A Pilot Study Comparing the Safety and Efficacy of Zortress (Everolimus) With Low Dose Tacrolimus to Early Conversion to Calcineurin Inhibitor-Free Regimen and Mycophenolic acid With Standard Dose Tacrolimus in Recipients of DCD and Elevated KDPI Kidneys

Assessment of Zortress (**EVE**rolimus) in **R**ecipients of **E**levated KDPI and **D**CD kidneys – **EVERED** trial

Version number: 03

Release date: 25-FEB-2015

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List of abbreviations

AE	adverse event
Alk Phos	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST (SGOT)	aspartate aminotransferase
ATG	antithymocyte globulin
BID	twice a day
BKV	BK Virus: virus isolated from renal transplant patient, initials B.K.
BPAR	biopsy proven acute rejection
CC	creatinine clearance
CDC	complement dependent cytotoxicity
CI	confidence interval
CIT	cold ischemic time
CKD	chronic kidney disease
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CRF	Case Report/Record Form
CSR	Clinical Study Report
DGF	delayed graft function
DSA	donor-specific antibodies
EC	Ethics Committee
ECG	Electrocardiogram
CRF	electronic Case Report/Record Form
ELISA	enzyme linked immunosorbent assay
ERL	Everolimus
GFR	glomerular filtration rate
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMS	Integrated Medical Safety
IN	Investigator Notification
i.v.	intravenous(ly)
IRB	Institutional Review Board
KDPI	Kidney Donor Profile Index
LLN	lower limit of normal
MDRD	modification of diet in renal disease
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
NG	nasogastric
OPTN/SRTR	Organ Procurement and Transplantation Network/Scientific Registry of Tranplant Recipients
PCR	polymerase chain reaction

p.o.	oral(ly)
QD	once a day
REB	Research Ethics Board
SAE	serious adverse event
SF-36	Medical Outcomes Trust Short Form 36 Health Survey
SOC	Standard of Care
SUSAR	Serious, unexpected, serious adverse reaction
TAC	Tacrolimus
ULN	upper limit of normal
MGTI	MedStar Georgetown Transplant Institute
WBC	white blood cells
WHO	World Health Organization

Protocol synopsis

Title of study: A Pilot Study Comparing the Safety and Efficacy of Zortress (Everolimus) With Low Dose Tacrolimus to Early Conversion to Calcineulin Inhibitor-Free Regimen and Mycophenolic acid With Standard Dose Tacrolimus in Recipients of elevated KDPI and DCD Kidneys

Purpose and rationale: The purpose of this pilot study is to evaluate the efficacy and safety of everolimus (1.5 mg/day) with standard therapy in recipients of DCD and kidneys from donors with Kidney Donor Profile Indices greater than 70 .

Objectives:

- The primary objective of the study is to evaluate efficacy of Everolimus treatment arms compared to Mycophenolate treatment arm with respect to the composite efficacy failure rate including treated Biopsy-Proven Acute Rejection (BPAR) episodes, delayed graft function, graft loss, and death or loss to follow-up. The efficacy will be assessed at 6, 12 and 24 months in recipients of DCD and KDPI kidneys.

- Secondary: To compare renal function (glomerular filtration rate calculated using the MDRD formula) of everolimus with low dose tacrolimus regimen to that of MMF/MPA with standard dose tacrolimus regimen at 24 months post-transplant. Other secondary objectives are: to compare the incidence of CMV and BKV, new onset diabetes mellitus, chronic kidney disease with associated proteinuria, adverse events, serious adverse events and tacrolimus associated adverse events.

Population:

The study population will consist of a representative group of male and female transplant recipients of DCD and elevated KDPI kidneys, 18-65 years of age undergoing renal transplantation. Approximately 50 patients are planned to be enrolled at MGTI.

