A 24-month, single center, pilot, open label, controlled trial to evaluate the efficacy and safety of calcineurin-inhibitor reduction with conversion at 2 months to Reduced Dose tacrolimus/everolimus in adult renal transplant recipients following Campath® induction and steroid avoidance

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Introduction

Campath-1H is a monoclonal antibody that was originally produced in a mouse against the human leukocyte antigen CD52.[1] CD52, a cell surface protein (antigen), is present on all lymphocytes and most monocytes. Campath-1H efficacy is related to its ability to cause profound depletion of T-lymphocytes long-term and B cell and monocyte depletion more transiently. Campath-1H not only depletes the blood of these cells, but it also penetrates to the lymphatic system to cause depletion there as well. Campath-1 was originally called Campath-1G (IgG2b) or Campath-1M (IgM) when it was a mouse antibody. It was genetically engineered so that the constant region of the mouse antibody was replaced with the human equivalent and it was renamed Campath-1H. Thus, Campath-1H only has mouse antibody segment at the binding site and the rest is of human origin; because of this, it is much less likely to elicit an anti-Campath® antibody response such as that which limits the re-use of OKT3® or Thymoglobulin®. In addition, because Campath-1H does not bind directly to the T-cell receptor (like OKT3®), it is much less likely to cause a cytokine release syndrome with a subsequent first dose reaction.

Background and Preliminary Data

Campath® was first used in the early 1980s by Peter Friend at Addenbrooke's Hospital at the University of Cambridge to treat acute rejection episodes of renal transplants. He combined Campath® with full dose triple drug immunosuppression of cyclosporine, Imuran® and steroids. Campath® was very effective at reversing rejection, but subsequently many of the treated patients died of overwhelming infections. This result led to concerns that it was too powerful of an immunosuppressant agent and it was not used again until the late 1980s. This time, instead of using Campath® for rejection, Peter Friend conducted a new trial using Campath® as an induction agent in renal transplantation. It was given for 10 days post-operatively and patients were then treated with full dose triple drug immunosuppression of cyclosporine, Imuran® and steroids.[2] This protocol was very effective at preventing rejection, but again a significant number of patients developed life-threatening infections and the antibody was not used again for nearly another decade.

In the late 1990s, Campath® was studied again in Cambridge under the leadership of Professor Sir Roy Calne. Campath-1H was administered as just two doses as an induction agent. The dose of Campath® was reduced, as was the intensity of post-operative maintenance immunosuppression, given the earlier failures due to over-immunosuppression. The first dose of 20 mg was given immediately pre-or post-operatively and the second dose of 20 mg was given about 1 day post-operatively. Patients were immunosuppressed intra-operatively and on post-op day 1 with high dose

steroids, and then maintained only on half-dose cyclosporine to aim for a trough level of about 100 ng/ml. After one year over 90% of the kidneys were still functioning and the rejection rate was lower than that in traditional triple drug immunosuppression.[3-5] Subsequently, the 5 year post-transplant follow-up of these 31 patients demonstrated a 71% 5 year-graft survival, again better than would be expected for a contemporary group of patients treated with triple drug immunosuppression.[6]

Other researchers explored the use of Campath® as an immunosuppressive agent for renal transplantation. The first was Stuart Knechtle at the University of Wisconsin who combined Campath® with monotherapy Rapamune® instead of cyclosporine as was done in Cambridge. Stuart Knechtle reasoned that Rapamune® rather than a calcineurin inhibitor such as cyclosporine might allow for tolerance mechanisms leading to graft acceptance following lymphocyte depletion (in fact, this work was funded by the Immune Tolerance Network). This idea was based on work in mice that supported this concept.[7] Therefore, rather than using half-dose cyclosporine monotherapy as had been successfully done in the Cambridge trial, Knechtle tried using Rapamune® monotherapy post-operatively. Campath® induction with 40 mg total dose was used in 29 primary human renal transplants and the patients were maintained on Rapamune® monotherapy (levels 8-15 ng/mL) post-transplantation. They found that Campath® profoundly depleted T- lymphocytes long-term and more transiently depleted B cells and monocytes. Unfortunately, there was a high rejection rate (8 of 29, 28%) with this combination with many of the rejections being a humoral rejection (5 of 8, 63 %) and one of these resulting in a graft loss.[8] All patients were alive and well after 3-29 months of follow up. One graft was lost because of rejection and seven of the 29 patients were converted to standard triple therapy on account of rejection. There were no systemic infections and no malignancies.

Allan Kirk at the NIH used Campath-1H alone without any subsequent immunosuppression in an attempt to induce tolerance. He did not see rejection for the first several weeks but then by the end of the first month or second month all the patients had rejections that were responsive to steroids and the initiation of Rapamune®. Interestingly, all of the rejections showed no evidence of lymphocytic infiltration on biopsy. Instead, macrophages appeared to be responsible for the rejection.[9] For this reason, Allan Kirk performed a follow-up study where he used deoxyspergualin as an anti-macrophage immunosuppressant post transplantation with Campath-1H induction. Unfortunately, this set of patients fared no better than the initial seven patients he had treated with Campath-1H alone.[10]

Stuart Knechtle and the Wisconsin group continued to use Campath-1H as their induction agent. After the questionable results with Campath-1H and monotherapy Rapamune®, they used Campath-1H in renal transplant recipients in combination with a calcineurin inhibitor, mycophenolate mofetil, and low-dose steroid therapy.[11] They published results treating 126 consecutive renal allograft recipients with 2 doses of Campath-1H antibody on days 0 and 1. Patients treated with Campath-1H were compared with patients who received Simulect® (an anti-CD25 antibody, n=799), Thymoglobulin® (a rabbit anti-human thymus polyclonal antibody preparation, n=160), or other antibody treatment (n=156) in combination with a calcineurin inhibitor, mycophenolate mofetil, and higher dose steroids. The Campath-1H group overall experienced less rejection than the other 3 groups (P=.037). Patients with delayed graft function experienced less

rejection with Campath-1H than control groups (P=.0096) and had improved graft survival (P=.0119). There was no difference in infection or malignancies between the 4 groups. Overall, they found that Campath-1H was well tolerated in renal transplant patients and led to significant reductions in incidence of rejection. In particular, they noted that patients with delayed graft function experienced significantly improved graft survival.

