Tacrolimus is the most commonly utilized calcineurin inhibitor after kidney transplantation. It is used in combination with mycophenolate mofetil and prednisone in order to provide sufficient immunosuppression to prevent acute rejection of transplanted organs. The development of a MeltDose tablet formulation has been designed to enhance the bioavailability of tacrolimus due to the low water solubility of the drug. In clinical trials, the utilization of MeltDose tablet formulations of tacrolimus has been shown to provide rapid achievement of target tacrolimus trough concentrations. This once daily dosing regimen has also led to lower peak concentrations and equivalent overall exposure when compared to immediate release and other extended release formulations of tacrolimus. Similar efficacy and safety profiles have been demonstrated when comparing the MeltDose formulation of tacrolimus to other available formulations.

Some transplant recipients have been shown to metabolize tacrolimus at a higher or lower rate compared to other patients, which can greatly impact post-transplant outcomes. This can be prompted by the patient having polymorphisms of the cytochrome P450 3A5 (CYP3A5) gene that they may possess moreso compared to others. If a patient is a CYP3A5*1 allele expressor, this leads to metabolically active CYP3A5 causing higher metabolism rates of tacrolimus. CYP3A5 expressors can require up to 2-fold higher tacrolimus doses to achieve similar trough concentrations compared to CYP3A5 non-expressors. This sparks the question as to what the optimal initial dosing of the MeltDose formulation of tacrolimus should be when used in the de novo setting for kidney transplant patients. Delayed achievement of target tacrolimus trough concentrations has been linked to higher rates of acute rejection as well as development of de novo donor-specific antibodies. Avoiding subtherapeutic and supratherapeutic concentrations of tacrolimus in the early post-transplant period will help to lower risk for acute rejection.

Tacrolimus, the immunosuppressant drug, is used for kidney transplant recipients. MeltDose tacrolimus is a lawfully marketed formulation of the tacrolimus drug. The de novo, or initial, use of MeltDose tacrolimus is a permittedunlabeled indication that is within the scope of medical practice and often used for this population. However, data surrounding this initial dosing is lacking. We hope to contribute to existing knowledge by identifying optimal dosing strategies for this more convenient once daily formulation of tacrolimus for kidney transplant patients.

6) Resources and Setting

Temple University Hospital performs approximately 60 kidney transplants (deceased and live donor) per year. As a result we intend to reach our target enrollment in 1-2 years. The study staff includes myself, transplant surgeon, and research coordinators. The clinicians have been working in kidney transplant for numerous years (ranging from 5 to 25 years), and the entire research team is CITI trained. Only investigators and members of the research team, who will be adequately informed about the protocol and study-related duties and are currently CITI trained, will have access to patient protected health information for the purposes of this study.

This is a single center prospective observational study. As a result all research procedures will be conducted at Temple University Hospital. The collection and analysis of research data will be conducted at Temple University Hospital using data captured in Alpha Imaging and EPIC. Only prospective data, from subject enrollment until 30 day visit are collected.

Participants enrolled are required to receive saliva sample for genetic testing, complete tremor questionnaire, and receive Meltdose formulation of tacrolimus. The difference between standard of care and the investigational procedures for this study are as follows:

Standard of Care

- All kidney transplant recipients at Temple University Hospital will receive a *de* novo combination maintenance immunosuppression regimen. This combination regimen includes tacrolimus immediate-release and mycophenolate mofetil with or without prednisone. Mycophenolate mofetil and prednisone are started on the day of transplantation. The day of initiation of tacrolimus immediate-release is decided per transplant surgeon discretion. Upon hospital discharge after transplant surgery, patients will be seen in the outpatient abdominal transplant surgery clinic three times weekly. Tacrolimus extended-release is associated with fewer tremors, has once-daily dosing to improve compliance, and requires lower total daily doses compared with tacrolimus immediate-release to achieve therapeutic tacrolimus trough concentrations. For those reasons, our current practice in patients who are receiving tacrolimus immediate release and require high

doses of tacrolimus immediate-release (10mg orally twice daily or greater), are experiencing significant tremors, or have medication non-compliance, those patients are converted from tacrolimus immediate-release to tacrolimus extended-release. Tacrolimus extended-release is not currently used *de novo*. The following table portrays the laboratory parameters that are drawn per standard of care at Temple University Hospital for kidney transplant recipients. Average length of inpatient stay is 4 days.

