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Title:

Once-daily regimen with Envarsus® to optimize immunosuppression management and adherence in kidney transplant recipients

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1. Study Objectives
    1. Primary objective
        1. Estimate change from baseline to six months in adherence superiority measure by MMAS-8 in patients converted to a once-daily immunosuppressant regimen of Envarsus®, everolimus, and prednisone versus patients converted to a twice-daily regimen of Envarsus® (once daily), MMF (twice daily), and prednisone (once daily).
    2. Secondary objectives
        1. Estimate the composite of treatment failure rate, defined as acute allograft rejection with a Banff grade 1A or higher, graft loss, or death at six months post-conversion, in patients converted to a once-daily immunosuppressant regimen of Envarsus®, everolimus, and prednisone versus patients converted to a twice-daily regimen of Envarsus®, MMF, and prednisone.
    3. **Outcomes 3.3.2 through 3.3.11 are considered exploratory**
        1. Examine subject specific change of the Memphis Medication Side Effect Scale (Appendix B2, 12) at the time of the conversion versus six months post-conversion, compared between the two arms (Appendix B2).
        2. Examine subject specific change in quality of life, using the SF-36 (Appendix B3) at the time of conversion versus six months post-conversion, compared between the two arms.
        3. 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 1a or higher, time to event analysis)
            3. Graft loss (time to event analysis)

        4. Examine the medication possession ratio (MPR) of adjunctive immunosuppressants (Everolimus or mycophenolate) during follow up between the two arms
            1. Compare the prevalence of patients with MPR >80%
        5. Compare rates of adverse events and severe adverse events between the two arms
        6. Perform exploratory analysis of subclinical rejection and IF/TA in patients with one year protocol biopsies as compared to three month protocol biopsies between the two arms

2. Background
    1. Rationale

Non-adherence in renal transplant recipients has been widely reported, with conservative estimates reporting a prevalence between 20 and 67% (1,2). While it is difficult to determine the degree of nonadherence necessary to affect graft outcomes, there are several studies demonstrating the costs, with a graft loss rate 7 times greater than in adherent patients and an associated $15-100 million annual costs. Due to the complex causes of nonadherence, no singular approach is likely to be effective (3). However, one of the most commonly cited reasons for nonadherence by patients is forgetfulness and disruptions in routine, with the evening dose of twice daily regimens the most likely to be affected (4). Tacrolimus LCP (Envarsus®) is a once-daily tacrolimus product that has demonstrated similar outcomes compared to twice-daily tacrolimus (tacrolimus IR) along with IL-2 receptor induction and mycophenolate mofetil adjunctive therapy with target concentrations of 4-11 ng/mL(5). In clinical trials that have studied the combination of tacrolimus and everolimus, such as the CRAD01AUS09 and ASSET studies, lower exposure to tacrolimus has demonstrated equivalent efficacy compared to standard

exposure tacrolimus, with a lower incidence of adverse effects. In these two studies, tacrolimus exposure after 3 months (the time of conversion for our study) was 4-6 ng/mL (US09) and 1.5-3 ng/mL (ASSET), both of which show adequate efficacy and safety in regards to biopsy-proven acute rejection (BPAR) and adverse events (6,7). Additionally, the currently enrolling TRANSFORM study (CRAD001A2433) utilizes a tacrolimus exposure of 2-5 ng/mL from month 2 to month 24 post-transplant. Envarsus, while demonstrating a unique drug-delivery profile, still maintains an equivalent correlation between exposure (AUC) and C0 values to tacrolimus IR, validating a low-exposure goal for Envarsus in combination with everolimus (8).

However, the combination of a once-daily product along with twice-daily products such as mycophenolate mofetil does not reduce the number of times per day immunosuppressive therapy is necessary. It has the potential, alternatively, to reduce adherence to the twice-daily product.

