Protocol v1.5
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Title:

The effect of conversion to once-daily Envarsus® on the neurologic toxicity burden in liver transplant recipients

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1) Study Objectives

a) Primary objective

i) Estimate the change from baseline to six months in neurotoxicity burden measured by a composite Patient Global Impression of Improvement (PGI-I) (Appendix B) score in patients converted to Envarsus daily ± adjunctive agent ± prednisone versus patients maintained on a standard therapy of Tacrolimus IR BID ± adjunctive agent ± prednisone

b) Secondary objectives

i) Estimate the change in the mean Fahn-Tolosa-Marin (FTM) score in patients with self-reported tremor from baseline to 6 months after enrollment

c) Exploratory Outcomes

i) Examine subject specific change of self-reported adherence using the IMAB-Q 10 (Appendix C) at the time of the conversion versus six months post-conversion, compared between the two arms

ii) Examine subject specific change in quality of life, using the SF-12 at the time of conversion versus six months post-conversion, compared between the two arms

iii) Examine subject specific change in memory, using the Medical Symptom Validity Test, at the time of conversion versus six months post-conversion, compared between the two arms

iv) Examine subject specific change in cognition, using the MoCA (Appendix E), at the time of conversion versus six months post-conversion, compared between the two arms

v) Examine subject specific change in cognition, using the MMSE, at the time of conversion versus six months post-conversion, compared between the two arms

vi) Measure and compare time-to-event analysis of secondary objective between the two arms
(1) Patient death (time to event analysis)
(2) Biopsy proven acute rejection (Banff RAI ≥ 5, time to event analysis)
(3) Graft loss (time to event analysis)

vii) Compare rates of adverse events and severe adverse events between the two arms

viii) Examine subject specific change in renal function, using the 4 variable MDRD, at the time of conversion versus six months post-conversion, compared between the two arms

2) Background

a) Rationale

Neurotoxicity associated with tacrolimus after liver transplant has been reported in 10 to 42% of recipients (1-7). These toxicities can range from mild (tremors, headaches) to severe (seizures, PRES memory loss) and are a significant cause of morbidity after liver transplantation. Neurotoxicities are the most frequent adverse events that lead to tacrolimus discontinuation in abdominal transplant recipients, which leads to an increased risk of acute rejection, including 31% in liver transplant recipients in the first year after conversion (8).

Although the vast majority of literature in liver transplant neurotoxicities focus on the acute, severe neurotoxicities (PRES, seizures), there is evidence that more mild neurotoxicities can persist and lead to significantly worse visuospatial/constructional ability, impaired cognitive function, and white brain matter changes (9).

In several chronic disease states, adverse drug events have clearly been established as a major risk factor for medication non-adherence (10-12). Additionally, adverse drug events are associated with significant healthcare utilization and costs (13,14).

Tacrolimus LCP (Envarsus®) is a once-daily tacrolimus product that has demonstrated an ability to maintain a similar Cmin to tacrolimus IR in converted liver transplant recipients with an average

conversion dosing ratio of 0.7, while also demonstrating significantly less variability in levels. In an extension study of this group, the pharmacokinetics of tacrolimus LCP remained stable up to 26 weeks post-conversion and there were no concerns for safety at up to 52 weeks on tacrolimus LCP (15). Tacrolimus LCP has also demonstrated a significant improvement in tremor compared to tacrolimus IR in kidney transplant recipients experiencing a clinically significant tremor (16). Hand tremors exist with a high incidence in liver transplant recipients, worsening after administration of cyclosporine or tacrolimus (16), and can be a major contributor to reduced quality of life. We hypothesize that tacrolimus LCP will show a lower neurotoxicity burden in multiple neurologic side effects, as compared to tacrolimus IR.

Supporting Data

Multicenter Open-label Conversion Trial for Abdominal Transplants Unable to Tolerate Tacrolimus

Overall Distribution of ADRs Prompting Conversion from Tacrolimus		
	Kidney (n=49)	Liver (n=108
Neurotoxicity	20 (41)	67 (62)
Gastrointestinal	9 (18)	29 (27)
Nephrotoxicity	4 (8)	20 (19)
Diabetes	21 (43)	16 (15)

ADRs in Multicenter Prospective, Randomized U.S. Trial

	Tacrolimus (n=250)	Cyclosporine/AZA (n=250)
Headache	64%	60%
Insomnia	64%	68%
Tremor	56%	46%
Paresthesia	40%	30%

3) Study interventions

a) Interventions, administration, and duration

i) Subjects will receive the current standard of care for up to 15 days and no longer than 1 year post-transplant. Standard of care is described as a regimen of tacrolimus IR (goal 12 hour trough: 3-10ng/mL) BID ± adjunctive agent ± prednisone. Subjects are randomized to one of the two arms to either receive their standard of care regimen or convert their tacrolimus IR BID to Envarsus QD

(1) Both products FDA approved for preventing rejection in kidney transplant and are used as a standard of care for all organ transplants

ii) Post-randomization, subjects will be converted to one of the two arms, as shown below, and followed for a total period of six months (primary endpoint), or until a terminal end point is reached.

(1) Arm 1: Control-- Tacrolimus IR (goal 12 hour trough: 3-10ng/mL) BID ± adjunctive agent ± prednisone x 6 months

(2) Arm 2: Intervention-- Envarsus (goal 24 hour trough: 3-10 ng/mL) daily ± adjunctive agent ± prednisone x 6 months

(a) Envarsus will be supplied from Veloxis Pharmaceuticals

b) Neurotoxicity assessment

i) Changes in neurotoxicity comorbidity burden will be assessed at all study visits noted on the Schedule of Evaluations, using the composite score from applying the PGI-I score to tremor, headache, insomnia, and paresthesia.