Table A

Setting	Tacrolimus immediate-release trough concentration	Serum creatinine	Glomerular filtration rate	Potassium	Blood glucose	Hemoglobin A1C
Day of Transplant		✓	✓	✓	✓	✓
Inpatient (lab parameters obtained every 24 hours)	✓ (once tacrolimus initiated)	✓	✓	✓	✓	
Outpatient (lab parameters obtained three times weekly on Mon, Wed, Fri	✓	✓	✓	✓	✓	

Investigational (Research)

- All kidney transplant recipients at Temple University Hospital will receive a *de* novo combination maintenance immunosuppression regimen. This combination regimen includes **tacrolimus extended-release** and mycophenolate mofetil with or without prednisone. Mycophenolate mofetil and prednisone are started on the day of transplantation. The day of initiation of tacrolimus extended-release is decided per transplant surgeon discretion. **The use of tacrolimus extended-release *de* novo differs from the standard of care. Goal tacrolimus trough concentrations for tacrolimus extended-release are identical to the way that goal tacrolimus trough concentrations are drawn for tacrolimus immediate-release at Temple.** Upon hospital discharge after transplant surgery, patients will be seen in the outpatient abdominal transplant surgery clinic three times weekly. **Table B portrays the laboratory parameters that are drawn per research protocol which is identical to laboratory parameters drawn for all kidney transplant patients at Temple University Hospital (Refer to Table A).** Average length of inpatient stay is expected to be 4 days. Table 2 portrays the timeline of data collection. **The data collected that differs from standard of care includes the QUEST Tremor Questionnaire at Day 30 and the required oral swab for testing of CYP3A5 metabolic enzyme activity.**

Table B

Setting	Tacrolimus extended-release trough concentration	Serum creatinine	Glomerular filtration rate	Potassium	Blood glucose	Hemoglobin A1C
Day of Transplant		✓	✓	✓	✓	✓
Inpatient (lab parameters obtained every 24 hours; approximately	✓ (once tacrolimus initiated)	✓	✓	✓	✓	

Days 0-4						
Outpatient (lab parameters obtained three times weekly on Mon, Wed, Fri; approx Days 4-30	✓	✓	✓	✓	✓	

Table C

Day 0	Study drug (tacrolimus) initiated at 0.13/mg/kg/day for all patients ***(the day of initiation decided per transplant surgeon discretion)***
Day 0-4	Inpatient laboratory parameters checked every 24 hours per Tables A and B
Day 4-30	Outpatient laboratory parameters checked three times weekly on Monday, Wednesday, and Friday per Tables A and B
Day 30 visit (+/- 5 days)	Draw tacrolimus trough levels, serum creatinine, estimated glomerular filtration rate, serum potassium, and blood glucose. Complete tremor questionnaire with participant.
During or prior to Day 30 visit	Oral swab performed to be analyzed for testing of metabolic enzymatic activity **(This will be performed to see if genetic testing results reflect how the participant is metabolizing tacrolimus [determined from tacrolimus extended-release doses used)**

All research procedures (e.g., data entry, data analysis) will be conducted at TUH. Temple University School of Pharmacy pharmacogenomics department will be used to store specimen for genetic testing. All specimen will be de-identified and stored in an appropriate and locked container at Temple University School of Pharmacy pharmacogenomics department—accessible only to research and pharmacogenomics department staff. Researchers involved in this study will possess a list that links the genetic testing results to the participant. This list will be stored in a password protected encrypted document on TUH computer.

Dose Titration Protocol

For the purpose of this study no changes will be made to dose titration strategies for enrolled patients. For enrolled participants tacrolimus will be titrated as per Temple University Hospital's standardized dose titration protocol. The following dose titration strategy is used to titrate tacrolimus extended-release and tacrolimus immediate-release for patients receiving standard of care and for patients who are enrolled in this study:

Tacrolimus Titration Protocol
Abdominal Organ Transplant

Tacrolimus Level	Target Level	Dose Adjustment*
< 2	8-10	Increase by 125%
	6-8	Increase by 100%
	5-8	Increase by 75%
2 - < 4	8-10	Increase by 100%
	6-8	Increase by 75%
	5-8	Increase by 50%
4 - < 6	8-10	Increase by 75%
	6-8	Increase by 50%
	5-8	Increase by 25%
6 - < 8	8-10	Increase by 50%
	6-8	No change
	5-8	No change
8 - < 11	8-10	No change
	6-8	No change
	5-8	Decrease by 50%
11 - < 12	8-10	No change
	6-8	Decrease by 50%
	5-8	Decrease by 50%
12 - < 14	8-10	Decrease by 25%
	6-8	Decrease by 50%
	5-8	Hold next dose, decrease by 50%
14 - < 16	8-10	Decrease by 50%
	6-8	Hold next dose, decrease by 50%
	5-8	Hold and recheck level
16 - < 18	8-10	Hold next dose, decrease by 50%
	6-8	Hold and recheck level
	5-8	Hold and recheck level
≥ 18	8-10	Hold and recheck level
	6-8	Hold and recheck level
	5-8	Hold and recheck level