Everolimus (Zortress®) is an mTOR inhibitor that has been studied and approved as an adjunctive immunosuppressant in kidney transplant recipients in a twice-daily regimen (6). However, due to the prolonged elimination half-life of everolimus (28±7 hours), a number of researchers have evaluated its ability to be used as a once-daily medication from a pharmacokinetic point of view. Kahan et al. demonstrated that, at steady state, the 24-hour AUC, Cmin, and Cmax increased proportionately to the administered dose. In addition, the relationship between the Cmin and the AUC after once-daily administration was excellent; confirming the ability to use Cmin levels to as an accurate predictor of drug exposure in once-daily everolimus regimens (9). Given this information, there have been subsequent clinical studies investigating a once-daily dosing interval with everolimus therapy. Carmellini et al. converted 12 patients to a once-daily regimen of everolimus and compared these patients to 12 subjects who maintained a twice-daily dosing regimen. The investigators demonstrated that conversion to once-daily everolimus in kidney transplant recipients did not significantly change their Cmin concentration. Further, there were no adverse events or acute rejection episodes 6 months after the conversion (12). In a larger study, Favi et al. compared 40 kidney transplant recipients randomized to once-daily everolimus with a target concentration of 2-6 ng/mL or twice-daily everolimus with a target concentration of 3-12 ng/mL. The investigators demonstrated equivalent renal function and acute rejection rates between the two groups, while the once-daily everolimus regimen demonstrated significantly improved cholesterol indices (13,14). In combination with tacrolimus-based regimens, it has also demonstrated excellent efficacy in preventing acute rejection, with significantly reduced tacrolimus exposure (goal trough concentrations: Everolimus 3-8 ng/mL) (6,7).

With the availability of well-studied once-daily formulations of tacrolimus, the ability to achieve a true once-daily immunosuppressant regimen along with Everolimus and steroids may finally be achievable and have the potential to optimize immunosuppression safety and efficacy in kidney transplantation.

2. Supporting data

1. 24-month, multinational open-label, randomized trial
    1.

	Everolimus 1.5mg per day with reduced exposure CsA N=277	Mycophenolic Acid 1.44 g per day with standard exposure CsA N=277
Efficacy Failure	70 (25.3)	67 (24.2)
Treated Acute Rejection	45 (16.2)	47 (17)
Death	7 (2.5)	6 (2.2)
Graft loss	12 (4.3)	9 (3.2)

	Everolimus 1.5mg per day with reduced exposure CsA N=277	Mycophenolic Acid 1.44 g per day with standard exposure CsA N=277
Any adverse reaction	271 (99)	270 (99)
Anemia	70 (26)	68 (25)
Leukopenia	8 (3)	33 (12_
Diarrhea	51 (19)	54 (20)
Nausea	79 (29)	85 (31)
Infections and infestations	169 (62)	185 (68)
UTI	60 (22)	63 (23)
URI	44 (16)	49 (18)
Blood creatinine increased	48 (18)	59 (22)
Hyperkalemia	49 (18)	48 (18)
Headache	49 (18)	40 (15)
Hypertension	81 (30)	82 (30)

2. Envarsus

	Envarsus XR +/- steroids, MMF/MPS or AZA N=162	Tacrolimus IR +/- steroids, MMF/MPS or AZA N=162
All infections	46%	48%
UTI	10%	14%
URI	26%	28%
BK virus	2%	2%
CMV	2%	1%
Serious Infections	8%	9%
NODAT	10%	11%
Diarrhea	14%	9%
Blood creatinine increased	12%	9%
Headache	9%	7%
Hypertension	4%	6%

	Envarsus XR +/- steroids, MMF/MPS or AZA N=162	Tacrolimus IR +/- steroids, MMF/MPS or AZA N=162
Treatment failure	4 (2.5%)	4 (2.5%)
BPACR	2 (1.2)	2 (1.2)
Graft failure	0	0
Death	2 (1.2)	1 (0.6)
eGFR at 12 months (ml/min)	62	61.4

3. In multiple chronic conditions it has been shown that once-daily regimens or dose reduction frequency through the selection of once-daily medications has improved adherence. Meta-analysis of medication adherence studies demonstrated that dose taking compliance decreases as medication regimens increase from QD, measured by MEMS (DOI: 10.1097/CRD.0b013e3180cabbe7).

TABLE 1. Rate of Adherence by Frequency of Regimen in Long-Term Clinical Treatment Studies

Frequency of Regimen	Mean Dose-Taking Compliance (%)	Standard Deviation (%)	Range (%)
QD (1 dose/d)	79	14	35–97
BID (2 doses/d)	69	15	38–90
TID (3 doses/d)	65	16	40–91
QID (4 doses/d)	51	20	33–81

This meta-analysis of 76 studies covered a range of therapeutic areas and included 26 cardiovascular studies (17 in patients with hypertension).