Inclusion/Exclusion criteria:

Inclusion criteria

- Male or female recipients 18-65 years of age undergoing primary or secondary kidney transplantation
- Recipients of primary or secondary cadaveric, DCD or elevated KDPI kidneys (defined as follows)
    - Donor whose heart has irreversibly stopped beating, previously referred to as non-heart-beating or asystolic donation
    - Donors whose KDPI is calculated at 70% or greater
- Patients who have given written informed consent to participate in the study

Exclusion criteria

- Cold ischemic time (CIT) > 30 hours
- ABO incompatible transplants, or T, or B cell crossmatch positive transplant
- Patients with a known hypersensitivity to any of the study drugs or to drugs of similar chemical classes
- Non-controlled DCD
- Donor age >70
- Patients with BMI >35 at baseline before surgery
- Pregnant or lactating females
- Females of childbearing potential unwilling to use an effective means of contraception or are planning to become pregnant
- Patients with platelet count <100,000/mm at the evaluation before randomization.
- Patients with an absolute neutrophil count of < 1,500/mm³ at baseline before surgery or white blood cell count of < 4,500/mm³
- Patients who are recipients of multiple solid organ transplants
- Patients who have severe hypercholesterolemia (>350 mg/dL) or hypertriglyceridemia (>500 mg/dL). Patients with controlled hyperlipidemia are acceptable
- Patients who have an abnormal liver profile such as ALT, AST, Alk Phos or total bilirubin >3 times the upper normal limit
- Patients who are treated with drugs that are strong inducers or inhibitors of cytochrome P450 3A4, such as terfenadine, astemizole, cisapride, erythromycin, azithromycin, itraconazole, rifampin or lovastatin
- Patients who received an investigational drug or who have been treated with a non-protocol immunosuppressive drug or treatment within 30 days or 5 half-lives prior to randomization
- Patients with a history of malignancy of any organ system, treated or untreated, within the past 2 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin
- Patients who are HIV positive or Hepatitis C (PCR+ only) or Hepatitis B surface antigen positive
- Recipients of organs from donors who test positive for Hepatitis B surface antigen or Hepatitis C (PCR+ only)
- Patients with a history of severe diarrhea, active peptic ulcer disease, or uncontrolled diabetes mellitus (Hgb A1c <7.0 %) at baseline
- Patients who have any surgical or medical condition, which in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism and excretion of study medication, and/or the presence of severe diarrhea or active peptic ulcer
- Patients who have cardiac failure (e.g. resting dyspnea, symptoms with less than ordinary activity, marked limitation of activity) at time of screening or any other severe cardiac disease as determined by the investigator
- Patients with abnormal physical or laboratory findings of clinical significance within 3 months of randomization which would interfere with the objectives of the study

- Patients with any history of coagulopathy or medical condition requiring long-term anticoagulation therapy after transplantation (Low dose aspirin treatment is allowed)
- Patients with known history of focal segmental glomerulosclerosis
- Presence of psychiatric illness (i.e., schizophrenia, bipolar, major depression) that, in the opinion of the investigator, would interfere with study requirements

Investigational and reference therapy:
The following pharmaceutical agents will be utilized:

Investigational drug: Everolimus will be provided by Novartis as 0.5 and 0.75 mg tablets.

Control drug: Either MMF or MPA will be administered. For this study, either MMF 1,000 mg BID or MPA 720 mg BID will be allowed since MMF and MPA are considered to be therapeutically equivalent.

Investigational or control drug will be administered as a dual immunosuppressive regimen with tacrolimus initially.

All patients will receive induction therapy, Campath or Simulect. Steroids will be administered and withdrawn according to our institutional practice.

Study Design:
After obtaining informed consents, patients will be screened for eligibility and randomized within 24h post-transplantation to receive either 1.5 mg of everolimus, 1.5 mg everolimus with CNI-free regimen conversion at month 3, or 1g/720mg of MMF/MPA (1:1:1) in combination with tacrolimus and corticosteroids.

Antibody Induction Therapy:
Campath (Alemtuzumab) 30 mg or Simulect (basiliximab) 20 mg will be administered at induction of anesthesia along with Solumedrol 500 mg intravenously.

Everolimus treatment arm 1:
Therapeutic drug monitoring of everolimus and tacrolimus is mandatory throughout the study. From Day 5 on, the everolimus 0.75 mg BID dose will be increased if the trough level is < 3 ng/mL, or reduced if the trough level is > 8 ng/mL. Tacrolimus will be initiated at 0.1 mg/kg/day and adjusted according to our standard practice to achieve target trough levels. From Day 3 on, a whole blood trough concentration will be targeted for 4 to 7 ng/mL. From Month 3, the target tacrolimus trough level will be 2 ng/mL to 5 ng/mL.