In May 2001, Campath® was approved by the FDA for the treatment of B-cell lymphomas.[12] It was to be used at a dose that was substantially higher than that which was necessary for renal transplantation induction. However, now that the drug was commercially available, it was possible that it could be used off-label for renal transplantation induction.

Dixon Kauffman and his colleagues at Northwestern University in Chicago were ready to take this approach. In fact, they realized that using Campath-1H instead of Simulect® would reduce their cost of induction by half and, compared with Thymoglobulin® induction, they could reduce their cost by nearly 90%. Thus, they replaced Thymoglobulin® with Campath® as their induction agent. They had been doing steroid avoidance trials and felt they would be more successful if they had better initial lymphocyte depletion.[13] They used a single-center, nonrandomized, retrospective, sequential study design to evaluate outcomes in kidney transplant recipients given either Campath® (n = 123) or Simulect® (n = 155) induction in combination with a prednisone-free maintenance protocol using tacrolimus and mycophenolate mofetil. Overall long-term patient and graft survival rates did not significantly differ between patients treated with Campath® and Simulect®. A lower rate of early (<3 months) rejection was observed in the Campath® (4.1%) versus the Simulect® (11.6%) group, but the rates for both groups were equivalent at 1 year. Patient and kidney survival and rejection rates were nearly identical between Caucasians and African Americans that received Campath®. Quality of renal function and incidence of infectious complications were similar in the two groups. Campath® induction therapy was similar in efficacy to Simulect® in a prednisone-free maintenance immunosuppressive protocol for an ethnically diverse population of kidney transplant recipients. This same group subsequently went on to show that Campath® was also safe to use in a steroid-free regimen in patients receiving simultaneous kidney and pancreas transplants.[14] In communication with Dr. Kauffman in October 2006, Northwestern University had used Campath® induction to prevent rejection in over 1000 renal transplant recipients followed by Prograf® and Cellcept® with a subsequent overall rejection rate of 11% at one year (9 % in recipients of living donor kidneys and 13% in recipients of deceased donor kidneys).(personal communication, M. Rees)

Peter Friend added another study to the Campath® story with a multi-center trial carried out in collaboration with Stuart Flechner at the Cleveland Clinic.[15] They performed a pilot study in which 22 kidney recipients (14 LD: 8 DCD) were given Campath® induction (30 mg day 0 and 1), steroids (500 mg mp day 0 and 1, none thereafter), Cellcept® (MMF) maintenance (500 mg b.i.d) and sirolimus (concentration controlled 8-12 ng/mL). With a mean follow-up of 15.9 months, patient survival was (21/22) 96% and graft survival (19/22) 87%. Acute rejections occurred in (8) 36.3% (two humoral). Of 19 surviving grafts, 18 (95%) remained steroid and 15 (79%) CNI-free. At 1 year, mean creatinine was 1.43 mg/dL. Overall infection rates were low, but 2 patients

developed severe acute respiratory distress syndrome (ARDS) at month 3 and 7, respectively, resulting in mortality in one and a graft loss in the other. No cancer or PTLD was observed. Leukopenia was common and MMF dose was reduced or eliminated in 6/22 (27%) patients. The reported higher than expected rate of acute rejection, leukopenia and possible pulmonary toxicity suggested excessive morbidity and the authors suggested that modifications such as an initial period of CNI use should be considered.

Another group to make an important contribution to the Campath® literature has been led by Ron Shapiro at the University of Pittsburgh and their protocol is explored in further detail as it served as the model for the initial use of Campath® at the University of Toledo (except of spaced weaning of Prograf®). Pittsburgh used Campath-1H as induction as only one dose on day zero. The dose was 0.5 mg/kg for patients up to the weight of 60 kg. Any patient whose weight is ≥ 60 kg is given a total dose of 30 mg Campath-1H intravenously. Recipients were pre-medicated with Tylenol® 650 mg PO, Benadryl® 25 mg IV, Pepcid® 20 mg IV and Methylprednisolone 1 gram IV. A second dose of Methylprednisolone was given just before the arterial clamps were removed. No further steroids were administered. The patients were given monotherapy Prograf® post-operatively aiming to keep the level at about 10 ng/ml for the first 4 months and then patients were slowly weaned to lower Prograf® doses with 62% of the patients being successfully weaned to every other day Prograf® dosing.

Pittsburgh has published several interval reports on their experience, but the most recent publication details their experience with Campath® pretreatment with tacrolimus monotherapy and subsequent spaced weaning in 200 consecutive live donor renal transplantations with a mean 3 years of follow-up.[16] Outcomes were reported for patients receiving living donor renal transplantation between March 2003 and December 2005. The actuarial 1-, 2- and 3-year patient survivals were 99.0%, 96.4%, and 93.3% while the graft survivals were and 98.0%, 90.8%, and 86.3%. The cumulative incidence of acute cellular rejection was 1.0% ≤ 1 month, 1.0% ≤ 3 months, 2.0% ≤ 6 months, 9.0% ≤ 12 months, 16.5% ≤ 18 months, 19.5% ≤ 24 months, 23.5% ≤ 30 months, 24.0% ≤ 36 months and 25% ≤ 42 months. Only 1.5% of the patient population experienced an incidence of acute cellular rejection beyond 2.5 years post-transplantation. Based on these results as well as data regarding the incidence of infection, chronic allograft nephropathy and other complications (CMV disease, posttransplant lymphoproliferative disorder and new onset insulin dependent diabetes mellitus posttransplant – only 1 out of 144), the authors conclude that the outcomes confirm the safety and efficacy of this approach at 3 years post-transplantation. Patient and graft survival results equate to those of living donor renal transplant recipients in the database of the Scientific Registry of Transplant Recipients.