Adapted from Clinical Therapeutics, Vol. 23, Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance, pgs. 1296–1310, Copyright 2001, with permission from Excerpta Medica, Inc.[44]

3. Study design
    1. Single-center, open-label, randomized comparative pilot trial.
    2. There will be 20 subjects in each arm, with a total study size of 40 subjects.
2. Allocation: Four random permuted-blocks of ten with equal arm allocation ratio will be used. Since no other stratification criteria are considered, larger block sizes will be appropriate. In each block, ten random numbers will be generated using SAS 9.4 with a range from zero to ninety nine. Even numbers will be assigned the intervention arm and odd numbers will be assigned the standard of care with resulting 1:1 allocation.
3. Intervention Model: Parallel assignment
4. 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 and its effect on adherence.
5. Selection and enrollment of subjects
    1. Inclusion criteria
        1. Male or female adult (≥18 years old) with a history of solitary kidney transplant within 3 months (±2 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.
        3. Women of childbearing potential and sexually active males must be willing to use contraception, as indicated in Section 6 of the protocol. Subjects who are not of reproductive potential (status post bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or vasectomy), not sexually active, whose current partner(s) is not of reproductive potential, or whose sexual activity is exclusively homosexual are eligible without requiring the use of contraception.
    2. Exclusion criteria
        1. Patients will be excluded if they are pregnant or nursing females or males with a pregnant female partner
        2. Recipient of multiple organ transplant
        3. Recipient of a non-renal organ
        4. Proteinuria > 800 mg/24 hour
        5. eGFR < 30 ml/min
        6. WBC ≤ 2k/mm^3

7. Plt ≤ 50k/mm^3
8. Triglycerides > 500 mg/dL
9. HIV positive (HIV ab +)
10. Unable to tolerate oral medications
11. Use of another investigational product within thirty days prior to receiving study medication
12. Acute graft rejection within the past month (Banff 1A or higher) or received an ABO incompatible donor organ.
13. 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

2. Study enrollment procedures

1. Subject Identification/Recruitment: Members of the research team will identify potentially eligible patients who have undergone solitary kidney transplantation in the past three months (±2 months). An initial evaluation of existing patient information may be performed 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.
2. 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 adherence 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.
3. 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.

4. Study interventions

1. Interventions, administration, and duration

1. For the first three months (±2 months) post-transplant, the pool of patients from which subject of this study will be recruited will receive the current standard of care. Standard of care is described as a regimen of tacrolimus IR BID (5-12ng/mL) + MMF 1g BID + prednisone QD Three months (±2 months) post-transplant and at the time of recruitment, they are randomized to one of the two arms to either receive a complete once-a-day regimen or to receive twice-daily regimen.
2. 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-- twice-daily regimen of Envarsus QD (5 - 12ng/mL) + MMF (goal dose 1g BID) + prednisone QD for 6 months

2. Arm 2: Intervention-- once-a-day regimen of Envarsus QD (2- 5ng/mL) + everolimus QD (3-8ng/mL) + prednisone QD for 6 months
    1. Envarsus will be supplied for both Arms from Veloxis Pharmaceuticals

2. Adherence assessment
1. Adherence to the study intervention will be assessed at all study visits noted on the Schedule of Evaluations (Section 5.1), using the eight point Morisky Medication Adherence Scale (MMAS-8) (17).

5. Clinical and laboratory evaluations
1. Schedule of evaluations

Data Collection Schedule

Report Form		**Baseline**	**Days Post-Conversion**							
			7±2	14±3	30±5	60±7	90±7	120±7	150±7	180±7
Informed Consent Obtained		X								
Randomization		X								
Review of Inclusion and Exclusion Criteria		X								
Medical History		X								
Kidney Transplant Recipient		X								
Vital Signs		X					X			X
Review of Medications and Dosing		X								
Clinical assessment*	Adverse events, dosage and adherence, rejection, infection, hospitalization				X	X	X	X	X	X
	MMAS-8, MMSE Scale, and SF36 (15,16,20)	X								X
Laboratory Assessments	CBC and Chem-7[1]	X*	O	O	O	O	O	O	O	X*
	Everolimus C0[2]		X*	X*	X*	X*	X	X*	X*	X*
	Tacrolimus C0[2]	X*	X*	X*	X*	X*	X	X*	X*	X*
End of Study										x

X=required; 0=optional: data will be collected if performed as standard of care; *=not current standard of care

Footnotes:

1. Includes sodium, potassium, chloride, CO2, BUN, SrCr, glucose, calcium, WBC, HgB, Hct, platelets
2. Tacrolimus and Everolimus concentrations will be 12- or 24-hour levels , drawn in the morning of each assessment

2. Timing of evaluation
    1. Pre-Randomization Evaluations
    <u>Baseline</u>

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.