4) Study Endpoints

i) Primary outcome- Treatment efficacy, defined difference in change from baseline to six month measure by composite PGI-I in both arms.

ii) Secondary outcomes

(a) Change in the FTM score in patients with self-reported tremor between baseline and six months post-enrollment in both arms

iii) Exploratory outcomes

(1) Safety outcomes of treatment failure rate, defined as acute allograft rejection with a Banff RAI 5 or higher, graft loss, death, adverse events, or severe adverse events at six months post-conversion in both arms.

(2) Change in self-reported medication adherence, defined as the IMAB-Q10, between baseline and six months post-conversion in both arms

(3) Change in the subject specific quality of life, defined as the SF-12, between baseline and six months post-conversion in both arms

(4) Change in subject specific memory, defined as the MSVT, between baseline and six months post-conversion in both arms

(5) Change in subject specific cognitive function, defined as the MoCA, between baseline and six months post-conversion in both arms

(6) Change in subject specific renal function, defined as the 4 variable MDRD, between baseline and six months post-conversion in both arms

5) Inclusion & Exclusion Criteria

i) Potentially eligible patients will be screened by the PI and study coordinator using inclusion and exclusion criteria below to determine if they qualify for the study.

ii) Inclusion criteria

(1) Male or female adult (≥18 years old) with a history of liver or liver/kidney transplant within 15 days to 12 months of transplant.

(2) Patients must be capable of understanding the purposes and risks of the study and have the ability to give written informed consent and be willing to participate and comply with the study. For those that consent virtually, subjects must be willing and able to use the Doxy.me platform and complete assessments virtually.

iii) Exclusion criteria

(1) Patients will be excluded if they are pregnant or nursing females or males with a pregnant female partner

(2) HIV positive (HIV ab +)

(3) Unable to tolerate oral medications

(4) Use of another investigational product within thirty days prior to receiving study medication

(5) Moderate acute cellular rejection (RAI ≥ 5) within the past month

(6) A condition that is known to cause tremor such as essential tremor, Parkinson disease, or enhanced physiologic tremor.

(7) Patients taking medications known to induce tremors or dopamine blocking agents

(8) A condition or disorder that, in the opinion of the investigator, may adversely affect the outcome of the study or the safety of the subject

6) Number of Subjects

a) There will be 15 subjects in each arm, 30 subjects total

7) Setting Where Research Will Be Conducted

a) Study activities, including consent, enrollment, and randomization, will occur in the Liver Transplant Clinic at the Medical University of South Carolina or through Doxy.me.

8) Recruitment Methods

a) Study enrollment procedures

i) Subject Identification/Recruitment: Members of the research team will identify potentially eligible patients who have undergone liver or liver/kidney transplantation within the past twelve months. An initial evaluation of existing patient information may be performed via chart review to determine potential eligibility. This initial review may be performed prior to consent; however no protocol driven tests or procedures may be performed until signed informed consent has been obtained.

ii) Informed Consent: A qualified member of the research team, Human Subjects Protection Trained, will approach and explain the study and offer participation. The study will be explained in a manner consistent with the level of education pertaining to the patient. Enrollment procedure will involve face-to-face meetings of the patients to inform and review informed consent documentation. The participant will sign the consent form prior to evaluation of self-reported measures. Copies of the informed consent will be appropriately placed in the corresponding chart and the patient will be provided with a copy of the signed consent form. Non-consenting individuals will also be ensured that no penalty will arise due to denying participation. Those who choose to participate in the trial will be informed that at any point they reserve the right to leave the study.

iii) Enrollment: Patients who give informed consent to study participation will go on to complete baseline procedures necessary to determine eligibility for randomization. Once deemed eligible for the study according to the inclusion/exclusion criteria, the patient will be enrolled as study participant. Information to be entered upon enrollment includes demographic information and date of transplant surgery. Enrolled subjects will be randomized to one of the treatment arms in the applicable cohort.

9) Consent Process

a) Informed Consent: A qualified member of the research team, Human Subjects Protection Trained, will approach and explain the study and offer participation. The study will be explained in a manner consistent with the level of education pertaining to the patient. Enrollment procedure will involve face-to-face meetings of the patients to inform and review informed consent documentation. The participant will sign the consent form prior to evaluation of self-reported measures. Copies of the informed consent will be appropriately placed in the corresponding chart and the patient will be provided with a copy of the signed consent form. Non-consenting individuals will also be ensured that no penalty will arise due to denying participation. Those who choose to participate in the trial will be informed that at any point they reserve the right to leave the study. For patients who are being seen only virtually via Doxy telemedicine visits, they will be identified at a standard of care telemedicine visit by the liver

transplant team and the study coordinator will follow up with the patient and set up a Doxy.me visit to obtain informed consent.

b) Enrollment: Patients who give informed consent to study participation will go on to complete baseline procedures necessary to determine eligibility for randomization. Once deemed eligible for the study according to the inclusion/exclusion criteria, the patient will be enrolled as study participant. Information to be entered upon enrollment includes demographic information and date of transplant surgery. Enrolled subjects will be randomized to one of the treatment arms in the applicable cohort.

c) Human subjects

i) Institutional review board (IRB) review and informed consent

ii) This protocol, the ICF, and any subsequent modifications must be reviewed and approved by the IRB. A signed and dated ICF must be obtained from the subject as defined in 21CFR50.3. The ICF must also be signed and dated by a member of the study staff qualified to be delegated the authority to obtain informed consent. A copy of the ICF must be given to the subject and the consent process must be documented in the subject's medical record. The PI or delegated sub-Investigator is responsible for ensuring that informed consent is obtained from each patient prior to conducting any study-related activities.