Ciancio et al. from Miami added a cautionary note to the use of Campath® in African Americans, although the number of patients in their study was too small to demonstrate clear significance.[17] In a retrospective study of the first 75 primary renal transplant patients given Campath® induction at the University of Miami, 20 were African American (27%), 32 were Hispanic (43%), and 23 were non-African American, non-Hispanic (31%). Immunosuppression consisted of Campath® given intraoperatively and 4 days later (0.3 mg/kg), with low-dose maintenance mycophenolate mofetil (500 mg twice daily) and tacrolimus (targeted trough levels of 5 to 7 ng/ml) and no corticosteroid

therapy after the first week. Median follow-up among ongoing survivors with a functioning graft was 45 months. Their 3-year actuarial patient and graft survival rates were 95% and 85% in African Americans, 89% and 78% in Hispanics, and 96% and 96% in non-African Americans, non-Hispanics, respectively (not significant). A potential shortcoming of this study was that bioavailability of tacrolimus was significantly lower among African Americans in comparison with the other patient subgroups (P=.002). While the incidence of biopsy-proven acute rejection was 20% (4/20) in African Americans, 19% (6/32) in Hispanics, and 13% (3/23) in non-African American, non-Hispanic (not significant), chronic allograft dysfunction occurred more frequently among African Americans (10/20) in comparison with Hispanics (8/32) and non-African American, non-Hispanics (8/23) (P=0.08, log-rank test). In addition, there was a trend at 6 and 12 months posttransplant for the mean serum creatinine to be less favorable among African American patients (P=0.08 and 0.07). No group had increased infection or malignancy.

The most convincing study demonstrating the value of Campath® as an antibody induction therapy allowing early glucocorticoid withdrawal in renal-transplant recipients was a randomized, prospective trial recently published by Hanaway et al.[18] In this study, the authors from five major US transplant programs compared induction therapy involving Campath® with the two most commonly used induction regimens in the US: Simulect® and Thymoglobulin®. They stratified patients into those at high immunologic risk (with a high risk defined by a repeat transplant, a peak or current value of panel-reactive antibodies of 20% or more, or black race) or low immunologic risk. The 139 high-risk patients received Campath® (one dose of 30 mg, in 70 patients) or Thymoglobulin® (a total of 6 mg per kilogram of body weight given over 4 days, in 69 patients). The 335 low-risk patients received Campath® (one dose of 30 mg, in 164 patients) or Simulect® (a total of 40 mg over 4 days, in 171 patients). All patients received Prograf® and Cellcept® and underwent a 5-day glucocorticoid taper in a regimen of early steroid withdrawal. The rate of biopsy-confirmed acute rejection was significantly lower in the Campath® group than in the conventional-therapy group at both 6 months (3% vs. 5%, P<0.001) and 12 months (5% vs. 17%, P<0.001). At 3 years, the rate of biopsy confirmed acute rejection in low-risk patients was lower with Campath® than with Simulect® (10% vs. 22%, P = 0.003), but among high-risk patients, no significant difference was seen between Campath® and Thymoglobulin® (18% vs. 15%, P = 0.63). Adverse event rates were similar among all four treatment groups. Thus, these investigators provided strong evidence that Campath® induction therapy could be used for all renal transplant recipients, regardless of immunologic risk. Patients can expect equivalent or improved results and transplant centers can reduce the cost of immunosuppressive drugs.

Based on these studies, and Dr. Rees' experience with Campath® at the University of Cambridge during his transplant fellowship with Peter Friend and Professor Sir Roy Calne from 1996-1999, the University of Toledo Transplant program's immunosuppressive regimen has utilized Campath® since March of 2006. Over the past nine years, we have evaluated three successive strategies. Beginning in March of 2006, we changed our standard of care immunosuppressive regimen from a conventional three-drug approach utilizing Neoral®, Cellcept® and Prednisone to an approach based on the Pittsburgh experience. We started with Campath® and pre-operative steroid induction,

followed by steroid-free maintenance on Prograf® monotherapy. After completing our first 50 patients with this regimen, we suspected an unacceptably high rejection rate and thus changed our approach to mirror the Northwestern experience by adding myfortic® to the maintenance immunosuppressive regimen. After accumulating an additional 100 patients with this new regimen, we then assessed the relative efficacy of these two approaches.

The following data is in preparation for publication. Data was collected retrospectively for all patients transplanted between 3/14/2006 to 12/31/2007 at The University of Toledo Medical Center. There were *no exclusion criteria* other than limiting data to two transplant surgeons resulting in a study population of 143 patients. The first study group was given Prograf® (P) alone (47 patients) following transplantation, with the later group receiving Prograf® and myfortic® (P/M) (96 patients). Prograf® target level was 8 -12 ng/ml for both groups and myfortic® target dose was 720 mg PO bid adjusted for diarrhea and leukopenia. All patients were treated with Valcyte® and Bactrim® prophylaxis for 6-12 months. Review of the study populations showed no significance differences between the two immunosuppression groups for demographic details, death censored graft survival, patient survival, graft survival, rejection rate, one or two year creatinine level, severity of rejection (Banff score) or humoral rejection. Death censored graft survival rates after one year were 97.8% (P) and 89.4% (P/M). Two year death censored graft survival was 88.9% (P) and 85.6% (P/M). One year patient survival was 93.6% (P) vs 95.8% (P/M) and two year patient survival was 93.6% (P) vs 90.6% (P/M). Creatinine level at one year was 1.7 ± 1.2 mg/dL (P) and 1.5 ± 0.6 mg/dL (P/M) and at two years was 1.7 ± 1.3 mg/dL (P) and 1.5 ± 0.4 mg/dL (P/M). One year overall biopsy-proven rejection rates were 21.3% (P) vs 15.6% (P/M) and two year overall biopsy-proven rejection rates were 25.5% (P) vs 19.8% (P/M). Though not achieving statistical significance, our analysis demonstrated a trend toward differences in response to therapy based on ethnicity. At two years, rejection rates were 22.6% for Caucasians in both study groups, whereas in African-Americans, rejection rates were 45.5% (P) and 13% (P/M) ($p=0.0789$). While observing a 45% rejection rate in African-Americans treated with Prograf® in the absence of myfortic®, this increased rejection rate did not correspond to worsening two year graft survival that was 90.9%. Like the Miami experience, our data suggests caution with Campath® induction in African Americans, with two caveats: 1) our increased rejection rates were only seen in the absence of myfortic®; and 2) in the Miami study their results were limited by lower Prograf® bioavailability in African Americans.

After publication of the study by Hanaway et al. in NEJM in late 2011, we decided that our 15-20% rejection rate with Prograf® and myfortic® with no steroid taper was unacceptable.[18] Therefore, we modified our protocol to eliminate the second dose of 500 mg methylprednisolone intraoperatively and instead have spread this out by adding a steroid taper for the first five days post-operatively as was done in the Hanaway study. Since adopting this policy, we have seen a significant reduction in our rejection rate.