2. Intervention and Evaluations

Once the subject has been successfully randomized, the patients will be directed to the hospital pharmacy to pick up study medications. Study evaluations must take place within the time window indicated on the Schedule of Evaluations (Section 5.1)

3. 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 (Section 5.1)
    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 (Section 5.1)
        1. Adverse events will be determined and defined according to Section 8 of the protocol
        2. Doses will be recorded of all immunosuppressants. The adjuvant immunosuppressant (mycophenolate or everolimus) will be counted and compared to the amount expected to be remaining based on the prescribed amount. An MPR will be calculated as follows: (Total Days' Supply in Period/(Last Fill Date - First Fill Date + Last Fill Days' Supply))
        3. Rejection and infection events will be recorded, as defined in Section 5.4)
        4. Hospitalization events will be determined by questioning the subject and review of hospital admissions in the EHR.
    3. Graft 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.

4. Definitions
    1. Acute rejection is defined as a renal allograft biopsy showing grade 1A 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 serum creatinine to within 10% of baseline and/or histologic clearance by Banff Criteria
    3. Resistant acute rejection is defined as no clinical or histologic improvement by renal biopsy within 7-10 days of initiation of treatment.
    4. Recurrent acute rejection is defined as rejection recurring more than two weeks after documented rejection reversal.
    5. Opportunistic Infections will be defined according the American Society of Transplant Recommendations for Screening, Monitoring, and

Reporting of Infectious Complications in Immunosuppression Trials in Recipients of Organ Transplantation (Appendix C1).

5. Treatment of Acute rejection:
    1. Acute rejection will be treated per institutional protocol, listed in Appendix C2.
6. Acceptable contraception methods

<u>Option 1 (monotherapy methods):</u>

1. Intrauterine devices (IUDs)
2. Tubal sterilization
3. Patient's partner had a vasectomy

<u>Option 2 (Choice one from category A AND one from category B):</u>

1. Category A:
    a. Estrogen and progesterone
        i. Oral contraceptive pill
        ii. Transdermal patch
        iii. Vaginal ring
    b. Progesterone only
        i. Injection
        ii. Implant
    c. Barrier method
        i. Diaphragm with spermicide
        ii. Cervical cap with spermicide
        iii. Contraceptive sponge
2. Category B:
    a. Male condom
    b. Female condom
    c. Diaphragm with spermicide (for use with hormone therapy)
    d. Cervical cap with spermicide (for use with hormone therapy)
    e. Contraceptive sponge (for use with hormone therapy)

7. Intervention Discontinuation Evaluations: At the scheduled time of intervention discontinuation (EOT, last date of study), the following evaluations must be completed: vital signs, clinical assessment, CBC, CHEM-7, Everolimus CO, 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 MMAS-8, MMSE Scale and SF-36 will be discussed with a qualified team member.

8. Adverse Events

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.

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)

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

- 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.
- **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.

- **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.
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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.

9. 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:
    1. Pregnancy: If a woman becomes pregnant or a male's female partner becomes pregnant while on-study, the subject will be required to instruct investigators immediately.
    2. Loss of graft: Defined as death or need for retransplant. Patients will be deemed a treatment failure and the intervention will be discontinued.****

10. Statistical considerations

1. Outcomes
    1. Primary outcome- Treatment efficacy, defined difference in change from baseline to six month measure by MMAS-8 in both arms.
2. Secondary objectives
    1. Secondary outcome- Safety outcomes of treatment failure rate, defined as acute allograft rejection with a Banff grade 1A or higher, graft loss, or death at one year post-conversion in both arms.

2. Sample size estimation for the primary outcome
    1. No formal power analysis conducted since this is a pilot study. However, the sample size proposed (n=40) would be able to observe a mean difference between groups in the change of MMAS-8 scores of 2 ± 2 points (95% CI 0.73,3.27) with 87% power. Additionally, a mean difference between groups in the change in the Memphis Side Effect Scale (MSES) of 5 ± 5 points (95% CI 1.83,8.17) would have 87% power in the current sample size. Given the average MSES score of 25 points in kidney transplant patients within 2 years of transplant, this appears to be a feasible outcome (11). In order to demonstrate noninferiority in treatment failure, it would require 400 subjects (200 in each group) to have 80% power, estimating a treatment failure rate of 20% and an acceptable difference of 10%. We expect that 70% of those approached meeting study inclusion/exclusion criteria will agree to participate and that 85% of those that consent and are enrolled in the study will complete all visits. If the 95% CIs for the actual enrollment and completion proportions are outside of these thresholds, then feasibility will not be met. If the 95% CIs encompass these expected values, then feasibility will be met.
3. Missing data and imputation methods
    1. 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.

