Conversion to Envarsus Post Kidney Transplant Protects Against BK Infection

Study Protocol & Statistical Analysis Plan

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Conversion from Tacrolimus to Envarsus in Rapid Metabolizers Post Kidney Transplant Protects Against BK Infection

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SHORT STUDY TITLE:	Conversion to Envarsus Post Kidney Transplant Protects Against BK Infection
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1. Study Hypotheses/Objectives

1.1. Hypotheses

High peak levels of tacrolimus predispose renal transplant recipients to BK infection. Conversion of tacrolimus to Envarsus will reduce incidence of BK viruria, viremia, and nephropathy.

1.2. Primary Safety Objective

Envarsus has shown a lower side effect profile in the ASTCOFF study but still carries the same potential risks as tacrolimus. Incidence of BK infection, graft loss, and other adverse events will be tracked.

1.3. Primary Efficacy Objective

The primary efficacy endpoint of the study is the composite of BK Virus infection, including viruria > 500 copies, viremia > 500 copies, or nephropathy as defined by Banff classification (sv 40 positivity with or without tubulitis or if/ta).

1.4. Secondary Efficacy Objective

The secondary end-points will assess incidence of rejection, graft failure, graft dysfunction as defined by >15% decrease in estimated glomerular filtration rate (eGFR), and proteinuria.

2. Background and Rationale

2.1. Background and Scientific Rationale

2.1.1. BK Viral Infection

Development of BK Infection post transplant is largely attributed to reactivation of virus in the donor allograft. Risk factors are multifactorial and can not be linked to an individual immunosuppression agent. Degree of immunosuppression is the most consistent risk factor, and reduction of immunosuppression is the most effective treatment. Rates of BK viruria, viremia, and nephropathy are 40%, 20%, and 1-10% respectively[10,19]. BK virus nephropathy (BKVN) is strongly and independently associated with poor graft survival. BKVN has a high graft failure rate at over 50%. Peak incidence of BK infection is in the first year post transplant.

2.1.2. Etiology of BK Infection

Several different studies identify donor and recipient characteristics as risk factors for BK infection. Several studies conflict on the role of depletional induction with thymoglobulin or campath versus non depletional induction with simulect as risk factors. Several studies conflict regarding the number of immunosuppression agents (two vs. three, generally steroid free vs. not) as risk factors. Studies show conflicting risks regarding tacrolimus vs cyclosporine regimens vs. CNI free regimens. Injury to the uroepithelial pathway has also been reported as a risk factor. There has not been one consistent identifiable cause of BK infection post transplant.

2.2. Rationale for use of Envarsus

Rapid metabolizers have an allelic variation at cyp 450 3a5 and require higher doses of tacrolimus to achieve goal trough drug levels for prevention of rejection. These patients have higher incidence of side effects related to high peak levels and have periods of heightened drug exposure. The use of a concentration/drug dose ratio < 1 for tacrolimus has been validated as an identifier for rapid metabolizers.[1-4] The use of Envarsus in place of short acting tacrolimus has been shown to provide equitable drug exposure and efficacy with respect to prevention of rejection and decreased side effects due to lower peak levels. It has also been shown to achieve therapeutic trough levels with lower dosing.[5-9]

2.3. Clinical Studies of Concentration/Dose (C/D) Ratios and BK infection

2.3.1. Validation of C/D Ratio

In the paper by Tholking[3] et al, renal transplant patients were grouped as slow or fast metabolizers according to their C/D ratio. Fast metabolizers had higher incidence of graft dysfunction, calcineurin inhibitor toxicity, and BK virus nephropathy. The use of C/D ratio as a marker of cyp 450 3a5 metabolism was further validated in several studies[1,2,4].

2.3.2. Clinical Studies of Rapid Metabolizers and BK Infection

Tholking et al have demonstrated and increased association with BK infection among transplant patients with low C/D ratios compared to those with high C/D ratios.

In a single center retrospective study[1] of 248 patients designed to investigate effect of metabolism on renal function, patients were grouped according to their C/D ratio (< 1 for fast metabolizers, and >1.55 for slow metabolizers) and had eGFR assessed at 2, 3, 6, 12, and 24 months. Incidence of BK viremia was 8% in the fast group and 1% in the slow group. BKVN was only diagnosed in the fast group with a 4% incidence.