Everolimus (Zortress®) inhibits the proliferation (growth or production) of T and B cells. It is an inhibitor of intracellular signal transduction (the relaying of signals inside a cell that communicates to the cell that it should activate or change) that targets the

mammalian target of rapamycin (mTOR). The mechanism of action of everolimus appears to be distinct from those of calcineurin inhibitors. It forms a complex with the cytoplasmic protein FKBP-12 (intracellular tacrolimus-binding protein) and binds to and interferes with the function of FRAP. FRAP is a key regulatory protein which governs cell metabolism, growth and proliferation. The blockage of this signal leads to inhibition of cell cycle progression from G1 to the S phase (cell cycle growth phases); thus not allowing cells to develop and multiply. Combining everolimus and a calcineurin inhibitor gives rise to synergistic immunosuppressive properties.

Tacrolimus (Prograf® or Hecoria®) inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity (enzyme that frees or removes phosphate from a chemical reaction) of calcineurin is inhibited. This effect may prevent the dephosphorylation (removal of a phosphate group) and translocation (chromosome rearrangement) of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (substances released by activated T-cells such as interleukin-2 or gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

Study Purpose and Rationale

It is now clear that immunosuppressive strategies for renal transplantation achieve excellent short-term and medium-term results. Unfortunately, the long-term results have not substantially improved in the last 20 years. The reasons for this failure to achieve better long-term results are complicated and include such things as allowing older and sicker people to be recipients, using poorer quality donor kidneys and the complications associated with long-term immunosuppression. Among the worst of the long-term effects of chronic immunosuppression are the nephrotoxicity of the calcineurin inhibitors and the myriad complications of steroids. The goal of many now in the transplant field is to limit the exposure of transplant recipients to both steroids and calcineurin inhibitors. The following protocol evaluates the reduction of calcineurin inhibitors in a protocol that has already successfully eliminated the long-term use of steroids. Given the substantial experience with Campath® detailed above, the following study protocol will be offered to all patients undergoing renal transplantation at the University of Toledo University Medical Center. This is a small pilot study; multiple comparisons will be made for descriptive purposes only.

Hypothesis:

Our hypothesis is that conversion to everolimus (Zortress®), allowing the reduction of calcineurin inhibitors, will reduce nephrotoxicity (measured by increased creatinine clearance) and lengthen overall graft survival (measured by 2-year graft survival).

Objectives:

1. The primary objective of the study is to compare the efficacy and the effects on renal function of calcineurin-inhibitor reduction with conversion at 2 months after transplantation to Reduced Dose tacrolimus/everolimus in adult renal transplant recipients. Efficacy will be defined using two co-primary endpoints.

    a. A composite efficacy end point [treated biopsy-proven rejection (BPAR), graft loss, death or loss to follow-up].

    b. Renal function at 24 months post transplantation using GFR as measured by the Modified Diet Renal Disease (MDRD) estimation.

2. Secondary objectives will be to:

    a. Compare the safety and tolerability of the experimental arm compared to the historical control arm.

    b. Compare the presence of proteinuria as defined by spot urine protein to creatinine ratio greater than 1.0 in the experimental arm to the historical control arm.

    c. Compare the presence of hyperlipidemia in the experimental arm to the historical control arm.

    d. Compare the incidence of impaired glucose tolerance (IGT) as assessed by fasting blood sugar, HbA1c and need for hypoglycemic medications in the experimental arm to the historical control arm.

    e. Compare the incidence of mouth ulcers in the experimental arm to the historical control arm.

    f. Compare the incidence of GI complaints including diarrhea in the experimental arm to the historical control arm.

    g. Compare the incidence of leukopenia as defined by WBC less than 1.0, absolute neutrophil count less than 500 or the need for exogenous granulocyte stimulating factor administration in the experimental arm to the historical control arm.

    h. Compare the incidence of thrombocytopenia at one year as defined by platelet count less than 50 or need to discontinue one of the study medications for more than 30 days in the experimental arm to the historical control arm.

    i. Compare the incidence of neurotoxicity as defined by incidence of new onset seizure activity or tremors in the experimental arm to the historical control arm.

    j. Compare the incidence of pneumonitis in the experimental arm to the historical control arm.

    k. Compare the incidence of serious infections as defined by need for hospitalization in the experimental arm to the historical control arm.

    l. Compare the incidence of CMV infection as defined by need for hospitalization in the experimental arm to the historical control arm.

    m. Compare the incidence of BK infection as defined by blood titers requiring reduction in immunosuppressive dose in the experimental arm to the historical control arm.

n. Compare the incidence of BK nephropathy as defined by biopsy in the experimental arm to the historical control arm. Note that biopsies will not be required as part of the study but will only be done as part of the patient's standard of care if rejection is suspected (i.e. if the serum creatinine increases by 25% and is not associated with elevated tacrolimus levels or clinical signs of dehydration/illness to account for elevated creatinine).

o. Compare the incidence of malignancies including PTLD in the experimental arm to the historical control arm.

p. Compare the incidence of cardiovascular complications such as dysrhythmias, coronary artery disease requiring intervention or myocardial infarction in the experimental arm to the historical control arm.

q. Compare the incidence of the development of donor specific antibody (DSA) in the first 24 months post-transplant in the experimental arm to the historical control arm.

Population:

Patients will include all patients age 18 or over who are receiving renal transplantation regardless of prior transplant, ECD kidney, living donor kidney, level of sensitization, or BMI.

Inclusion Criteria: At Screening: (2 months to 6 months after transplantation ± 10 days)

• Male or female renal allograft recipients at least 18 years old.
• Patients who have given written informed consent to participate in the study. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.
• Patient who has received a kidney transplant from a deceased or living unrelated-/related donor.
• Recipient of a kidney allograft with a cold ischemia time (CIT) < 36 hours.
• Female patients must have a negative pregnancy test prior to study enrollment.
• Patients on CNI (tacrolimus and myfortic®) without steroid maintenance following Campath® induction.
• Patients with an acceptable allograft function defined by a serum creatinine < 2.5 mg/dL (250 μmol/L) and an actual eGFR (MDRD4) ≥ 30 mL/min/1.73m2 (without renal replacement therapy).
• No evidence of rejection since the time of transplantation.