11. Human subjects

1. Institutional review board (IRB) review and informed consent

1. 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.
    2. 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.
2. 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 20 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:

1. A 6-month rejection rate difference between arms > 20%, or if > 40% in either arm
2. A difference in grade 3 or higher infections (based on CTCAE) between arms of > 20%
3. A graft loss difference between arms > 20%

12. Publication of research findings

1. 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.

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14. Appendix A
15. Appendix B

Appendix A: Scientific Registry of Transplant Recipients (15)
Program Summary: MUSC

Medical University of South Carolina
Center Code: SCMU
Transplant Program (Organ): Kidney
Release Date: June 16, 2016
Based on Data Available: April 30, 2016

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

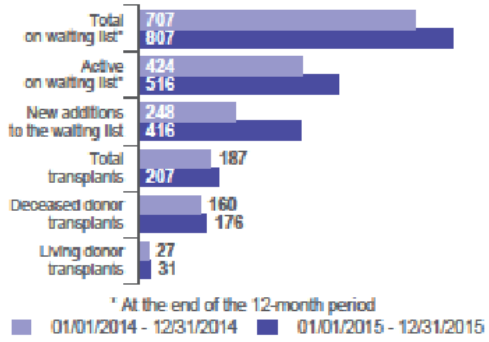
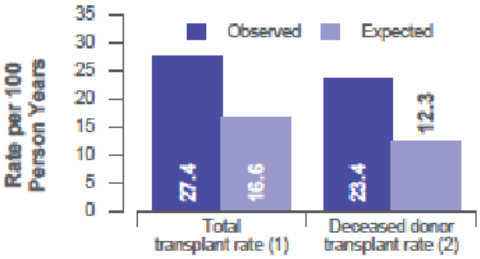


Table A1. Census of transplant recipients

Recipients	01/01/2014-12/31/2014	01/01/2015-12/31/2015
Transplanted at this center	187	207
Followed by this center*	1,372	1,134
...transplanted at this program	1,345	1,111
...transplanted elsewhere	27	23

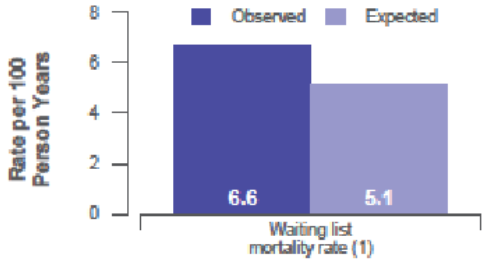
* Recipients followed are transplant recipients for whom the center has submitted a post-transplant follow-up form for a transplant that took place before the 12-month interval for each column.

Figure A2. Transplant rates 01/01/2015 - 12/31/2015



(1) Statistically higher (p<0.01)
(2) Statistically higher (p<0.01)

Figure A3. Waiting list mortality rates 01/01/2015 - 12/31/2015



(1) Not significantly different (p=0.087)

Figure A4. First-year adult graft and patient survival: 01/01/2013 - 06/30/2015

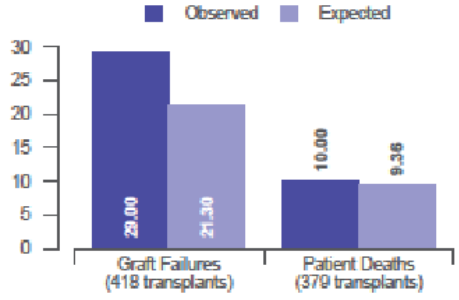
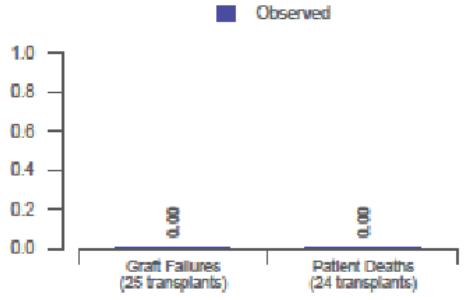


Figure A5. First-year pediatric graft and patient survival: 01/01/2013 - 06/30/2015



The data reported here were prepared by the Scientific Registry of Transplant Recipients (SRTR) under contract with the Health Resources and Services Administration (HRSA).