(1) No deviations from or changes to the study protocol should be initiated except when necessary to eliminate immediate hazard to the subject. However, the IRB and Study Sponsor must be informed of this as soon as possible thereafter. It is the PI's responsibility to report SAEs occurring during the study to the IRB, as required and as soon as possible.

10) Study design

i) Single-center, open-label, randomized comparative trial for a duration of 6 months.

ii) There will be 15 subjects in each arm, with a total study size of 30 subjects.

b) Allocation: Three random permuted-blocks of ten, with equal arm allocation ratio will be used. In each block, REDCap will be used to ensure 1:1 randomization, with resulting 1:1 allocation in the overall cohort.

c) Intervention Model: Parallel assignment

d) Masking: This will be an open-label study as masking is not feasible given we are comparing twice-a-day to once-a-day regimen.

e) Timing of evaluation

i) Pre-Randomization Evaluations

1. Baseline
2. Evaluations listed under the baseline visit may be performed up to 14 days prior to randomization. Once the subject has been successfully screened and accepted for randomization, randomization must be completed within 48 hours.

ii) Intervention and Evaluations

1. Once the subject has been successfully randomized, study medication will be picked up from IDS by the study team to be dispensed to the subject or study medication will be shipped to the subject by IDS. Study evaluations must take place within the time window indicated on the Schedule of Evaluations (Section 3)

f) Clinical and laboratory evaluations

i) Schedule of evaluations

Data Collection Schedule

Report Form		Baseline	Days Post-Conversion							
			7±2	14±3	30±5	60±7	90±10	120±10	150±10	180±10
Informed Consent Obtained[vi]		X								
Randomization		X								
Review of Inclusion and Exclusion Criteria		X								
Medical History		X								
Liver Transplant Recipient		X								
Review of Medications and Dosing		X								X
Clinical assessment*	Adverse events, rejection, graft loss, death						X			X
	PGI-I, IMAB-Q 10, MSVT, MoCA, and SF-12, MMSE[v]	X								X
	Fahn-Tolosa-Marin[iv]	X								X
Laboratory Assessments	CBC and Chem-7[i]	O	O	O	O	O	O	O	O	O
	LFTs[ii]	O	O	O	O	O	O	O	O	O
	Tacrolimus C0[iii]	O	O	O	O	O	O	O	O	O
End of Study										X

X=required ; 0=optional: data will be collected if performed as standard of care

Footnotes:

i) Includes sodium, potassium, chloride, CO2, BUN, SrCr, glucose, calcium, WBC, HgB, Hct, platelets
ii) Includes AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein
iii) Tacrolimus concentrations will be 12- or 24-hour levels, drawn in the morning of each assessment
iv) Only required for patients with self-reported tremor
v) MSVT,MMSE, MoCA, FTM will be completed through a Doxy.me visit. PGI-I, IMAB-Q 10 and SF-10 will be sent to the subject through REDCap to be completed. Necessary materials (ball point pen and paper) to complete the MoCA, MMSE, and FTM will be shipped to the subject prior to the Doxy.me visit.
vi) For subjects consented through Doxy.Me, this will be done prior to the baseline visit with the assessments.

11) Specimen Collection and Assessments

i) Clinical and Laboratory Assessments:
(1) Laboratory evaluations will be performed at certified laboratories according to the study schedule. Required tests are specified in the Schedule of Evaluations. Laboratory

specimens will not be stored for the study or sent to any outside facilities. Specimens will not be used for future research.

(2) All subjects will undergo clinical assessment by the investigator or the investigator's designee in the manner and at the times specified in the Schedule of Evaluations
   (a) Adverse events will be determined and defined according to the protocol
   (b) Doses will be recorded of all immunosuppressants.
   (c) Rejection and infection events will be recorded, as defined in the protocol

(3) Renal function assessment will be monitored at regular intervals using the 4-variable abbreviated MDRD equation. It will be monitored at baseline and the end of the study for study outcomes and any time points dictated by standard of care follow-up in between those time points.

ii) Definitions
   (1) Acute rejection is defined as a liver allograft biopsy showing RAI 5 or greater, by the 1997 Banff Criteria and all updates since then. Biopsies will be performed when clinically warranted, based on changes in allograft function.
   (2) Rejection reversal is defined as return of liver function tests to within 20% of baseline and/or histologic clearance by Banff Criteria
   (3) Recurrent acute rejection is defined as rejection recurring more than two weeks after documented rejection reversal.

iii) Treatment of Acute rejection:
   (1) Acute rejection will be treated per provider discretion.

iv) Opportunistic Infections
   (1) Opportunistic infections will be defined as outlined in Appendix F

v) Intervention Discontinuation Evaluations: At the scheduled time of intervention discontinuation (EOT, last date of study), the following evaluations must be completed: clinical assessment, CBC, CHEM-7, LFTs, Tacrolimus CO. In case of subject withdrawal from study, the patient will return to standard of care medications and request to continue with final assessment using PGI-I, IMAB-Q 10, MSVT, MoCA, SF-12, MMSE, and FTM (if applicable) will be discussed with a qualified team member.