Everolimus treatment arm 2:
Therapeutic drug monitoring of everolimus and tacrolimus is mandatory throughout the study. From Day 5 on, the everolimus 0.75 mg BID dose will be increased if the trough level is < 3 ng/mL, or reduced if the trough level is > 8 ng/mL. Tacrolimus will be initiated at 0.1 mg/kg/day and adjusted according to our standard practice to achieve target trough levels. From Day 3 on, a whole blood trough concentration will be targeted for 4 to 7 ng/mL. From Month 3 (+/- 2 weeks), tacrolimus will be withdrawn and MMF/MPA will be initiated.

MMF/MPA treatment arm 3 (SOC):
MMF/MPA dose will be initiated as 1 g BID (2 g/day)/720 mg BID (1,440 mg/day). Adjustments should be made for adverse events including but not limited to gastrointestinal intolerance and a decrease in WBC. The tacrolimus will be initiated and adjusted to achieve a target whole blood trough concentration of 8 ng/mL to 12 ng/mL. From Month 12 on, the target tacrolimus trough level will be decreased to 6 ng/mL to 8 ng/mL. Steroids will be administered according to our standard practice.

Efficacy assessments:
• Composite efficacy failure rate (treated BPAR, graft loss, death or loss to follow-up)
• Incidence of graft loss, death, or loss to follow-up
• Calculated GFR (eGFR) using the abbreviated MDRD formula

Other assessments:
• Laboratory evaluations of kidney function (including serum creatinine)
• CMV and BKV events
• Glucose intolerance
• Everolimus trough blood levels
• Tacrolimus trough blood levels
• Association with proteinuria
• Vital signs
• Infections and Adverse events
• Serious adverse events
• SF-36 Health Survey questionnaires

Statistical analysis:

All data will be analyzed using the intent-to-treat approach as well as on-treatment based approach. Comparisons between treatment groups experiencing composite efficacy failure and each component will be analyzed with Fisher's exact test. The Chi-square and/or one-way analysis of variance (ANOVA) will be used for acute rejection episodes and creatinine levels respectively.

Sample size justification:

Since this is a pilot study, the sample size estimation method proposed by Julious was considered in order to minimize the sample size (14). Julious proposes to employ sample size of 12 per group for a pilot study (14). Assuming the drop out rate of 20% along with the ease of blocked randomization, we propose the sample size of 16 per arm, totaling 48 patients. The estimated effect size, α, and β corresponding to this sample size are 0.9, 0.05 (two-sided), and 0.2 respectively (15). A block size of 12 along with an allocation ratio of 1:1:1 will be employed as a randomization scheme.

Recruitment/Treatment Periods:

The recruitment period is planned for 24 months. The treatment period is 24 months. A biopsy will be required at Month 3, 12 and 24. Month 3 and 12 biopsies are done according to the institutional practice. No follow-up period is planned. Discontinued patients will be followed for renal function and incidence of efficacy failure at 3, 6, 12, and 24 months post-randomization. Serious adverse events will be recorded for 4 weeks after completing treatment.

1. Background

Every year, as the waitlist for kidney transplants grows, the number of deaths among patients wait-listed also grows. A serious shortage of this vital organ is reported to be responsible for the death of almost half of elderly patients on the waitlist (1). One approach to meet this growing demand is to expand the criteria for kidney donors to ones that have been previously unacceptable. The use of elevated KDPI and Donation after Cardiac Death (DCD) kidneys is increasing; 1,792 and 1,136 cases respectively, compared to 7,503 standard kidneys in 2008 (2). The number of available elevated KDPI kidneys rise every year; however, because of "less than ideal" (or delicate, problematic, etc) condition of these kidneys, and technical challenges it may impose, many centers do not accept these cases.

MedStar Georgetown Transplant Institute (MGTI), like many other transplant programs nationwide, maintain renal transplant patients on double- maintenance therapy of calcineurin inhibitors (CNI), and Mycophenolic acid (MPA) with steroid withdrawal, as well as antibody induction therapy. Although CNIs are one of the most common immunosuppressants prescribed, its nephrotoxicity and incidences with polyoma viral infection have been reported to be associated with less acute and subclinical rejection (12). Because of these side effects, a substantial number of clinical trials were and are being conducted to minimize and/or eliminate CNIs: However, no CNI-reduced/free standard therapy has been established so far.