The fast metabolizer group also had significantly higher rates of CNI nephrotoxicity. The authors hypothesized that these findings are related to overexposure of tacrolimus during the peak hours after tacrolimus intake.

A second retrospective study[4] assessed C/D ratio in 192 renal transplant patients, 92 of whom had BK viremia and 92 whom did not. Patients with BK viremia had lower tacrolimus C/D ratios at 1, 3, and 6 months post transplant.

2.4 Clinical Studies of Envarsus

2.4.1

Data from a randomized, double blinded study of Envarsus versus tacrolimus by Budde[5] and data from the open label phase III MELT Trial both demonstrated non inferiority of Envarsus.

In the phase III RCT by Budde, de novo kidney transplant patients were placed on

tacrolimus vs Envarsus along with mycophenolate mofetil (MMF) and prednisone and followed for endpoints of death, graft failure, or biopsy proven rejection. At 12 months, overall survival was 97% in both Envarsus and tacrolimus recipients; graft survival was 97 and 96%, respectively, and graft and patient survival combined was 94 % in both groups. The incidence of clinically suspected and treated rejection was 14 versus 16% in Envarsus versus tacrolimus recipients, and no significant treatment differences were found in the number of biopsy-proven acute rejection episodes. A total of 195 Envarsus and 199 tacrolimus recipients completed 24 months of follow-up on their assigned treatment. At 24 months, the treatment failure rate was 23.1 versus 27.3 %, respectively, with a treatment difference of 4.14 (95 % CI 11.38 to +3.17), again demonstrating noninferiority. The incidence of the individual events comprising treatment failure were similar between treatment groups at 24 months: biopsy-proven acute rejection occurred in 17.2 % of Envarsus and 18.2 % of tacrolimus recipients, graft failure in 4.1 and 5.5 %, respectively, death in 4.1 and 4.7 %, and lost to follow-up in 1.5 and 2.9 %. Renal function was also similar between treatment groups over the 24-month period. The total daily tacrolimus dose was 25 % lower in Envarsus than in tacrolimus recipients in the second year of treatment; C_{trough} values remained similar.

2.4.2

In the conversion study or MELT Trial[6], findings at 12 months were similar with respect to non inferiority for endpoints of death, graft failure or rejection. The primary endpoint was the efficacy failure rate at 12 months (*n*= 162 in each group); efficacy failure comprised death, graft loss, loss to follow-up or locally read biopsy-proven acute rejection. Envarsus was noninferior to tacrolimus with regard to the efficacy failure rate at 12 months in stable, previously treated kidney transplant recipients. The biopsy-proven acute rejection rate was 0.6 versus 2.5 %, respectively. At 12 months, patient survival was 98.8 % in the Envarsus and 99.4 % in the tacrolimus group. The death-censored graft survival rate at 12 months was 100 % in both groups.

Envarsus has an oral bioavailability that is 40% higher than that of tacrolimus in kidney transplant recipients. Moreover, Envarsus is associated with a significantly reduced peak-trough fluctuation ratio and a significantly longer time to C_{max} than tacrolimus, as well as significantly lower mean values for percentage degree of fluctuation and percentage degree of swing. Envarsus was also associated with a significantly lower C_{max}.

2.4.3 Post Hoc Analyses

Exploratory, post-hoc, subgroup analyses of pooled data from both phase III trials found that Envarsus was associated with a significantly lower treatment failure rate than tacrolimus in Black patients and patients older than 65. Patient numbers were much lower for Black (93) than non-Black (768) patients and for patients aged >65 (84) than those aged <65 (777) years.

2.4.4 Pharmacokinetic Study

The ASTCOFF[7] is a cross over PK study that randomized stable kidney transplant patients in a 1:1:0.8 dose conversion for Tacrolimus-IR, Tacrolimus-ER, and Envarsus. Significantly higher exposure on a per mg basis, lower intraday fluctuation and longer time to C_{max} were associated with Envarsus.

3. Study Design

3.1. Description of Study Design

This will be a single center prospective case control study. We expect 40% of patients will develop BK viruria, 20% BK viremia, 5% BK viral nephropathy (BKVN). Patients will be managed using standard of care for our center (thymoglobulin induction, tacrolimus/mycophenolate/prednisone). Target tacrolimus level is 8-12 ng/mL for the first 6 months post transplant and 6-9 ng/mL thereafter. BK urine/serum is routinely monitored during the first year post transplant. A population of 100 patients is calculated to show significant difference for p value < 0.05.