12) Data Management

a) Data management will be overseen and data analysis will be independently reviewed by an Investigator on the study who has no related financial interest. This member will serve as independent monitor to oversee data collection and management, and to verify the integrity of data and interpretation of study results. Data reports, including patient recruitment and randomization numbers, clinical outcomes (acute rejections, infections and hospitalizations), AEs and SAEs will be reviewed quarterly**.**

b) Dichotomous data will be analyzed using Chi Square or Fischer Exact, when appropriate, and continuous data points will be analyzed using Student's t-test or Mann Whitney U, for parametric and nonparametric data, respectively.

c) Sample size estimation for the primary outcome

i) The proposed sample size (n=30) would be able to demonstrate a mean difference in neurologic toxicity burden, using the Patient Global Impression of Improvement (PGI-I) rating of 20 ± 15 with greater than 80% power using a two-tailed t-test with an alpha set at 0.05. Based on reported neurologic toxicities from the literature (headache 64%, insomnia 64%, tremor 56%, paresthesia 40%), a mean score of 45 is expected at baseline. Using the independent samples t-test comparing two groups with a two-sided significance level of

0.05, a sample size of 14 subjects per group would be required to obtain a power of at least 0.8 if the two groups have a mean of 25 ± 15 neurologic toxicity burden in the Envarsus cohort at the conclusion of the study and mean of 45 ± 20 neurologic toxicity burden at baseline and follow up in the tacrolimus IR group. Estimating a 10% drop out rate, we propose a sample size of 15 subjects per group. This sample size will provide adequate power to show a statistical and clinical difference in the neurologic toxicity burden between the two groups.

d) Missing data and imputation methods

i) Under the intention-to-treat principle, all subjects are included in the analysis. Extensive efforts will be made to keep all missing data to a minimum and minimize loss to follow-up (LTFU). However, it is likely that some missing data may occur.

e) Data Handling and Record Keeping

i) In order to protect subjects against any risk regarding loss of personal information, all obligations under the Health Portability and Accountability Act (HIPPA) will be met. Additionally, all data will be collected and stored through the secure network server and behind the MUSC firewall. We will use electronic CRF forms to gather all study information (redcap.musc.edu). Data will only be stored on campus computers under the MUSC secure network. Data collection forms will be maintained within an office, which is a locked office facility on campus. Only approved study members will have access to patient data.

ii) Any data or information shared for dissemination will be de-identified and the confidentiality of all participants will be strictly maintained. The only persons with access to protected health information (PHI) will include study investigators, research coordinators and those approved by the MUSC IRB. All data will be secured on MUSC servers, behind firewalls, with passwords protecting entry in these systems. All PHI will be obtained and managed in accordance with the HIPAA Privacy Rule (45 CFR Parts 160 and 164).

13) Provisions to Monitor Data and Ensure Subject Safety

a) Study modification/discontinuation

(1) The study may be modified or discontinued at any time by the IRB, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

(2) After 16 subjects have been randomized and completed follow-up, efficacy and safety endpoints will be reviewed by a blinded Safety Monitor to identify if the risk profile is as expected. If significantly increased risk is identified in either or both arms of the study, sufficient to increase the risk over the potential benefit of the study, the study will be discontinued. Examples are included below:

(a) A 6-month rejection rate difference between arms > 20%

(b) A difference in grade 3 or higher infections (based on CTCAE) between arms of > 20%

(c) A graft loss difference between arms > 20%

b) Adverse Events

i) An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments. Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

(1) they induce clinical signs or symptoms,
(2) they are considered clinically significant,
(3) they require therapy

ii) Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subject with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Adverse events should be recorded in the Adverse Events CRF with them accompanied by the following information:

(1) severity of adverse events will be determined using the grading system outlined in the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE), as it best fits the diagnostic terminology used in naming the event at the site clinical level.
(2) possibility of relationship to the study treatment (no/yes)
(3) its duration (start and end dates) or if the event is ongoing an outcome of not recovered or not resolved should be reported.
(4) whether it constitutes a serious adverse event (SAE), if so report date should be provided
(5) action taken regarding study treatment
(6) whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
(7) its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

iii) An SAE is any adverse event which meets any one of the following criteria:

(1) An SAE is any adverse event that is life-threatening or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity; or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE. Also specifically excluded from this definition of SAE

is any event judged by the Principal Investigator to represent progression of the malignancy under study, unless it results in death within the SAE Reporting Period.

c) **Reporting of Serious Adverse Events**. Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), certain SAEs will be reported to Veloxis by ("SAEs," as defined below) that occur during the SAE reporting period (as defined below) in a Study subject assigned to receive the Veloxis Product. The subset of SAEs to be reported for this Study are those that fit into either of the following categories: (1) a death, regardless of whether it is considered related to treatment with the Veloxis Product, or (2) an SAE that is assessed by the Principal Investigator as both related to treatment with the Veloxis Product and unexpected for that Product. An event should be considered "related" to the Veloxis Product if a relationship is at least a reasonable possibility, and "unexpectedness" should be based upon current Product labeling. Principal Investigator will report such SAEs using either Institution's Internal Adverse Event Report form or an FDA MEDWATCH form together with the Reportable Adverse Event Fax Cover Sheet provided by Veloxis. SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.

d) **SAE Reporting Period**. The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Veloxis Product through 72 hours after discontinuation of the Veloxis Product. In addition, any and all related SAEs that occur after the reporting period of which the Principal Investigator becomes aware should also be reported.

i) AEs and SAEs will be reported in accordance with the FDA Guidelines for Post-Marketing Reporting of Adverse Events 21 CRF 314.80 and 21 CRF 600.80 http://www.fda.gov/medwatch/report/regs.htm. Any serious adverse event or a non-serious adverse event that is related to the study and unexpected will be reported to the FDA, per reporting guidelines, as soon as possible, but no later than 15 working days. Further, all serious adverse events that are related to the study and are unexpected must be reported to The Medical University of South Carolina IRB within 10 days per The Medical University of South Carolina IRB Unanticipated Problems and Adverse Events Policy and Procedures reporting guidelines.

14) Withdrawal of Subjects

a) Criteria for intervention discontinuation

(1) The intervention will be withheld/discontinued for AE of grade 3 or higher or if requested by the study participant.

(2) Additionally, the intervention will be discontinued if the subject meets criteria for the following reasons:

(a) Loss of graft: Defined as death or need for retransplant. Patients will be deemed a treatment failure and the intervention will be discontinued.