*Doses are to be adjusted based on total daily dose

Tacrolimus Trough Level Goals

KIDNEY TRANSPLANT

Time from Transplant	Goal Tacrolimus Trough Level
0-6 months	8-10 ng/mL
7-12 months	6-8 ng/mL
>12 months	5-8 ng/mL

7) Prior Approvals

Veloxis Pharmaceuticals approved budget for funding of study

8) Study Design

Single center prospective observational study

a) Recruitment Methods

Patients will be identified when an organ from live or deceased donor becomes available for kidney transplant. Prior to receiving their kidney transplant, subjects will be screened for inclusion/exclusion criteria on the day of transplantation. During the pre-operative preparation for transplant, patients will be consented for surgery and consented for the study at the same time if they volunteer to be included. The transplant surgeon performing the transplant operation will be responsible for screening the patients for inclusion and exclusion criteria as well as obtaining informed consent. Patients will need to provide informed consent to be included in the study, and will receive a copy of their consent. Each potential participant will be approached by the transplant surgeon and informed of all information pertinent to the study prior to providing consent. No advertisements for recruitment will be performed and no compensation will be provided for participation.

b) Inclusion and Exclusion Criteria

Inclusion Criteria

- Adult patient who is 18 years of age or older receiving a kidney transplant at the Temple University Hospital's Kidney Transplant Program who are capable of understanding consent and volunteer to take part in the study

Exclusion Criteria

- Scheduled for multiple organ transplant at enrollment
- Non-English speaking
- Pregnant women
- Moderate-severe hepatic impairment (Child Pugh > 10 or bilirubin > 2)
- Existing contraindications to tacrolimus-based products including known hypersensitivity to tacrolimus or any other component of the formulation
- Receiving concomitant medications known to have strong drug-drug interaction potential with tacrolimus including fluconazole, voriconazole, posaconazole, isavuconazole, itraconazole, ketoconazole, diltiazem, verapamil, metronidazole, erythromycin, clarithromycin, rifampin, rifabutin, rifapentine, phenytoin, fosphenytoin, phenobarbital, primidone, carbamazepine, St. John's Wort, efavirenz, neivrapine, etravirine, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, cobicistat

c) Study Timelines

Study enrollment and informed consent process will begin once IRB approval is granted. Each subject will be active in the study until their one month visit—occurring day 30 +/- 5 days. We anticipate it will take 12 months to enroll the first 35 subjects. After the first 35 subjects are enrolled, an interim analysis will be performed to evaluate the efficacy and safety of the initial dose provided. A report of results will be distributed to Veloxis Pharmacuieticals® to assess the efficacy and safety of the utilization of tacrolius extended-release. A statistical analysis will be completed to identify the correlation with achieving a therapeutic tacrolimus trough concentration with using tacrolimus extended-release in the de novo setting. If required, an additional 35 patients will be enrolled. We anticipate that after enrollment of all subjects, data analyses will be completed 3-6 months after recruitment has ceased.

d) Study Procedures and Data Analysis

Study procedures:

This study is a single center prospective observational study conducted at Temple University Hospital (TUH). All participants will be consented for all procedures involved in this study. This study will utilize the QUEST questionnaire (attached) to evaluate the severity of tremors at 1 month. Data to be collected includes tacrolimus trough levels, study drug dosing, hemoglobin A1c, incidence and severity of tremors, potassium, glomerular filtration rate, and rejection episodes (See Table B).