Exclusion criteria At Screening: (2 months to 6 months after transplantation ± 10 days)

• Recipient of ABO incompatible allograft or a positive cross-match.
• Patient who is human immunodeficiency virus (HIV) positive.
• Patient who received an allograft from a Hepatitis B surface Antigen (HBsAg) or a Hepatitis C Virus (HCV) positive donor.

• HBsAg and/or a HCV positive patient with evidence of elevated LFTs (ALT/AST levels ≥ 2.5 times ULN). Viral serology results obtained within 6 months prior to screening are acceptable.
• Patient with severe restrictive (TLC < 50%) or obstructive pulmonary (FEV1 < 50) disorders.
• Patient with severe allergy requiring acute (within 4 weeks of baseline) or chronic treatment that would prevent patient from potential exposure to everolimus, or with hypersensitivity to drugs similar to everolimus (e.g. macrolides).
• Patients with a known hypersensitivity/contraindication to any of the immunosuppressants or their classes, or to any of the excipients.
• Patient with severe hypercholesterolemia (> 300 mg/dL) or hypertriglyceridemia (> 400 mg/dL) that cannot be controlled despite lipid lowering therapy.
• Patient with white blood cell (WBC) count ≤ 1,000 /mm^3 (and absolute neutrophil count of <500) or a platelet count ≤ 50,000 /mm^3.
• History of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases. (Localized basal cell carcinoma of the skin at any time, or small (less than 4 cm) or low-grade renal cancers, bladder cancers or treated prostate cancer with no evidence of disease after 2 years are allowable)
• Graft loss.
• Patient on renal replacement therapy.
• Patient who experienced biopsy proven rejection.
• Proteinuria > 1 g/day (as calculated from the urinary protein-to-creatinine ratio). Protein-to creatinine ratios are only calculated if protein is 1+ or greater on urine dipstick as negative or trace amounts do not correlate to measurements near 1 g/day.
• Patients with recurrence of Focal Segmental Glomerulosclerosis (FSGS).
• Patient who has a current severe systemic infection according to the investigator judgment requiring continued therapy that would interfere with the objectives of the study.

- Patients with ongoing wound healing problems, clinically significant infection requiring continued therapy or other severe surgical complication in the opinion of the investigator.
- Presence of intractable immunosuppressant complications or side effects.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive serum human chorionic gonadotrophin laboratory test (>5 mIU/mL)
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods. The two methods can be a double barrier method or a barrier method plus a hormonal method.
    - Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progestational agent. Acceptable contraception methods will be discussed with all women of child-bearing potential.

- Reliable contraception should be maintained throughout the study and for 8 weeks after study drug discontinuation. For women who become pregnant while using Myfortic® or within 8 weeks of discontinuing therapy, we will report the pregnancy to the Mycophenolate Pregnancy Reference Registry (1-800-617-8191) and will strongly encourage the patient to enroll in the pregnancy registry.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Study Duration:

We plan to enroll 11 patients per year. Given this assumption, the enrollment will take five years. Adding two years of follow-up care, we will be able to complete the study in 7 years.

Study Design:

1. Single center pilot study utilizing historical control
2. A single treatment arm
3. Eleven patients per year
4. Five years to enroll 55 patients.
5. Enroll all patients who meet the inclusion criteria at 2 months and up to 6 months (±10 days) post kidney transplantation and are willing to consent for this trial.
6. Patients would have study visits, serum creatinine measurements and other clinically relevant parameters measured monthly until 6 months, then q3 months until 2 years post-transplantation.
7. Graft survival would be measured by the absence of the need for dialysis.
8. It would not be mandatory, but a renal biopsy would be recommended at 2 years to look for underlying early signs of calcineurin toxicity/chronic allograft nephropathy.
9. Secondary endpoints would include such parameters as post-transplant diabetes, proteinuria, lipid levels, mouth sores, neurotoxicity, pneumonitis, CMV, PTLD, BK-nephropathy, malignancies, cardiovascular complications, etc.
10. Our historical control will be composed of patients transplanted at the University of Toledo Medical Center between October 2011 and the beginning of this trial. All of those patients will have been treated with the exact same protocol as in this study except that they will not have been converted to the treatment arm above, but will have remained on tacrolimus and myfortic®, unless the clinical situation warranted changing immunosuppression. We expect that the control group will consist of approximately 50-55 patients and will have similar demographics to the patients that will be enrolled in this trial, given that we will use the same inclusion and exclusion criteria to select all patients from October 2011 until the start of this trial to populate

the historical control group. The reason for October 2011 as the starting point for the historical control is that this is the date when we modified our protocol to add a five day taper of steroids immediately after transplantation. Prior to that we only gave steroids immediately prior to the transplantation procedure. Thus, to be consistent with the patients in this trial, we believe the most accurate historical control should have the same treatment with steroids perioperatively. We will utilize all patients available in the historical control dataset and will not attempt to match for the demographics present in the experimental arm. The control group will consist of a historical control; prospective patients who are not willing to participate in the study will not be considered part of the control group.

11. For patients who are unable to tolerate the protocol-specified study treatment scheme or experience an adverse event, dose adjustments and/or interruptions of the medications in the treatment arm are permitted in order to keep the patient on the treatment. For everolimus (Zortress®), doses can be reduced by half or interrupted completely until an adverse event is resolved. If everolimus (Zortress®) is discontinued for longer than 14 consecutive days the patient must be discontinued from study treatment permanently. Maintaining the patients at a lower dose for tolerability issues is allowed. If tacrolimus (Prograf® or Hecoria®) is interrupted for longer than 14 consecutive days, study treatment must be discontinued permanently and the patient switched over to another of the center's standard of care regimens.

    The criteria for removing a subject from the study medication to the standard of care immunosuppression may include any of the following circumstances:

    1. Discontinuation of study medication for longer than the study protocol allows (as described above)
    2. Pregnancy
    3. Voluntary withdrawal (withdrawal of consent to study)
    4. Lost to follow-up or failure to return for study visits
    5. Lack of compliance

    Patients may voluntarily discontinue from the study for any reason at any time or may be considered discontinued if they state an intention to withdraw, die or fail to return for visits, or become lost to follow-up for any other reason. Patients who elect not to remain on study medications will receive the UTMC standard of care immunosuppressive regimen at the discretion of the investigator.