One of the immunosuppressants currently being evaluated to replace CNIs in patients with CNI nephropathy is the mammalian Target of Rapamycin (mTOR) inhibitor, Sirolimus. Everolimus is a derivative of Sirolimus and belongs to this class of immunosuppressants, therefore, both drugs have similar side effect profile (4, 5). The half-life of Everolimus is almost half of Sirolimus (Everolimus 30 hours vs Sirolimus 62 hours), which makes its dose adjustment easier although it would require more frequent dosing. In clinical trials, Everolimus has demonstrated its potential role as a safe alternative in minimizing and/or eliminating CNI such as Cyclosporin A and Tacrolimus (6-9, 18).

Although the need for CNI-reduced/free therapy exists for all donor types, a growing recipient population of DCD and elevated KDPI kidneys warrants greater protection from nephrotoxicity due to their suboptimal pathology. In a pilot study conducted at University of British Columbia, CNI-free regimen using Sirolimus, MPA and steroids in high KDPI recipients demonstrated significantly better renal function with comparable graft and patient survival after a 2-year follow-up, compared to CNI, MPA and steroid therapy (10,11). So far, no study was conducted using Everolimus in DCD and/or an elevated KDPI population (clinical trials.gov).

Here, we propose to evaluate the efficacy and safety comparing Everolimus in combination with CNI-minimization regimen with standard therapy in recipients of / DCD and elevated KDPI kidneys. This study will provide pivotal information on the use of Everolimus in growing population of kidney transplant recipients.

Objectives:

The primary objective of the study is to evaluate efficacy of Everolimus treatment arms compared to MMF/MPA treatment arm with respect to primary efficacy failure rate, namely, the composite efficacy endpoint, treated BPAR episodes, delayed graft function, graft loss, death or loss to follow-up, at 24 months in recipients of DCD or elevated KDPI kidneys.

2. Purpose and rationale

The purpose of this pilot study is to evaluate concentration-controlled everolimus with low dose tacrolimus compared to early conversion to CNI-free regimen and MMF/MPA with standard dose tacrolimus in de novo renal transplant recipients of / DCD and elevated KDPI kidneys. Given tacrolimus and MMF/MPA is a widely prescribed immunosuppressive regimen in the United States, comparisons of tacrolimus and MMF/MPA regimens to investigational therapies and treatment regimens are needed. Also, considering the fact that DCD and elevated KDPI is a fast growing fraction of donors, evaluation of various regimens' effects on rather delicate DCD and elevated KDPI kidneys is necessary.

3. Objective

The objective of this study is to evaluate efficacy of concentration-controlled everolimus in combination with low dose tacrolimus and early conversion to CNI-free regimen in *de novo* renal transplant recipients of DCD and elevated KDPI kidneys.

3.1 Primary objective

The primary objective of this study is to evaluate concentration-controlled everolimus and low dose tacrolimus compared to MMF/MPA with standard dose tacrolimus at 24 months post-transplant with respect to the composite efficacy failure rates (treated biopsy proven acute rejection episodes (BPAR), graft loss, death, loss to follow-up) in *de novo* renal transplant recipients.

3.2 Secondary objectives

The key secondary objective is to compare renal function of the everolimus treatment arms to the MMF/MPA treatment arm at 12 and 24 months post-transplantation. Renal function will be measured by the calculated glomerular filtration rate (GFR), using the MDRD (Modification of Diet in Renal Disease) formula (20).

Other secondary objectives include:

- The incidence of treated BPAR at 12 months
- The incidence of graft loss at 12 months
- The incidence of death or loss to follow up at 12 months
- Incidence of adverse events (AEs)
- Incidence of serious adverse events (SAEs)
- Incidence of new onset diabetes mellitus defined as non-diabetic patients before transplantation, who are receiving glucose lowering treatment for more than 30 days

post-transplant, or with a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) with 2 fasting plasma glucose values ≥ 126 mg/dL (7 mmol/L).