15) Risks to Subjects

a) An increased risk of getting some kinds of cancer, including skin and lymph gland cancer (lymphoma)

b) An increased risk of infections. As immediate release tacrolimus can lower the ability of the immune system to fight infections, serious infections can happen in people taking immediate

release tacrolimus that can cause death. Patients should call their doctor right away if they have symptoms of an infection such as fever; sweats or chills; cough or flu-like symptoms; muscle aches; or warm, red, or painful areas on their skin

c) High blood sugar (diabetes)
d) Kidney injury and decreased kidney function
e) Nervous system problems including encephalopathy, delirium, seizures, coma, tremors, paresthesia, headache, mental status changes, and changes in motor and sensory functions
f) High levels of potassium in the blood (potassium is important for nerve and muscle function)
g) High blood pressure
h) Heart problems (myocardial hypertrophy)

i) The most common side effects for Envarsus® Daily and Tacrolimus IR in people receiving kidney transplant are

	Envarsus XR	Tacrolimus IR
Infection	70%	65%
Tremors	19%	17%
High Blood Pressure	23%	23%
Kidney Problems	10%	10%
Constipation	18%	25%
Diarrhea	31%	34%
Headache	15%	10%
Trouble Sleeping	13%	11%
Nausea	13%	15%
Low levels of phosphate in blood	13%	15%
Swelling of hands, ankles or legs	16%	21%
Weakness	10%	10%
High levels of potassium in blood	15%	11%
Low red blood cell count (anemia)	26%	29%

j) Unknown Risks
k) Risk of loss of confidentiality

16) Potential Benefits to Subjects/Others

a) The subject may experience improved outcomes in the intervention group compared to the control group, however this cannot be guaranteed. The intervention group may potentially show a lower neurotoxicity burden as compared to the control group. The study is likely to improve knowledge of the neurological effects of extended release tacrolimus versus immediate release tacrolimus.

17) Sharing Results with Participants

a) Publication of the results of this trial will be reviewed and approved by all coinvestigators. Final results will be submitted to ClinicalTrials.gov. Any presentation, abstract, or manuscript will be made available for review by the sponsor prior to submission.

b) Results are not shared with participants unless they necessitate a change in patient care

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Appendix A: Scientific Registry of Transplant Recipients
Program Summary: MUSC

SCIENTIFIC REGISTRY OF TRANSPLANT RECIPIENTS

Medical University of South Carolina
Center Code: SCMU
Transplant Program (Organ): Liver
Release Date: January 5, 2018
Based on Data Available: October 31, 2017

SRTR Program-Specific Report
Feedback?: SRTR@SRTR.org
1.877.970.SRTR (7787)
http://www.srtr.org

A. Program Summary

Figure A1. Waiting list and transplant activity

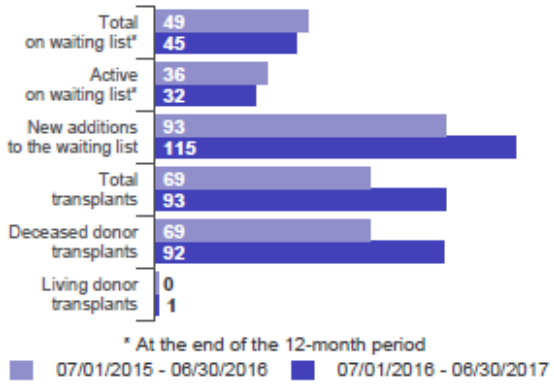


Table A1. Census of transplant recipients

Recipients	07/01/2015-06/30/2016	07/01/2016-06/30/2017
Transplanted at this center	69	93
Followed by this center*	658	658
...transplanted at this program	620	614
...transplanted elsewhere	38	44

* Recipients followed are transplant recipients for whom the center has submitted a post-transplant follow-up form for a transplant that took place before the 12-month interval for each column.