Brief Immunosuppressive Management:

1. Induction therapy will consist of: 540 mg of myfortic® by mouth, 500 mg of Solu-medrol® IV, and 30 mg of Campath® IV pre-operatively. .

2. Post-operatively patients will be treated with tacrolimus to maintain a level of 10-12 ng/ml for the first 2 months. In the historical control arm, all of the patients will have been treated after the first three months such that the tacrolimus target level was reduced to 8-10 ng/ml until the end of the first year. After the first year the tacrolimus target level would be 6-8 ng/ml in the historical control tacrolimus/myfortic® arm. Concomitantly the historical control arm patients would have been treated post-operatively with 540 mg PO BID of myfortic®

unless diarrhea or leukopenia required lowering this dose. All patients would have received a five day taper of steroids at which time steroids were discontinued.

3. In this proposed pilot study, after two months of maintenance therapy of tacrolimus and myfortic® as described above, all patients will receive the following treatment: Their myfortic® will be weaned off quickly and everolimus initiated to achieve a target level of 3-8 ng/ml with a mean of 6 ng/ml. Once achieving a therapeutic dose of everolimus, the tacrolimus dose will be reduced to target a level of 3-5 ng/ml.

Detailed Renal Transplantation Immunosuppression and Management Protocol

1. The standard of care immunosuppressive regimen will be provided to all patients at the University of Toledo Medical Center for the first two months following renal transplantation. Beginning at 2 months (Screening) and not longer than 6 months (± 10 days) after renal transplantation, patients will be offered the opportunity to participate in a clinical trial to evaluate the efficacy and safety of calcineurin-inhibitor reduction. Informed consent will be obtained from all patients prior to enrollment. In addition, either at the time of evaluation for listing or actual listing on the deceased donor transplantation waiting list, patients will be counseled about immunosuppression trials being offered to patients undergoing renal transplantation at The University of Toledo Medical Center.
2. The initial standard of care immunosuppressive regimen for patients undergoing renal transplantation at The University of Toledo Medical Center consists of Campath® induction, myfortic® and methylprednisolone (Solu-medrol®) on call to the OR, with a five day steroid taper to no steroids by post-operative day five. Post-operatively patients will be maintained on tacrolimus (target level of 10 ng/ml) and myfortic® aiming for a dose of 540 mg PO BID with adjustment for diarrhea and leukopenia.
3. Patients are called to be admitted by the transplant coordinator after discussion with either the surgeon or nephrologists on call. Counseling about standard of care and investigational immunosuppressive regimens will be provided prior to proceeding with renal transplantation.
4. A urology resident admits the patient to the hospital and makes sure that cardiac and other pre-transplant evaluation information is up to date. The resident ensures that the patient does not have a history of recent infection, newly diagnosed cancers, recent cardiac events or newly diagnosed vascular complications.
5. The transplant surgeon evaluates the recipient and consents them to use Campath® in an off-label fashion as the immunosuppressive induction agent either as part of the study described herein or as part of the standard of care.
6. The patient is pre-medicated with:
    a. Tylenol® 650 mg PO
    b. Benadryl® 25 mg IV
    c. Pepcid® 20 mg IV
    d. Methylprednisolone 500 mg IV

e. myfortic® 540 mg PO

7. Following the pre-medication above, the patient is administered Campath® over 2-3 hours. The dose is 0.5 mg/kg for patients up to the weight of 60 kg. Any patient whose weight is ≥ 60 kg is given a total dose of 30 mg Campath® intravenously. Only one dose of Campath® is given on Day 0.
8. Patients are to be observed closely for the possibility of a cytokine release response, although this response is much less frequent with Campath® than has been observed with OKT3®.
9. The renal transplantation operation is then performed with the goal of completing the Campath® infusion prior to removing the arterial vascular clamps and re-establishing blood flow to the transplanted kidney.
10. Just prior to removing the arterial vascular clamps, 40 mg of Lasix® and 12.5 grams of mannitol will be administered IV.
11. Post-operatively, during hospitalization (expected to last 4-5 days), the following medications are initiated:
    a. Tacrolimus 0.15 mg/kg PO BID adjusted to achieve a target (serum level of 10 ng/ml).
    b. myfortic® 540 mg PO BID is initiated and adjusted for diarrhea or leukopenia defined as a WBC < 1.0 or an absolute neutrophil count < 500.
    c. Valcyte® 450 PO mg daily for CMV-mismatched recipients or 450 mg PO every other day for non-CMV-mismatched recipients.
    d. Bactrim® DS one tab PO daily for PCP prophylaxis.
    e. Mycelex® Troche one troche PO QID.
    f. Flagyl® 500 mg PO TID to prevent Clostridium difficile infection.
    g. The following steroid taper will be followed:
        i. Post-op day 1: Prednisone 250 mg PO daily.
        ii. Post-op day 2: Prednisone 125 mg PO daily.
        iii. Post-op day 3: Prednisone 60 mg PO daily.
        iv. Post-op day 4: Prednisone 30 mg PO daily.
        v. Post-op day 5: Prednisone 15 mg PO daily.
12. If delayed graft function is suspected, tacrolimus may be held for the first few days until the creatinine level begins to fall spontaneously.
13. Target tacrolimus levels for the first 2 months post-operatively will be 10-12 ng/ml with a target level goal of 10 ng/ml. After three months, the standard of care approach calls for the tacrolimus target level to be reduced to 8-10 ng/ml (with a target level of 8 ng/ml) until the end of the first year. After the first year, patients without evidence of rejection would have their tacrolimus dose reduced to achieve a trough level of 6-8 ng/ml (with a target level of 6 ng/ml). This approach was used for patients in the historical control arm.
14. No patients are to be treated for rejection without first obtaining a renal biopsy to confirm a cellular or humoral rejection.
15. Cellular rejections scored as Banff 1 will be treated with three, daily pulses of 250-500 mg methylprednisolone on three consecutive days and by confirming a therapeutic level of tacrolimus. Cellular rejections scored as Banff 2 or for those rejections that are not responsive to steroids alone, Thymoglobulin® will be used for a 10-14 day course. Depending on the level of rejection,

ongoing steroid therapy can be administered after agreement by the treating physicians. Generally, hospitalization is required for at least the first few days of the treatment of rejection using Thymoglobulin®. During the first dose of Thymoglobulin®, blood pressure and vital signs will be monitored every 15 minutes for the first hour, then every 30 minutes for the next two hours, then every one hour for the next 3 hours and then per routine protocol if stable.