- Incidence of CMV (viremia or viruria) and BKV (viremia or viruria)
- Incidence of proteinuria by more than 3 fold or proteinuria reaching 1.5gm/day
- The comparison of the health related quality of life for patients treated with everolimus plus low dose tacrolimus to CellCept plus standard dose tacrolimus

4 Study Design

This is a 24 month, Single Center, Open-Label, Randomized**,** Parallel assignment, non-inferiority pilot study of safety and efficacy, comparing Everolimus with low-dose Tacrolimus (2 arms; 1 arm will involve a conversion to MMF/MPA at month 3) and the standard of care (with standard dose Tacrolimus and MMF/MPA) in recipients of DCD and elevated KDPI kidneys. For this study, either MMF 1,000 mg BID or MPA 720 mg BID will be allowed since MMF and MPA are considered to be therapeutically equivalent.

All study patients must give a signed informed consent voluntarily prior to any study-related activities. Once a signed consent is obtained, baseline assessment including laboratory testing will take place to determine patient's eligibility to participate in the study. Baseline assessments will occur in the time period starting 3 weeks pre-transplantation and ending at the time of transplantation. Eligible patients will receive Campath or Simulect as an induction therapy according to the institutional practice.

Randomization will occur within 24-hour of transplantation. Fifty patients who meet the inclusion/exclusion criteria will be randomized to receive their first dose of study drug (0.75 mg Everolimus (2 arms) or 1,000/720 mg MMF/MPA) within 24 hours of transplantation (Figure 4-1). The first dose of Tacrolimus will be given to all study participants according to our standard practice. Patients will be assigned to either continuation on low-dose Tacrolimus (Arm 1), to conversion from low-dose Tacrolimus to Mycophenolate at month 3 (Arm 2), or to standard therapy with Tacrolimus and Mycophenolate (Arm 3).

Everolimus and Tacrolimus levels will be monitored throughout the study, and respective doses will be adjusted according to the desired trough levels. Patients will be started on 0.75mg BID. Everolimus will be dosed to target trough levels of 3 to 8 ng/ml, starting on Day 7.

Earlier increase in Everolimus level may decrease Tacrolimus exposure, which may lead to under-immunosuppression; increasing the risk of acute rejection (16). Therefore, Day 7±1 was chosen to initiate the first dose adjustment for Everolimus after careful consideration of the half-life of this drug and turnaround time of the trough level availability. The target Everolimus trough level was determined based on the Novartis B201 and B251 studies (17).

For Arms 1 and 2, the initial Tacrolimus dose of 0.03 mg/kg (based on ideal body weight) will be given within 24 hours of transplant. Subsequently, the target Tacrolimus trough levels will be 4 to 7 ng/ml from Day 1 to Month 3, and 2 to 5 ng/ml from Month 3 until study completion. For Arm 3, the initial dosing and adjustment will follow the institutional practice.

Patients on Arm 2 will be converted between weeks 12 and 14, after the protocol biopsy. Conversion of Tacrolimus to MMF/MPA (arm 2) will be done abruptly. On the day of conversion, MMF/MPA 1,000/720 mg will be given twice a day while no Tacrolimus will be given. In other words, there is no overlapping of Tacrolimus and MMF/MPA dosing.

For Arm 2 (after Month 3) and arm 3, MMF/MPA will be initiated at 1,000/720 mg and administered according to our standard practice in corresponding arms. Adjustment of doses may occur due to side effects, and in such cases, adjustment will follow the institutional standard practice.

All groups will be treated with corticosteroids, and prednisone will be tapered off or withdrawn according to standard practice.