Table C

Day 0	Study drug (tacrolimus) initiated at 0.13/mg/kg/day for all patients ***(the day of initiation decided per transplant surgeon discretion)***
Day 0-4	Inpatient laboratory parameters checked every 24 hours per Tables A and B
Day 4-30	Outpatient laboratory parameters checked three times weekly on Monday, Wednesday, and Friday per Tables A and B
Day 30 visit (+/- 5 days)	Draw tacrolimus trough levels, serum creatinine, estimated glomerular filtration rate, serum potassium, and blood glucose. Complete tremor questionnaire with participant.
During or prior to Day 30 visit	Oral swab performed to be analyzed for testing of metabolic enzymatic activity **(This will be performed to determine ability of the patient to metabolize tacrolimus)**

Data and Specimen Banking:

Saliva collection kits will be used to collect subject saliva samples and genetic testing will be performed and stored at Temple University School of Pharmacy pharmacogenomics department. Data to be collected from this swab is to identify CYP3A5 genotype for metabolism of tacrolimus. This information will assist in identifying dosage requirements for the extended-release tacrolimus product. Informed consent will be obtained separately for this procedure. Study coordinators will collect and analyze saliva from saliva collection kits and the results will be recorded and stored as part of the research dataset. These saliva samples will be obtained during outpatient study visits and then stored in a locked file cabinet in the locked research office. Each saliva collection kit will be de-identified before transport to Pharmacy for analysis. *Researchers involved in this study will possess a list that links the genetic testing results to the participant. This list will be stored in a password protected encrypted document on TUH computer.*

When ready for genetic testing, within the week, the saliva will be analyzed and stored in a locked -70 degree freezer in Temple University School of Pharmacy, accessible only to research and pharmacogenomics department staff. Subject results for genetic testing will not be transcribed into the electronic medical record or used to impact their care in any way . All de-identified data extracted from the medical record and the questionnaire data are stored in password protected and encrypted Temple University Hospital computer systems. The findings associated with genetic testing would only be used to analyze dose requirements and achievement of therapeutic concentrations for research purposes at the end of the study. This genetic information will not be known while the patient is within the one month time period by research staff or impact their clinical care at all. Patients will not be informed of the results of their genetic testing. Staff within the pharmacogenomics department will have access to these specimen. Informed consent will allow release of this data for purposes of this human research only.

Data analysis:

To ensure subject confidentiality, all information from electronic medical records will be stored in a de-identified fashion. Data collected from electronic medical record will include

demographic information, comorbidities related to transplant, cause of kidney disease, incidence and severity of tremors, study drug dosing, other immunosupressants prescribed, relevant labs (e.g., Cr, K, eGFR, HbA1c, blood glucose, tacrolimus level) and all other pertinent prospective data (e.g., rejection episodes). Only prospective data created between Day 0-Day 30 visit will be collected for the purpose of this research—no retrospective data will be collected. All PHI will be removed from this dataset and subjects will be assigned an arbitrary study ID number. This de-identified dataset will be kept in a separate locked drawer and locked office accessible to only research staff and entered into encrypted password-protected online database, Research Electronic Data Capture (REDCap™, ©Vanderbilt University). Access to REDCAPTM will be granted to Adam Diamond, PharmD, BCPS, Amanda DeSenna, BA, BSN, RN, Hannah Sufrin, and Antonio Di Carlo MD, CM, FACS, FRCSC. Documents containing personal health information (e.g., consent, HIPAA form) will be kept in a separate locked drawer in a locked office accessible only to study investigators. Raw data will be exported into a password-protected Excel data sheet stored on Temple hospital computer in a locked research space for data analysis.

Data analysis will be performed by study staff with the assistance of a hospital appointed statistician. From REDCap, raw data will be exported into an Excel sheet and analyzed in SPSS®, version 21.0 for Windows (SPSS, Inc., Chicago, IL). Continuous data such as baseline demographics and laboratory values that are normally distributed will be presented as mean (SD) and non-normally distributed data as median (25-75% interquartile range). Other baseline characteristics and outcomes will be analyzed with the following tests: Chi-square or Fisher's exact tests for categorical data, and Student's T-tests or Mann-Whitney U tests for continuous data. Kaplan Meier statistical testing will be utilized to evaluate time to therapeutic trough concentration. Subgroup analysis stratified by CYP3A5 genotype will be performed. All tests will be two-tailed, and p-values < 0.05 will be considered statistically significant.

e) Withdrawal of Subjects

Participants are volunteers and will be permitted to withdraw at any time during the duration of the study. Each participant will be made aware of the eligibility to withdraw at any time at the sole discretion of the participant. Participants will remain eligible for study participation even if they do not want to complete the saliva collection kit to determine CYP3A5 genotype. If this occurs we will write a note to file and not obtain their saliva sample. As volunteers, participants are not required to do any aspect of the study that they do not want to do. The participant will be withdrawn from the study only if they contact the Principal Investigator by phone or mail to decline further study participation. If notification of withdrawal is obtained from a subject, data collection on this subject will cease immediately and no data already collected will be utilized in data analysis.