16. Humoral rejections will be treated with IVIG 100 mg/kg followed by a one volume exchange plasmapheresis on an every other day basis until the creatinine begins to fall or a decision is made to hold off on further treatment. In extreme cases, re-dosing Campath® can be considered or use of the anti-B cell agent, Rituximab (anti-CD20) can be used. These decisions will be made after consultation between the transplant surgeon and attending nephrologists.
17. The intention-to-treat concept will be applied to patients who experience biopsy-proven rejection to avoid missing outcomes. For patients in the study, low-dose myfortic® may be added back to the patient's immunosuppression regimen. Short-term treatment with oral corticosteroids may be required, but long-term steroid use will be avoided.
18. For patients with elevated, post-transplant creatinine but without biopsy proven evidence of cellular or humoral rejection, causes of elevated creatinine other than rejection should be considered. These include intercurrent illness, dehydration, BK-nephropathy and tacrolimus toxicity. Dose reduction of tacrolimus can be attempted to assess for the possibility of calcineurin-inhibitor nephrotoxicity. If dose reduction of tacrolimus is not acceptable, then everolimus (first choice) or Neoral® (second choice) will be used as replacement therapy.
19. Upon discharge from the hospital, all patients will be treated with the following prophylactic medications:
    a. Valcyte® 450 mg PO daily to prevent subsequent CMV infection (unless leukopenia or other side effects warrant further dose reduction or discontinuation). Valcyte® will be administered for 6 months if there is no CMV mismatch and for 12 months if there is a CMV mismatch.
    b. Bactrim DS® one tablet PO Monday, Wednesday and Friday to prevent subsequent pneumocystis carinii pneumonia. In hospital desensitization with Dr. Nelson can be performed if the patient has a known sulfa allergy or Dapsone replacement can be used. Bactrim® will be administered for at least one year following transplantation. Length of therapy after one year will be determined by physician and patient preference.
    c. Mycelex® Troche one lozenge PO QID to prevent oral thrush. Mycelex troche® therapy will be continued for 6 months post-transplantation.
    d. Flagyl® 500 mg PO TID to prevent Clostridium difficile infection only during in-hospital stays of transplant patients.
20. BK viral titers will be assessed at three month intervals for the first year post-operatively.
21. Post-transplant PRAs (to determine the presence or absence of donor specific antibodies – DSA) will be assessed at the patient's screening visit, at three month intervals for the first year post-operatively and every 6 months in the

second year post-operatively. PRAs may also be assessed at the discretion of the principal investigator or measured as part of the patient's standard of care/routine treatment.

22. For patients who are prescribed myfortic® as part of an intention-to-treat adverse event, MPA levels will be assessed on an as needed basis.
23. Patients who have CMV-mismatched kidneys may be followed with CMV viral titers. Patients suspected of rejection episodes due to elevated creatinine levels should also be assessed for the possibility of BK-nephropathy by following urine cytology, looking for viral inclusion bodies on electron microscopy of biopsy specimens and by following BK viral titers in urine and or blood.

Conversion at 2-6 Months (±10 days) to the Study Protocol

1. Only patients who have reached the two month (± 10 days) post-operative mark without prior evidence of rejection will be offered the opportunity to participate in the study.
2. At the two month mark (± 10 days), patients will be counseled about participation in the study and informed consent obtained prior to participation. Our control group will consist of a historical control; prospective patients who are not willing to participate in the study will not be considered part of the control group.
3. Study participants will be maintained on the following immunosuppression regimen:
    a. Their myfortic® will be weaned off quickly and everolimus initiated to achieve a target level of 3-8 ng/ml with a mean of 6 ng/ml. Once achieving a therapeutic dose of everolimus, the tacrolimus dose will be reduced to target a level of 3-5 ng/ml with a mean of 4 ng/ml.
    b. As noted above, patients in the historical control group will have remained on tacrolimus and myfortic® according to the target levels outlined in #13 above. Briefly, the tacrolimus target level would be reduced to 8-10 ng/ml (with a target level of 8 ng/ml) until the end of the first year and after the first year the tacrolimus target level would be further reduced to 6-8 ng/ml (with a target level of 6 ng/ml) if no evidence of rejection had been encountered.

AE Reporting

Any suspected serious adverse event (SAE) will be reported to the Novartis drug safety and epidemiology team overseeing the study within 24 hours of investigator awareness that an SAE has occurred. An SAE report form will completed for any serious adverse event occurring after the subject has provided informed consent and until 4 weeks after the subject has stopped study participation. A serious adverse event (SAE) report form will be faxed to the number provided by the Novartis clinical trials team.

The form will contain the following information:

Investigator contact details

Date of report
Subject description/study number / initials
Subject treatment arm
Study commencement date for subject
Subject information - date of birth, sex, ethnicity, height and weight
Subject's past medical history
Subject's current immunosuppressive regimen and dosages
SAE description
Narrative description of the SAE and details of drug and non-drug treatment
Onset Date and either Ongoing or End Date
Concomitant medications
Seriousness criteria (see below)
Outcome (Death, Recovered or Recovered with Sequelae)
Relationship to immunosuppressive medication regimen (suspected, not suspected or unknown).
Assessment of causality including alternative explanations and consideration of any co-suspect medications based on the data available at the time.
Signature of investigator

Clinically significant follow-up information and/or new data that has become available will be faxed to Novartis within 24 hours of the investigator becoming aware that it is available. It will be indicated whether the new information should be added to the previously reported information or should replace the previously reported information. The report type will be labeled as "initial" or "follow-up". Any SAEs that occur which are not associated with a previous report will require a new SAE report form.