Appendix B1: Morisky Medication Adherence (MMAS) Scale

MMAS-8	**Points**
Do you sometimes forget to take your pills?	1
People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?	1
Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?	1
When you travel or leave home, do you sometimes forget to bring along your medicine	1
Did you take all your medicine yesterday?	1
When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	1
Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	1
How often do you have difficulty remembering to take all of your medicine? A. Never/rarely B. Once in a while C. Sometimes D. Usually E. All the time	0-5

Adherence	**MMAS-8 Score**
High Adherence	0
Medium Adherence	1-2
Low Adherence	3-8

Appendix B2: Memphis Medication Side Effect (MMSE) Scale

The following questions describe problems you might be having because of the transplant or the medicine you are taking. For each problem, you will be asked how frequently you experience it (the first row) and how troubling it is (the second row). Please answer every question.

	Not at all	Very little	Sometimes or Moderately troubling	Often or Very troubling	All the time or Extremely troubling
Enlarged gums					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Increased hunger					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Staying asleep					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Weight gain					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Increased hair growth					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Infections					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Trembling hands					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□

High blood pressure					

Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Easy bruising					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Loss of interest in sex					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Sexual performance					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Diabetes					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Hair Loss					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□

	Not at all	Very little	Sometimes or Moderately troubling	Often or Very troubling	All the time or Extremely troubling
Stomach pain					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Nausea					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Diarrhea					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□

Vomiting					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Stomach gas					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Indigestion					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Mood Changes					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Depression					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Nervousness or anxiety					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□

Irritability					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Anger					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Keeping a positive attitude					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□

	Not at all	Very little	Sometimes or Moderately troubling	Often or Very troubling	All the time or Extremely troubling
Feelings of uselessness					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Being worried					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Worthlessness					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Hopelessness					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Ability to concentrate					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Completing daily errands					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Participating in social activities					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Doing housework					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□

Doing yardwork					
Do you have this problem?	□	□	□	□	□

How troubling is it?	□	□	□	□	□
Performing my job					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Participating in physical activities					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Participating in leisure pastimes					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Driving					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□

	Not at all	Very little	Sometimes or Moderately troubling	Often or Very troubling	All the time or Extremely troubling
Being independent					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Ability to travel on vacations					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Reading					
Do you have this problem?	□	□	□	□	□

How troubling is it?	□	□	□	□	□
Decreased muscle strength					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Climbing stairs					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Walking					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Bone pain					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Stiff joints					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Foot pain					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Hip pain					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□

Appendix B3: RAND 36-Item Health Survey 1.0 Questionnaire Items

SF-36 Resources

- **Terms and Conditions for Using the SF-36**
- **MOS 36-Item Short Form Survey Instrument (SF-36) (English PDF)**
- **MOS 36-Item Short Form Survey Instrument (SF-36) (Arabic PDF)**
- **Scoring Instructions for MOS 36-Item Short Form Survey Instrument (SF-36)**

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- **1 - Excellent**
- **2 - Very good**
- **3 - Good**
- **4 - Fair**
- **5 - Poor**

2. Compared to one year ago, how would you rate your health in general now?

- **1 - Much better now than one year ago**
- **2 - Somewhat better now than one year ago**
- **3 - About the same**
- **4 - Somewhat worse now than one year ago**
- **5 - Much worse now than one year ago**

The following items 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
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing several flights of stairs	1	2	3
7. Climbing one flight of stairs	1	2	3
8. Bending, kneeling, or stooping	1	2	3
9. Walking more than a mile	1	2	3
10. Walking several blocks	1	2	3
11. Walking one block	1	2	3
12. Bathing or dressing yourself	1	2	3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

During the past 4 weeks, 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)?

	Yes	No
17. Cut down the amount of time you spent on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- **1 - Not at all**
- **2 - Slightly**
- **3 - Moderately**
- **4 - Quite a bit**
- **5 - Extremely**

21. How much bodily pain have you had during the past 4 weeks?

- **1 - None**
- **2 - Very mild**
- **3 - Mild**
- **4 - Moderate**
- **5 - Severe**
- **6 - Very severe**

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- **1 - Not at all**
- **2 - A little bit**

3 - Moderately

4 - Quite a bit

5 - Extremely

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	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. 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.)?