Population:

Study Group: Post transplant patients (kidney transplant alone) with standard of care immunosuppression, no prior rejection, prior BK or opportunistic infection, and negative BK screening at post-transplant month 1, who have a tacrolimus concentration/dose of < 1 and a steady state therapeutic level will be eligible. Patients who consent to participate will be converted to Envarsus at 20% reduction in tacrolimus dose.

Control Group: Post transplant patients (kidney transplant alone performed between 10-2016 and time of consideration for study control group) with standard of care immunosuppression, no prior rejection, prior BK or opportunistic infection, who had a negative BK screening at post-transplant month 1 and tacrolimus concentration/dose of < 1 at post-transplant month 1, and BK data available for months 2, 3, 6, 9, 12 post transplant.

Study visits: Post-transplant Months 2, 3, 6, 9, 12

3.2. Primary Safety Endpoints

The safety of Envarsus treatment will be assessed by:
The timing and incidence of study defined Grade 3 or higher infection

3.3. Primary Efficacy Endpoint

The efficacy primary endpoint of the study is the composite of BK Virus Infection, including viruria > 500 copies, viremia > 500 copies, or nephropathy as defined by Banff classification (g/msv 40 positivity with or without tubulitis or if/ta).

3.4. Secondary Efficacy Endpoints

The secondary end-points to evaluate the effect of Envarsus conversion will

include: incidence of rejection, graft failure, graft dysfunction as defined by a 15% decrease in estimated glomerular filtration rate (eGFR), and proteinuria.

4. Rationale for Study Population

4.1. Enrollment Eligibility Criteria

4.1.1. Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

1. Patient must be able to understand and provide informed consent
2. Age ≥18 years of age at the time of study entry
3. Recipient of a deceased or living donor kidney transplantation
4. Maintenance immunosuppression consisting of tacrolimus/MMF/MPA (≥1000 mg/720 mg daily) ± prednisone (≤10 mg/day)
5. Patient is less than or at 8 weeks post transplant with a negative serum BK Virus screen at 3-4 weeks post transplant
6. Patient has a tacrolimus drug dose/concentration of > 1 with therapeutic tacrolimus levels.
7. Women of childbearing potential defined as all women physiologically capable of becoming pregnant, must have reviewed Mycophenolate REMS and have a negative pregnancy test upon study entry.
8. Female (and male) subjects with reproductive potential must agree to use a highly effective method of birth control for the duration of the study. Please note that according to the US product information for MMF/MPA, two reliable forms of contraception must be used simultaneously unless female sterilization, male sterilization, post-menopausal status or total abstinence is the chosen method.

Acceptable methods of highly effective birth control include:

- Condom with spermicide
- Diaphragm and sperm ide
- Cervical cap and spermicide
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraction
- Intrauterine device (IUD)

Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks prior to screening.

Male sterilization at least 6 months prior to screening. For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.

Post menopausal women defined as being not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea.

4.1.2 Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a patient to give written informed consent or comply with study protocol
2. History of graft loss from acute rejection within 1 year after any previous kidney transplant
3. History of previous liver, heart, pancreas, or lung transplant
4. History of cellular rejection of current allograft prior to enrollment
5. Serum BK virus ≥500 copies/mL by PCR at the time of study entry
6. Female subjects who are pregnant or breast feeding
7. Participation in any other studies with investigational drugs or regimens in the preceding year from the time of study entry
8. Any condition or prior treatment which, in the opinion of the investigator, precludes study participation
9. Patients requiring the use of azathioprine or mTOR inhibitors
10. Patients with active peptic ulcer disease

5. Investigational Agent: Envarsus

5.1. Formulation of Envarsus

Similar to tacrolimus, Envarsus is a macrolide antibiotic. It has a unique drug delivery technology designed to enhance the bioavailability. The technology breaks the drug particles down into the smallest possible units, which are then sprayed onto a carrier, forming a granulate, and then compressed into tablets with a stable dissolution profile and particle size. The smaller drug particle size creates greater drug surface area and greater absorption.