Seriousness criteria (as per Novartis established definitions)

1. Death: *The subject died.*
2. Life-threatening: *The reporter believes the subject was at immediate risk of Death from the event as it occurred, e.g. aplastic anemia, anaphylaxis with peripheral circulatory collapse, suicide attempt by taking an excessive amount of study treatment. It does not include an event that, had it occurred in a more severe form, might have caused death.*
3. Required or prolonged inpatient hospitalization: *The subject had to be admitted to hospital as an in-patient or hospitalization of the subject had to be extended as a result of an AE.*

An SAE form will not be completed if the hospitalization:

- was for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- involved treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- was for general care, not associated with any deterioration in condition
- involved only treatment on an emergency, outpatient basis for an event not fulfilling any of the other definitions of serious and not resulting in hospital admission.

4. Resulted in persistent or significant disability/incapacity: *The event results in a substantial disruption of a person's ability to conduct normal life functions. The extent of the disability does not need to be permanent.*
5. Congenital anomaly / birth defect: *Any anatomical malformation or organ malfunction occurring in the offspring of a trial patient or subject.*
6. Other significant medical events: *Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. There may be other events judged to be medically serious or which are significant by specification in certain clinical trials.*

Suspected transmission of an infectious agent via a medicinal product should always be considered serious and assessed as medically significant in the absence of any other seriousness criteria. Cases of newly diagnosed cancer must be reported on a SAE form under 'other significant medical events' or hospitalization, death etc as appropriate. Cases of overdose which are life-threatening or result in death, hospitalization, significant disability or are considered medically significant should be reported on a SAE form. Overdose without clinical manifestation or leading to non-serious adverse events should not be reported on a SAE form.

Any AE, SAE or unanticipated problem occurring as a part of this trial that is considered related or possibly related to the patient's study treatment (immunosuppressive regimen) will also be reported to the University of Toledo Biomedical IRB Department for Human Research Protections on their corresponding internal adverse event reporting form within 7 days of the investigator becoming aware of the event as required by policy and in conformance with HHS and FDA regulations. Any pregnancies will be reported to Novartis within 24 hours of the investigator becoming aware of it.

The University of Toledo Biomedical IRB will have the authority to terminate IRB approval of research that is associated with unexpected serious harm to subjects.

Statistical Section:

This will be a small, pilot study to test whether conversion to everolimus (Zortress®), allowing the reduction of calcineurin inhibitors, will reduce nephrotoxicity (measured by increased creatinine clearance) and lengthen overall graft survival (measured by 2-3 year graft survival). As it is not a large study (55 patients, 11 patients per year), it is not powered to achieve statistical significance. The statistical significance will also be impaired by the use of a historical control group. However, the data generated will be published irrespective of the results, thus making the data available for meta-analysis.

This trial is designed as a parallel-group study. Analysis of data for this design is simple and interpretation of the result is straightforward. Given the limited number of

patients in the trial it may not be meaningful to apply analysis of (co)variance for the statistical evaluation of a continuous variables such as creatinine clearance, but we will attempt to use this method with the guidance of our statistician, Dr. Khuder.[19,20] Likewise, the limited number of patients in the trial may prevent meaningful analysis of time-to-event variables such as graft survival. Nonetheless, we will work with Dr. Khuder to use methods appropriate for survival analysis including the Kaplan-Meier method and Cox's proportional hazards regression to see if meaningful differences exist between our study groups and our historical control.[21,22] If warranted, for safety analyses the AEs and SAEs could be summarized by treatment group but no statistical tests performed due to the population size as a pilot study. In addition, the PI and Co-PI will meet with other members of the clinical transplant team to review the results of this study on a quarterly basis to ensure that no significant adverse events warrant the discontinuation of the trial. Given the small number of patients in the trial, we will analyze the data after we have enrolled 10 patients. If the study immunosuppression regimen has a > 40% Banff 2a rejection rate or greater than 20% patient death rate, then that arm will be prematurely terminated. Serious adverse events will also be analyzed and may serve as grounds for study discontinuation.

Everolimus IIRP Pilot Study Evaluation and Visit Schedule

Treatment Period														
			Months											
	Screening (Visit 1)	**Baseline (Visit 2)**	**1 (3)**	**2 (4)**	**3 (5)**	**4 (6)**	**5 (7)**	**6 (8)**	**9 (9)**	**12 (10)**	**15 (11)**	**18 (12)**	**21 (13)**	**24 (14)**
VISIT TIME WINDOWS	2-6 Mos ± 10 days		±7 days						±14 days		±30 days			
INFORMED CONSENT	X													
BACKGROUND INFORMATION	X													
MEDICAL HISTORY	X													
INCLUSION/EXCLUSION CRITERIA	X													
TRANSPLANT INFORMATION	X													
VIRAL SEROLOGY	X													
BK VIRAL TITERS			X		X			X	X	X		X		X
EBV VIRAL TITERS (if neg)	X							X		X		X		X
CMV VIRAL TITERS (if neg)	X													
DSA EVALUATION	X		X		X			X		X		X		X
PHYSICAL EXAM	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VITAL SIGNS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PREGNANCY TEST (if applicable)	X		X		X			X	X	X		X		X
PRIOR & CONCOMITANT MEDICATIONS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAFETY LABORATORY TESTS**	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SERUM CREATININE	X	X	X	X	X	X	X	X	X	X	X	X	X	X
STUDY MEDICATION ADMINISTRATION (if applicable)		X	X	X	X	X	X	X	X	X	X	X	X	X
EVEROLIMUS LEVEL (if applicable)			X	X	X	X	X	X	X	X	X	X	X	X
TACROLIMUS LEVEL (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MYFORTIC LEVEL (if applicable)	X				X			X	X	X		X		X
OTHER IMMUNOSUPP THERAPIES	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SUSPECTED ACUTE REJECTION RECORD	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HOSPITALIZATION RECORD			X	X	X	X	X	X	X	X	X	X	X	X
DIALYSIS RECORD			X	X	X	X	X	X	X	X	X	X	X	X
AE & INFECTION LOG			X	X	X	X	X	X	X	X	X	X	X	X
SERIOUS ADVERSE EVENTS			X	X	X	X	X	X	X	X	X	X	X	X
GRAFT LOSS			X	X	X	X	X	X	X	X	X	X	X	X
END OF TREATMENT /END OF STUDY														X

** Safety Labs include: Chem 13; AST, ALT, CBC w/ Diff; Lipid Profile; Magnesium, Inorganic Phosphate

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