1 - All of the time

2 - Most of the time

3 - Some of the time

4 - A little of the time

5 - None of the time

How TRUE or FALSE is each of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	**1**	**2**	**3**	**4**	**5**
34. I am as healthy as anybody I know	**1**	**2**	**3**	**4**	**5**
35. I expect my health to get worse	**1**	**2**	**3**	**4**	**5**
36. My health is excellent	**1**	**2**	**3**	**4**	**5**

Appendix C1: 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. BK Virus:

A. BK Viremia:

1. Quantitative BK viral DNA load in blood above the detection threshold for the laboratory assay on two separate occasions.

B. BK Virus Associated Nephropathy (BKVAN)

1. Renal biopsy associated with BKVAN per current Banff criteria.

III. 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

Appendix C2: Treatment of Acute Cellular Rejection

Treatment of Acute Cellular Rejection

Banff 1997 Diagnostic Categories for Acute Cellular Rejection

Per Banff 1997 diagnostic categories, acute/active cellular rejection (T-cell mediated rejection) histopathological findings include:

IA: Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of moderate tubulitis (>4 mononuclear cells/tubular cross section or group of 10 tubular cells)

IB: Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of severe tubulitis (>10 mononuclear cells/tubular cross-section or group of 10 tubular cells)

IIA: Cases with mild to moderate intimal arteritis (v1)

IIB: Cases with severe intimal arteritis comprising >25% of the luminal area (v2)

III: Cases with 'transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

Biopsy Results*	Treatment	Other Requirements	Follow-Up
Borderline rejection	Methylprednisolone 250 mg every 24 hours for 3 doses	☐ Increase level of maintenance immunosuppression (maximize MMF dosing, increase tacrolimus levels to upper limit of target range. ☐ Assess for non-adherence. ☐ If diabetic, ensure patient is monitoring blood sugars frequently.	☐ Consider re-biopsy in 7 days if inadequate response to therapy ☐ Patient should have labs weekly ☐ Patient should be seen in clinic with labs one week after completing treatment
Banff '97 1A cellular rejection	Methylprednisolone 500 mg every 24 hours for 3 doses	☐ Increase level of maintenance immunosuppression (maximize MMF dosing, increase tacrolimus levels to upper limit of target range. ☐ Assess for non-adherence. ☐ If diabetic, ensure patient is monitoring blood sugars frequently.	☐ Consider re-biopsy in 7 days if inadequate response to therapy ☐ Patient should have labs weekly ☐ Patient should be seen in clinic with labs one week after completing treatment
Banff '97 1B or greater rejection (with viable tissue and ability to obtain maintenance immunosuppressants in order to be adherent going forward)	Thymoglobulin® 1.5 mg/kg/day for 7 doses (10 mg/kg) or 7 days of total suppression *Pre-medicate patient with methylprednisolone 500 mg IV x 1 prior to first dose of Thymoglobulin® in addition to acetaminophen and diphenhydramine.* *May consider giving additional doses of methylprednisolone 250 mg IV prior to subsequent doses.* *Always consider patient's prior Thymoglobulin exposure when determining treatment	☐ Must have daily CBCs for Thymoglobulin® dosing. If WBC 2,000-3,000 or PLT 50,000-75,000, give **half dose**. If WBC <2,000 or PLT <50,000, **hold dose**. ☐ Increase level of maintenance immunosuppression (maximize MMF dosing, increase tacrolimus levels to upper limit of target range (**tacrolimus levels must be ≥ 8 ng/mL at the time of last Thymoglobulin® dose**). ☐ Assess for non-adherence. ☐ Patient must be restarted on anti-microbial prophylaxis including **CMV prophylaxis, PCP prophylaxis, and fungal prophylaxis** (follow initial protocols with regards to dosing and duration).	☐ Consider re-biopsy in 7 days if inadequate response to therapy ☐ Patient should have labs weekly ☐ Patient should be seen in clinic with labs one week after completing treatment
Features of AMR and cellular rejection	Please refer to AMR protocol for details.		
Calcineurin inhibitor toxicity with no evidence of rejection (vacuolization of tubules, arteriolar hyalinosis)	Consider patient's candidacy for mTOR conversion. Refer to mTOR conversion/CNI minimization protocol for details.		

* Note: Biopsy should be performed within 48 hours of suspicion for acute rejection