Figure A2. Transplant rates 07/01/2015 - 06/30/2017

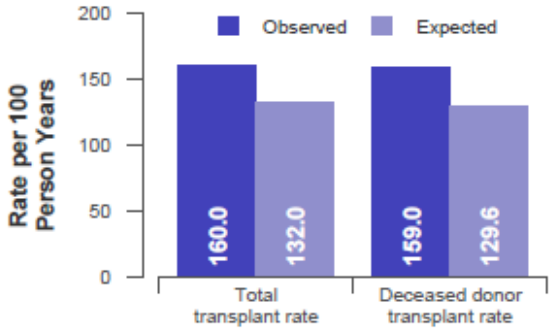


Figure A3. Waiting list mortality rates 07/01/2015 - 06/30/2017

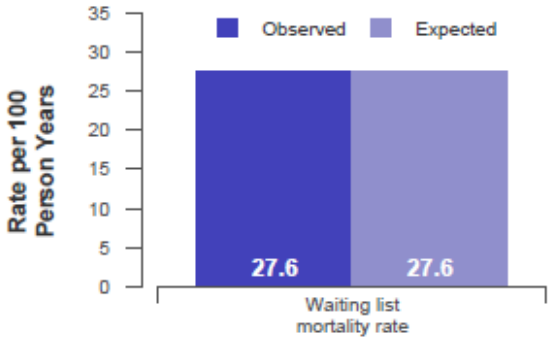


Figure A4. First-year adult graft and patient survival: 07/01/2014 - 12/31/2016

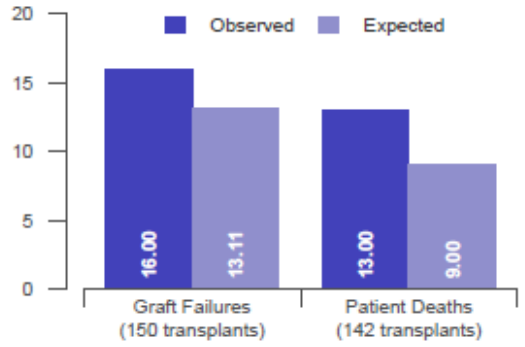
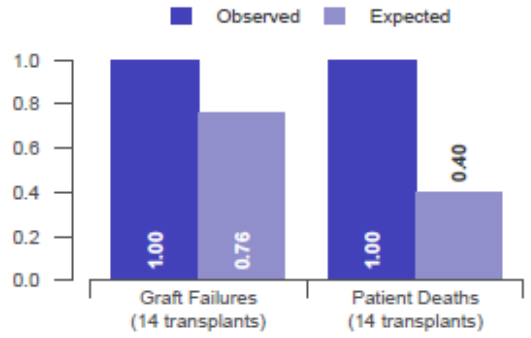


Figure A5. First-year pediatric graft and patient survival: 07/01/2014 - 12/31/2016



Appendix B: Patient Global Impression of Improvement (PGI-I)

Record ID	
Check the box that best describes how your tremor is now, compared to how it was before your liver transplant: * must provide value	○ Very much better ○ Much better ○ A little better ○ No change ○ A little worse ○ Much worse ○ Very much worse
Check the box that best describes how your headaches are now, compared to how they were before your liver transplant: * must provide value	○ Very much better ○ Much better ○ A little better ○ No change ○ A little worse ○ Much worse ○ Very much worse
Check the box that best describes how your insomnia (can't sleep) is now, compared to how it was before your liver transplant: * must provide value	○ Very much better ○ Much better ○ A little better ○ No change ○ A little worse ○ Much worse ○ Very much worse
Check the box that best describes how your paresthesias (tingling or numbness) is now, compared to how it was before your liver transplant: * must provide value	○ Very much better ○ Much better ○ A little better ○ No change ○ A little worse ○ Much worse ○ Very much worse

Appendix C: IMAB-Q10 Questionnaire

People have different experiences of trying to take their medicines as prescribed (right dose and right time). We understand that things can 'get in the way' of following your doctor's recommendations about taking your medicines. This questionnaire lists 10 different statements about taking your medicines.

	Statement	**Strongly agree**	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**
1	I know how to take my medicines as prescribed					
2	I am physically able to take my medicines as prescribed					
3	I remember to take my medicines as prescribed					
4	I can easily get hold of my prescribed medicines from the pharmacy or surgery					
5	I feel confident about all aspects of managing (ordering, collecting and taking) my medicines					
6	I worry about the unwanted effects (e.g. harmful effects or side effects) of taking my medicines					
7	Taking my medicines as prescribed is a burden to me					
8	Life gets in the way of me taking my medicines as prescribed					
9	I don't think I could cope if my medication regime kept changing					
10	I worry about what other people would think of me if they knew I took medicines					

Appendix D: Fahn, Tolosa, Marin Tremor Rating Scale

Fahn, Tolosa, Marin Tremor Rating Scale

1-9 Tremor (rate tremor)
- 1) At rest (in repose). For head and trunk, when lying down
- 2) With posture holding
  - UE: arms outstretched, wrists mildly extended, fingers spread apart
  - LE: legs flexed at hips and knees; foot dorsi-flexed
    - tongue: when protruded
    - head and trunk: when sitting or standing
- 3) with Action(ACT) and Intention(INT):
  - UE: finger to nose and other actions
  - LE: toe to finger in flexed posture

Definitions for 1-9
0 = None
1 = Slight. May be intermittent
2 = Moderate amplitude. May be intermittent
3 = Marked amplitude
4 = Severe amplitude

1. Face tremor ..... REST _____

2. Tongue tremor ..... REST _____

POST _____

3. Voice tremor ..... ACT/INT _____

4. Head tremor ..... REST _____

POST _____

5. Right upper extremity tremor ..... REST _____

POST _____

ACT/INT _____

6. Left upper extremity tremor ..... REST _____

POST _____

ACT/INT _____

7. Trunk tremor ..... REST _____

POST _____

8. Right lower extremity tremor ..... REST _____

POST _____

ACT/INT _____

9. Left lower extremity tremor ..... REST _____

POST _____

ACT/INT _____

10. Handwriting ..... _____

Have patient write the standard sentence: "This is a sample of my best handwriting", sign his or her name and write the date.
0 = Normal
1 = Mildly abnormal. Slightly untidy, tremulous
2 = Moderately abnormal. Legible, but with considerable tremor.
3 = Marked abnormal. Illegible
4 = Severely abnormal. Unable to keep pencil or pen on paper without holding hand down with other hand.

11-13. Ask the patient to join both points of the various drawings without crossing the lines. Test each hand, beginning with the lesser, without leaning the hand or the arm on the table.

Definitions for 11-13
0 = Normal
1 = Slightly tremulous. May cross lines occasionally.
2 = Moderately tremulous or crosses lines frequently.
3 = Accomplishes the task with great difficulty. Many errors.
4 = Unable to complete drawing.

11. Drawing A

Right _____

Left _____

12. Drawing B Right _____

Left _____

13. Drawing C Right _____

Left _____

14. Pouring Right _____
Use firm plastic cups, about 8 cm tall, filled with water to 1 cm from top. Ask patient to pour water from one cup to another. Test each hand separately. Left _____
0 = Normal
1 = More careful that a person without tremor, but no water is spilled.
2 = Spills a small amount of water (up to 10% of the total amount).
3 = Spills a considerable amount of water (> 10-50%)
4 = Unable to pour water without spilling most of the water.