5.2. Dosage, Preparation, and Administration

5.2.1. Dosage

Envarsus pills come in 0.75 mg, 1 mg and 4 mg concentration tablets

5.2.2. Conversion Plan

Patients will convert from current tacrolimus dose to an Envarsus dose that is 80% of the total tacrolimus dose. They will take Envarsus once daily in the morning and have 24-hour trough levels monitored at the standard of care interval for tacrolimus. Dosing will be titrated to achieve goal levels.

5.3. Premature Discontinuation of Envarsus

Envarsus will be stopped and will not be restarted if there is a hypersensitivity reaction, a CTCAE >2, CRS or any serious adverse event.

6. Other Medications

6.1. Immunosuppressive Medications

6.1.1. Tacrolimus

Target tacrolimus trough levels for this study are standard of care at the transplant center, 8-12 ng/mL the first 6 months post transplant and 6-9 ng/mL post-transplant months 7-12.

6.1.2 Mycophenolate Mofetil (MMF)/ Mycophenolic Acid (MPA)

All enrolled subjects will be on MMF/MPA at the time of study entry at a minimum dose of 1000 mg/720 mg per day. Once subjects are enrolled in the study, doses may be adjusted at the discretion of the study investigator for gastrointestinal intolerance, cytopenias, infections or other conditions that require dose adjustment. All mycophenolate prescribers in the study will be required to enroll in the FDA mycophenolate REMS (risk evaluation and mitigation strategy) program.

6.1.3 Prednisone

Use of corticosteroids is standard of care at the center and considered part of the treatment regimen in this trial.

6.1.4 Other Immunosuppressive Medications

Patients requiring the use of azathioprine or mTOR inhibitors will not be enrolled in this study.

6.2. Anti-Infective Prophylactic Medications

Anti-infective prophylaxis medications will be per standard of care.

6.3. Prohibited Medications

6.3.1. Vaccinations

The use of live vaccines will be prohibited during trial participation, as per standard of care for kidney transplant recipients. Examples include (but are not limited to) the following: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines. Subjects should not receive any vaccination (live or inactivated) within 5 days prior to study enrollment.

6.3.2. Medication Interactions

Administration of medications known to interact with tacrolimus and cyclosporine metabolism are allowed but tacrolimus and cyclosporine levels should be carefully monitored, and dosing titrated to maintain the target levels to minimize toxicity while maintaining efficacy.

6.4. Treatment of Rejection

Patients who are clinically suspected to have a rejection will undergo a kidney biopsy as part of their standard of care. Biopsies will be read locally according to the

Banff criteria and if acute rejection is diagnosed, it will be treated according to the current standard of care.

7. Standard Care Procedures While On Study

7.1. Blood Draws

Blood draws are necessary after kidney transplantation to monitor allograft function.

7.2. Kidney Biopsy

Study participants will have an allograft biopsy performed for medical indications such as allograft dysfunction or proteinuria and these results analyzed by an experienced renal pathologist. Patients may undergo a routine surveillance biopsy per institutional protocol.

8. Known and Potential Risks and Benefits to Participants

8.1. Risks of Envarsus

The most common adverse reactions to treatment with Envarsus are similar to the adverse reactions listed below with tacrolimus.

8.2. Risks of Tacrolimus and Mycophenolate Mofetil/Mycophenolic Acid

Subjects will be on tacrolimus and mycophenolate at the time of study entry. Potential risks applicable to their use in this study are listed below.

8.2.1. Risks of Tacrolimus

Post-Transplant Diabetes Mellitus: Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of tacrolimus-treated kidney transplant patients without pre-transplant history of diabetes mellitus in the Phase III study. The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these PTDM patients at one year and in 50% at 2 years post- transplant. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM.

Nephrotoxicity: Tacrolimus can cause nephrotoxicity, particularly when used in high doses. Nephrotoxicity was reported in approximately 52% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving tacrolimus in the U.S. and European randomized trials, respectively, and in 59% of heart transplantation patients in a European randomized trial. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Care should be taken in using tacrolimus with other nephrotoxic drugs.

Hyperkalemia: Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients and in 45% and 13% of liver transplant recipients treated with tacrolimus in the U.S. and European randomized trials, respectively, and in 8% of heart transplant

recipients in a European randomized trial and may require treatment. Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during tacrolimus therapy.