f) Privacy & Confidentiality

Each participant will be made aware of rules and regulations regarding protected health information (PHI) as outlined under HIPAA. HIPAA authorizations will be obtained from each participant at the beginning of the study. All study staff and investigators will be CITI trained and receive training regarding HIPAA authorizations and the storage and protection of PHI. The information collected from each chart will be de-identified and assigned an arbitrary number. The dataset only with corresponding arbitrary number will be accessible only to study investigators within REDCap and in the form of a password-protected excel sheet. Consents, HIPAA form, and any other original copies with PHI will be stored in a locked separate drawer in a locked room accessible only to research staff. All saliva collection kits will be deidentified before being sent to the lab for genetic testing. Results of genetic testing will not be recorded into their chart, and will be used for research purposes only. Genetic testing results will not be shared with participants. The protected health information will not be reused or disclosed to

any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the protected health information would be permitted.

9) Risks to Subjects

The *use of tacrolimus extended-release de novo for the investigational purpose of conducting this research* study will not involve more than minimal risk to the patient.

The currently known risks of tacrolimus extended-release (Envarsus®) include:

- Headache
- Diarrhea
- Swelling in the legs
- Tremors
- High blood pressure
- High cholesterol
- High blood sugars
- High potassium
- Increased serum creatinine
- Upper respiratory tract infection
- Urinary tract infection
- Common cold
- Viral infections
- Fungal infections
- Increased risk of lymphoma
- Increased risk of skin cancer

Risks associated with the use of all tacrolimus products which includes tacrolimus-extended release (Envarsus®) and tacrolimus immediate-release:

- Headache
- Diarrhea
- Swelling in the legs
- Tremors
- High blood pressure
- High cholesterol
- High blood sugars

- High potassium
- Increased serum creatinine
- Upper respiratory tract infection
- Urinary tract infection
- Common cold
- Viral infections
- Fungal infections
- Increased risk of lymphoma
- Increased risk of skin cancer

The risk for acute organ rejection is present in all patients after kidney transplant on any immune suppressing therapies. Tacrolimus extended-release doses will be adjusted to achieve blood concentrations consistent with standard of care to minimize risk for organ rejection.

The greatest additional risk provided to participants enrolled in this study is maintaining confidentiality due to data collection for Epic and Alpha EMR as well as the collection of saliva samples for genetic testing. The Temple University and the study investigators will protect all patient records and personal information to the extent permitted by law. Patient identifiers will be kept private and physical forms will be filed in a locked cabinet and electronically stored in a password protected and encrypted manner. Personal health information will be kept confidential.

In the event of research related injury, the patient should immediately notify research team and they will arrange for them to receive medical care. Temple University, Temple University Health System and its subsidiaries will not provide monetary compensation or free medical care in the event of research-related injury. The patient or their insurance company will be billed for medical care if this occurs. *Potential Benefits to Subjects*

This prospective study will not directly benefit enrolled subjects.

10) Costs to Subjects

The subject may also be responsible pay for the cost of the study medication, which is the tacrolimus extended-release form. This depends on their insurance, as the copay of the study medication (tacrolimus extended-release form) may be higher than tacrolimus immediate-release form. In most cases the copay would be a similar cost for the study medication.

11) Informed Consent

No procedure will be performed if informed consent is not obtained. During the pre-operative preparation for transplant, patients will be consented for surgery and consented for the study if they volunteer to be included. The transplant surgeon performing the transplant operation will be responsible for screening the patients for inclusion and exclusion criteria as well as obtaining the informed consent. Non-English speaking patients will not be enrolled. Investigator Guidance for informed consent (HRP-802) will be followed.

12)Vulnerable Populations

Not applicable. Participants who are pregnant, under 21 years, cannot consent for themselves, or prisoners will not be included.

13)Sharing of Results or Incidental Findings with Subjects

The genetic testing will not be included in their medical record, so this will not impact subject care in any way. Results of required genetic testing will not be shared with participants. All prospective data collected for this study is included in the medical record so incidental findings are not anticipated. In the event that any incidental findings are discovered in your medical record or by any other means during the study process by research staff you will be notified within 24 hours by the Principal Investigator by phone.