15. Speaking _____
This includes spastic dysphonia if present
0 = Normal
1 = Mild voice tremulousness when "nervous" only
2 = Mild voice tremor, constant
3 = Moderate voice tremor
4 = Severe voice tremor. Some words difficult to understand.

16. Feeding other than liquids ____
0 = Normal
1 = Mildly normal. Can bring all solids to mouth, spilling only rarely.
2 = Moderately abnormal. Frequent spills of peas and similar foods.
May bring head at least halfway to meet food.
3 = Markedly abnormal. Unable to cut or uses hands to feed.
4 = Severely abnormal. Needs help to feed.

17. Bringing liquids to mouth ____
0 = Normal
1 = Mildly abnormal. Can still use a spoon, but not if it is completely full
2 = Moderately abnormal. Unable to use spoon; uses cup or glass
3 = Markedly abnormal. Can drink from cup or glass, but needs two hands
4 = Severely abnormal. Must use a straw.

18 Hygiene ____
0 = Normal
1 = Mildly abnormal. Able to do everything, but is more careful than the average person
2 = Moderately abnormal. Able to do everything, but with errors;
uses electric razor because of tremor
3 = Markedly abnormal. Unable to do most fine tasks, such as putting on lipstick or shaving
(even with electric razor), unless using two hands.
4 = Severely abnormal. Unable to do any fine-movement tasks.

19. Dressing ____
0 = Normal
1 = Mildly abnormal. Able to do everything, but is more careful than the average person.
2 = Moderately abnormal. Able to do everything, but with errors.
3 = Markedly abnormal. Needs some help with buttoning or other activities, such as tying shoelaces.
4 = Severely abnormal. Requires assistance even for gross motor activities.

20. Writing ____
0 = Normal
1 = Mildly abnormal. Legible. Continues to write letters
2 = Moderately abnormal. Legible, but no longer writes letters.
3 = Markedly abnormal. Illegible
4 = Severely abnormal. Unable to sign checks or other documents requiring a signature.

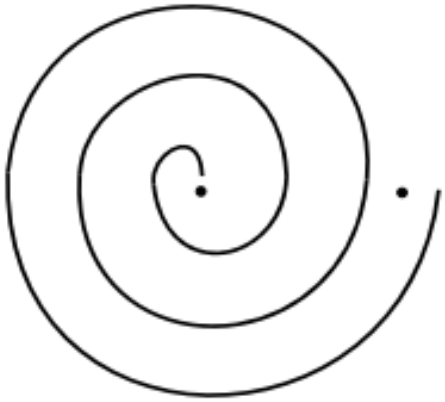
21.Working ____
0 = Tremor does not interfere with job
1 = Able to work, but needs to be more careful than the average person
2 = Able to do everything, but with errors. Poorer than usual performance because of tremor
3 = Unable to do regular job. May have changed to a different job because of tremor.
Tremor limits housework, such as ironing.
4 = Unable to do any outside job; housework is very limited.

Non-Dominant Hand

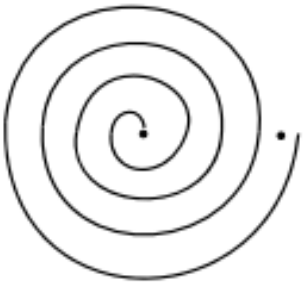
Drawings A, B, and C and make with the _____ Left Hand

_____ Right Hand

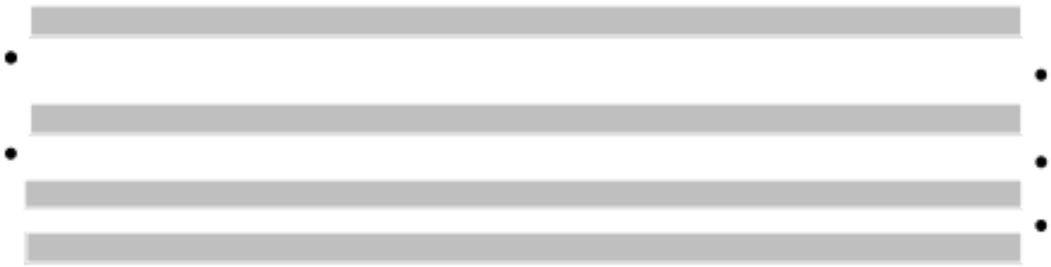
DRAWING A



DRAWING B



DRAWING C



Dominant Hand

Handwriting: This is a sample of my best handwriting

_____

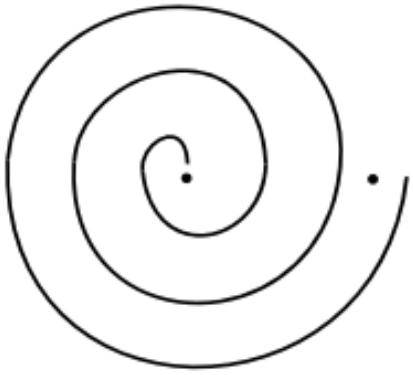
Signature: _____

Date: _____

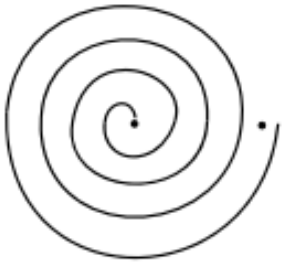
Drawings A, B, and C and make with the _____ Left Hand