Neurotoxicity: Tacrolimus can cause neurotoxicity, particularly when used in high doses. Neurotoxicity, including tremor, headache, and other changes in motor function, mental status, and sensory function were reported in approximately 55% of liver transplant recipients in the two randomized studies. Tremor occurred more often in tacrolimus-treated kidney transplant patients (54%) and heart transplant patients (15%) compared to cyclosporine-treated patients. The incidence of other neurological events in kidney transplant and heart transplant patients was similar in the two treatment groups. Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment. Seizures have occurred in adult and pediatric patients receiving tacrolimus. Coma and delirium also have been associated with high plasma concentrations of tacrolimus. Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). Symptoms indicating PRES include headache, altered mental status, seizures, visual disturbances and hypertension. Diagnosis may be confirmed by radiological procedure. If PRES is suspected or diagnosed, blood pressure control should be maintained and immediate reduction of immunosuppression is advised. This syndrome is characterized by reversal of symptoms upon reduction or discontinuation of immunosuppression.

Malignancy and Lymphoproliferative Disorders: As in patients receiving other immunosuppressants, patients receiving tacrolimus are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. A lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. The risk of LPD appears greatest in young children who are at risk for primary EBV infection while immunosuppressed or who are switched to tacrolimus following long-term immunosuppression therapy. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

Latent Viral Infections: Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML) which have been observed in patients receiving tacrolimus. These infections may lead to serious, including fatal, outcomes.

8.2.2. Risks of Mycophenolate Mofetil/ Mycophenolic Acid

Embryofetal Toxicity: Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant female. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital

malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, kidney and nervous system.

All prescribers at this center have already been enrolled in the MMF REMS program. Of note, all study participants will already have been on a maintenance regimen containing MMF/MPA and will not be started on it as part of the study. All females must be willing to use FDA approved methods of birth control acceptable during the entire period of the study.

For those females who are discovered to be pregnant either at study screening or enrollment or during the study and who are on MMF/MPA or within 6 weeks of discontinuing therapy, the study investigators will report the pregnancy to the Mycophenolate Pregnancy registry (1-800-617-8191) and strongly encourage the patient to enroll in the pregnancy registry. When appropriate, pregnant patients will be switched to alternative immunosuppression with less potential for embryo-fetal toxicity after a discussion of maternal and fetal risks and benefits.

Lymphoma and Malignancy: Patients receiving immunosuppressive regimens involving combinations of drugs, including MMF, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving MMF (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients. In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed.

Combination with Other Immunosuppressive Agents: MMF has been administered in combination with the following agents in clinical trials: antithymocyte globulin (ATGAM®), OKT3 (Orthoclone OKT® 3), cyclosporine (Sandimmune®, Neoral®), tacrolimus (Prograf®), and corticosteroids. The efficacy and safety of the use of MMF in combination with other immunosuppressive agents have not been determined.

Serious Infections: Patients receiving immunosuppressants, including MMF, are at increased risk of developing bacterial, fungal, protozoal and new or reactivated viral infections, including opportunistic infections. These infections may lead to serious, including fatal outcomes. Because of the danger of over suppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

New or Reactivated Viral Infections: Polyomavirus associated nephropathy (PVAN), JC virus associated progressive multifocal leukoencephalopathy (PML), cytomegalovirus (CMV) infections, reactivation of hepatitis B (HBV) or hepatitis C (HCV) have been reported in patients treated with immunosuppressants, including MMF. Reduction in immunosuppression should be considered for patients who develop evidence of new or reactivated viral infections. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. The risk of CMV viremia and CMV disease is highest among transplant recipients seronegative for CMV at time of transplant who receive a graft from a CMV seropositive donor. Therapeutic approaches to limiting CMV disease exist and should be routinely provided. Patient monitoring may help detect patients at risk for CMV disease. Viral reactivation has been reported in patients infected with HBV or HCV. Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended.