_____ Right Hand

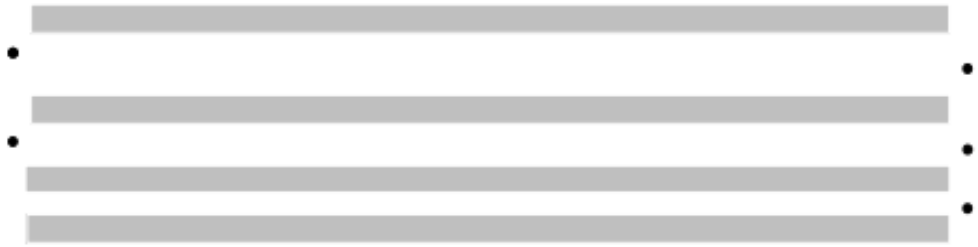
DRAWING A



DRAWING B



DRAWING C



Appendix E: Montreal Cognitive Assessment (MoCA)

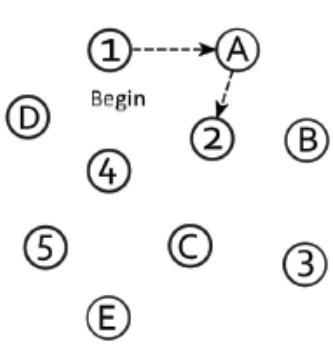
MONTREAL COGNITIVE ASSESSMENT (MoCA®)

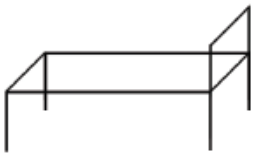
Version 8.3 English

Name:
Education: Date of birth:
Sex: DATE:

VISUOSPATIAL / EXECUTIVE — POINTS

Copy bed





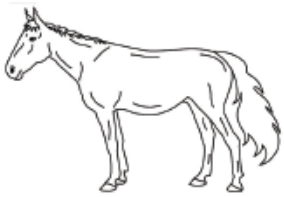
[ ] [ ]

Draw CLOCK (Five past ten)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING



[ ]

[ ]

[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	LEG	COTTON	SCHOOL	TOMATO	WHITE
1st TRIAL					
2nd TRIAL					

NO POINTS

ATTENTION Read list of digits (1 digit/sec.).

Subject has to repeat them in the forward order. [ ] 2 4 8 1 5

Subject has to repeat them in the backward order. [ ] 4 2 7

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors.

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 60. [ ] 53 [ ] 46 [ ] 39 [ ] 32 [ ] 25

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat: The child walked his dog in the park after midnight. [ ]

The artist finished his painting at the right moment for the exhibition. [ ]

__/2

Language Fluency. Name maximum number of words in one minute that begin with the letter B. [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] hammer - screwdriver [ ] matches - lamp

__/2

DELAYED RECALL

	(MIS)	Has to recall words	LEG	COTTON	SCHOOL	TOMATO	WHITE	Points for UNCUED recall only
Memory Index Score (MIS)	X3	WITH NO CUE	[ ]	[ ]	[ ]	[ ]	[ ]	
	X2	Category cue						MIS = ____ /15
	X1	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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MIS: /15
(Normal ≥ 26/30)

TOTAL __/30

Administered by: _____

Training and Certification are required to ensure accuracy.

Add 1 point if ≤ 12 yr education

Appendix F: SF-12

In general, would you say your health is:

* must provide value

- Excellent
- Very good
- Good
- Fair
- Poor

reset

The following questions are about activities you might do during a typical day. Does YOUR HEALTH NOW LIMIT YOU in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf * must provide value			
Climbing SEVERAL flights of stairs * must provide value			

reset

reset

During the PAST 4 WEEKS, how much of the time have you had any of the following problems with your work or other regular daily activities AS A RESULT OF YOUR PHYSICAL HEALTH?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
ACCOMPLISHED LESS than you would like * must provide value					
Were limited in the KIND of work or other activities * must provide value					

reset

reset

During the PAST 4 WEEKS, how much of the time have you had any of the following problems with your work or other regular daily activities AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
ACCOMPLISHED LESS than you would like * must provide value					
Did work or other activities LESS CAREFULLY THAN USUAL * must provide value					

reset

reset

During the PAST 4 WEEKS, how much did PAIN interfere with your normal work (including both work outside the home and housework)?

* must provide value

- ○ Not at all
- ○ A little bit
- ○ Moderately
- ○ Quite a bit
- ○ Extremely

reset

These questions are about how you feel and how things have been with you DURING THE PAST 4 WEEKS. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the PAST 4 WEEKS...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Have you felt calm and peaceful? * must provide value	○	○	○	○	○
Did you have a lot of energy? * must provide value	○	○	○	○	○
Have you felt downhearted and depressed? * must provide value	○	○	○	○	○

reset reset reset

During the PAST 4 WEEKS, how much of the time has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your social activities (like visiting with friends, relatives, etc.)?

* must provide value

- ○ All of the time
- ○ Most of the time
- ○ Some of the time
- ○ A little of the time
- ○ None of the time

reset

Appendix G: Mini-Mental Status Examination

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

***Instructions:* Ask the questions in the order listed. Score one point for each correct response within each question or activity.**

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

Appendix H: Definitions for Opportunistic Infections

I. Cytomegalovirus:

A. Active Infection:

1. Evidence of active viral replication (positive CMV DNA PCR, evidence of viral infection by on histologic samples)

B. CMV Disease

1. Evidence of Active Infection with attributable symptoms

a. CMV Syndrome: one or more of the following:

1. Fever > 38° C for at least 2 days

2. New or increased malaise

3. Leukopenia

4. ≥ 5% atypical lymphocytes

5. Thrombocytopenia

6. Elevation of hepatic transaminases to 2x ULN plus evidence of viral replication

b. CMV Tissue-invasive disease:

1. Evidence of organ dysfunction in the absence of other documented cause

AND

Evidence of CMV in blood by viral culture or CMV DNA PCR

II. Other Opportunistic Infections:

A. For definitions of herpes simplex, varicella zoster, Epstein Barr Virus, parvovirus and adenovirus, see American Journal of Transplantation 2006; 6: 262–274