Neutropenia: Severe neutropenia [absolute neutrophil count (ANC) $<0.5 \times 10^3$/uL] developed in up to 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients receiving MMF 3g daily. Patients receiving MMF should be monitored for neutropenia. The development of neutropenia may be related to MMF itself, concomitant medications, viral infections, or some combination of these causes. If neutropenia develops (ANC $<1.3 \times 10^3$/uL), dosing with MMF should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately. Neutropenia has been observed most frequently in the period from 31 to 180 days post-transplant in patients treated for prevention of renal, cardiac, and hepatic rejection. Patients receiving MMF should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Pure Red Cell Aplasia (PRCA): Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MMF in combination with other immunosuppressive agents. The mechanism for MMF induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of MMF therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

Gastrointestinal Disorders: Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with MMF 3 g daily. In pediatric renal transplant patients, 5/148 cases of gastrointestinal bleeding (requiring hospitalization) were observed.

Gastrointestinal perforations have rarely been observed. Most patients receiving MMF were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with MMF. Because MMF has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, MMF should be administered with caution in patients with active serious digestive system disease.

Patients with Renal Impairment: Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m^2) who have received single doses of MMF showed higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of MMF greater than 1 g administered twice a day to renal transplant patients should be avoided and they should be carefully observed.

Patients with HGPRT Deficiency: MMF is an IMPDH (inosine monophosphate dehydrogenase) inhibitor; therefore, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Phenylketonurics: MMF Oral Suspension contains aspartame, a source of phenylalanine (0.56 mg phenylalanine/mL suspension). Therefore, care should be taken if MMF Oral Suspension is administered to patients with phenylketonuria.

8.3. Risks of Standard Care Procedures While On Study

8.3.1. Risks of Blood Draws

Risks of blood draw or venipuncture are typically minimal with temporary local discomfort. More serious risks would include ecchymosis and, rarely, localized infection.

8.3.2. Risks of Kidney Biopsy

There is a risk of bleeding associated with transplant kidney biopsies. Transient hematuria occurs in 3 to 10% of patients and may prolong hospitalization, require bladder catheterization for clot drainage, or in approximately 1% of patients, require blood transfusion. Ureteral obstruction from blood clot may require percutaneous nephrostomy in <1% of patients. Massive hemorrhage requiring surgical exploration, transplant nephrectomy, or arterial embolization occurs in approximately 0.1 % of patients. Death from massive hemorrhage is rare.

8.4. Potential Benefits

This study might not provide direct or immediate benefit to the participants, but it is hoped that the information gained may benefit future kidney transplant patients.

8.4.1. Decrease in BK Infection

It is possible that use of Envarsus in place of tacrolimus will reduce incidence of

BK viruria, viremia, and nephropathy.

8.4.2. Prolongation in Graft Survival

The reduced incidence of BK infection may result in improved graft function and ultimately survival. It is difficult to predict the magnitude of this effect and it may not be apparent for months or years after treatment.

9. Study Visits

9.1. Enrollment

The research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study procedures. A participant is considered enrolled in the trial once the consent form has been signed.

9.2. Follow -Up Visits

The initial visit and subsequent visits on study days 30, 120, 210, and 300 will include routine evaluation with physical examination and laboratory studies. These laboratory studies include BK urine and serum testing, CBC, renal function panel, eGFR, CNI and MPA drug levels, urinalysis, donor specific antibody testing, and urine protein/creatinine ratio according to the center's standard of care.

Please refer to Appendix 1 for schedule of events.

9.3. Unscheduled Visits

If creatinine increases or other concerns arise between regularly scheduled visits, participants will return to the study site for an “unscheduled” visit.

9.4. Visit Time Frames/ Windows

Study visits should take place within the time frames specified below in Table 1. The designated visit windows for each scheduled study visit are indicated in Appendix 1 Schedule of Events.

Table 1. Study Visits

Visit No.	**Study Visit Label**	**Time Frame Post Transplant**
Screen	Study Eligibility	Approximately 1 month
1	Enrollment Day 0/ Visit 1	Approximately 2 months
2	Study Day 30/ Visit 2	Approximately 3 months
3	Study Day 120/ Visit 3	Approximately 6 months
4	Study Day 210/ Visit 4	Approximately 9 months
5	Study Day 300/ Visit 5	Approximately 12 months

10. Criteria for Participant Completion and Premature Study Termination

Participants may be prematurely terminated from the study for the following reasons:

- The participant elects to withdraw consent from all future study activities, including follow-up.
- The participant is "lost to follow-up" 3 months after the date of a missed study visit (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
- The participant dies.
- The Investigator no longer believes participation is in the best interest of the participant.
- CTCAE Grade 3 or higher drug-related reaction
- A decision is made by the investigators and/or study supporter to stop the study

11. Safety Monitoring and Reporting

11.1. Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly to the Supporter. Appropriate notifications per local institutional guidelines will also be made to Institutional Review Boards (IRBs) and health authorities.

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0:
https://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

11.2. Definitions

11.2.1. Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)":
https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/advevntguid.pdf

11.2.1.1. Suspected Adverse Event

Any adverse event for which there is a reasonable possibility that the investigational drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser

degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

11.2.1.2. Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the package insert or is not listed at the specificity, severity or rate of occurrence that has been observed. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator Brochure or package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a).

11.2.2. Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Supporter, it results in any of the following outcomes (21 CFR 312.32(a)):

- Death.
- A life-threatening event: An AE or SAE is considered "life-threatening" if, in the view of either the investigator or Supporter, its occurrence places the subject at immediate risk of death. It does not include an AE or SAE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
- Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

11.3. Grading and Attribution of Adverse Events

11.3.1. Grading Criteria

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) *version 4.0.* This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Principal Investigator and has been deemed appropriate for the subject population to be studied in this protocol.

Infections will be graded using the study-specific scale as described below:

Grade 1 = asymptomatic; clinical or diagnostic observation only; intervention with oral antibiotic, antifungal, or antiviral agent only; no invasive intervention required

Grade 2 = symptomatic; intervention with intravenous antibiotic, antifungal, or antiviral agent; invasive intervention may be required

Grade 3 = any infection associated with hemodynamic compromise requiring pressors; any infection necessitating ICU level of care; any infection necessitating operative intervention; any infection involving the central nervous system; any infection with a positive fungal blood culture; any proven or probable aspergillus infection; any tissue invasive fungal infection; any pneumocystis jiroveci infection

Grade 4 = life-threatening infection

Grade 5 = death resulting from infection

All other adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

Infection events grade 2 or higher; and all other events CTCAE grade 2 or higher will be recorded on the appropriate AE form for this study.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that does not meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events, but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

11.3.2. Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen will initially be determined by the site investigator and recorded on the

appropriate AE/SAE form. Final determination of attribution for safety reporting will be determined by the Supporter after consultation with the Investigator. The relationship of an adverse event to study therapy regimen will be determined using the descriptors and definitions provided in Table 2 below.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site:
https://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

Table 2. Attribution of Adverse Events

Code	Descriptor	**Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)**
Unrelated Category		
1	Unrelated	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
Related Categories		
2	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Definite	The adverse event is clearly related.

Attribution of adverse event to tacrolimus, MMF/MPA, and prednisone will not be assessed in this study because these medications are used as standard of care for kidney transplant recipients.

Attribution assessment for the following study interventions will be made when a SAE is reported:

Study Therapy:
Envarsus

11.4. Collection and Recording of Adverse Events

11.4.1. Collection Period

Adverse events will be collected from the time of first study mandated activity

until a subject completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent), or is withdrawn from the study.

11.4.2. Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Interviewing the subject [e.g., using a checklist, structured questioning, diary, etc.] .
- Receiving an unsolicited complaint from the subject.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 14.3, *Grading and Attribution of Adverse Events.*

11.4.3. Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 14.2, *Definitions)* on the appropriate AE/SAE form regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

11.5. Reporting of Serious Adverse Events and Adverse Events

11.5.1. Reporting of Serious Adverse Events to Sponsor

This section describes the responsibilities of the site investigator to report serious adverse events to the Supporter via the AE/SAE form. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

The PI will report all serious adverse events (see Section 13.2.3, *Serious Adverse Event)*, to the Supporter, regardless of relationship or expectedness, within 24 hours of discovering the event.

For serious adverse events, all requested information on the AE/SAE CRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE form will be updated and submitted to the Supporter.

11.5.2. Reporting of Adverse Events to IRB

The investigator shall report adverse events, including expedited reports, in a timely fashion to their respective IRB in accordance with their local IRB guidelines.

11.6. Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study participant or a partner of a study participant. A pregnant participant shall not receive MMF. The investigator shall counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The investigator shall report to the Supporter all pregnancies within 1 business day of becoming aware of the event. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. When possible, similar information shall be obtained for a pregnancy occurring in a partner of a study participant.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities.

For all pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion, an SAE shall be submitted to the Supporter using the SAE reporting procedures described above.

11.7. Reporting of Other Safety Information

An investigator shall notify the site IRB according to the site's IRB guidelines when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event.

12. Statistical Considerations and Analytical Plan

This is a single center prospective study comparing incidence of BK infection in rapid metabolizers converted from tacrolimus to Envarsus against a recent historical control of rapidly metabolizing recipients who had BK screening at similar points, but remained on tacrolimus.

This study has both safety and efficacy endpoints.

We will use standard descriptive statistics for continuous and categorical data to define adverse events, and clinical outcomes as noted above. Analysis will be undertaken utilizing UAB statistical support in the School of Public Health and Transplant Quality, Informatics and Outcomes.

The enrollment plan is based on a power calculation. A population of 100 patients is calculated

to show significant difference for p value < 0.05.

Our results will be submitted to national/international nephrology/transplant meetings, and as a primary manuscript reporting the primary efficacy and safety data, and secondary manuscripts reporting different secondary endpoints, as appropriate.

We expect the changes over time in these assays to be approximately linear. If after examination of the data, this appears to not be the case, then we will either transform the assay measures or model the time axis time points as an unordered factor (similar to repeated measures ANOVA, but without the requirement for fully balanced data).

We will use descriptive analyses to summarize subject characteristics of our study population. Dichotomous variables will be summarized as proportions with 95% confidence intervals. Continuous variables will be summarized using means, standard deviations, and 95% confidence intervals if they are symmetric and unimodal. Otherwise, they will be summarized using the median and the interquartile range. Simple t-, chi-squared, or Fisher's exact test, as appropriate, will be used to compare quantitative measures across treatment groups. The following variables will be summarized:

- Baseline and demographic characteristics
- Use of concomitant medications
- Reasons for early termination
- All reportable AEs

No formal interim analyses of this study are planned.

13. Identification and Access to Source Data

13.1. Source Data

Source documents and source data are considered to be the original documentation where subject information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

13.2. Access to Source Data

The site investigator and site staff will make all source data available to representatives of the Supporter, as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

14. Protocol Deviations

14.1. Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence,

or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation - A major protocol deviation is a variance from the IRB approved protocol that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol deviations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

14.2. Reporting and Managing Protocol Deviations

The study Principal Investigator has the responsibility to identify, document and report protocol deviations as directed by the study protocol to Supporter. However, protocol deviations may also be identified during other forms of study conduct review. Upon determination that a protocol deviation has occurred, the Principal Investigator will be responsible for reporting deviations to the local IRB, per local IRB guidelines.

15. Ethical Considerations and Compliance with Good Clinical Practice

15.1. Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

15.2. Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The Principal Investigator or designee listed on the FDA 1572 will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant. The consent process will be ongoing and documented. The

consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

15.3. Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information whenever possible. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study Supporter, or their representatives.

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APPENDIX 1: SCHEDULE OF EVENTS

Visit Label	**Study Eligibility**	**Enrollment Day 0**	**Study Day**			
Days after Randomization	---	---	**30**	**120**	**210**	**300**
Visit Number	**Screen**	**1**	**2**	**3**	**4**	**5**
Visit Window	**≤ 4 weeks post transplant**	**≤ 8 weeks post transplant**	**± 14 days**			
Study Eligibility	X					
Informed Consent		X				
Demographics	X					
Medical/Transplant History	X					
Physical Examination/Vital Signs		X	X	X	X	X
Review/Collect Immunosuppressive Medication Data		X	X	X	X	X
Review/Collect Biopsy Results		X[1]	X[1]	X[1]	X[1]	X[1]
Adverse Event/Serious Adverse Event Assessment		X	X	X	X	X
BKV by PCR in urine and serum	X	X	X	X	X	X
CBC (with differential and platelets)	X	X	X	X	X	X
Renal Function Panel (to include Na, K, Cl, CO_2, BUN, Glucose, Creatinine, eGFR)	X	X	X	X	X	X
Hepatic Function Panel (to include ALT, T Bilirubin, D Bilirubin)	X			X		X
Tacrolimus Level	X	X	X	X	X	X
Urine Protein/Creatinine Ratio	X	X	X	X	X	X

[1] Biopsy results will only be collected if a standard care 'for cause' or surveillance biopsy is performed while the participant is on the study.