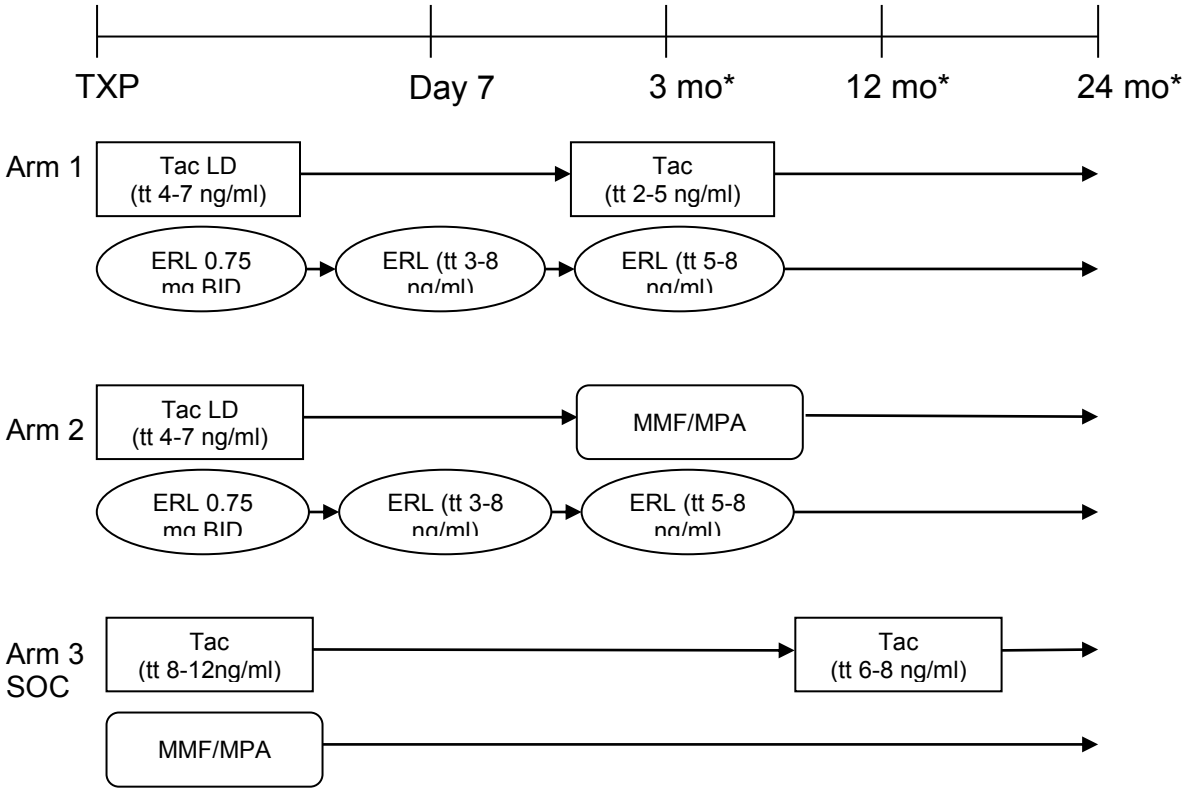
For patients experiencing delayed graft function (DGF), Tacrolimus can be held up to 14 days. If this period is more than 14 consecutive days or more than two episodes of 7 days or longer, study drug discontinuation will be discussed among the study team including nephrologists. In all suspected rejection episodes, biopsy will be performed, and all patients will be treated as per our standard practice based on biopsy findings.

For patients on Arm 1 and 2 experiencing severe side effects such as complications due to delayed wound healing and mouth sores, Everolimus can be held up to 14 days. Patients who will require a prolonged discontinuation of Everolimus longer than 14 days will be withdrawn, and will be monitored as a regular follow-up until 1 month after the discontinuation. Then, patients will be monitored at a reduced follow-up schedule (Table 1).

During the 24 month study period, patients will be monitored according to the study visit schedule as listed in Table 1. The assessment to address the primary objective will be performed at month 6, 12, and 24. No interim analysis is planned. All withdrawn patients will be monitored at a reduced follow-up schedule.

Figure 4-1. Treatment Scheme

*: Biopsy tt: Target Trough level
LD: 0.1 mg/kg/day SOC: Standard of Care



5 Population

Male and female renal transplantation patients, 18 to 65 years of age, receiving a cadaveric, or non-HLA identical living related donor kidney may enter the study. It is anticipated that MGTI will enroll approximately 50 patients. Patients who discontinue the study prematurely will not be replaced.

5.1 Inclusion Criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

- Male or female recipients 18-65 years of age undergoing primary or secondary kidney transplantation
- Recipients of primary or secondary cadaveric, DCD and elevated KDPI kidney (defined as follows)
  - Donor whose heart has irreversibly stopped beating, previously referred to as non-heart-beating or asystolic donation

    OR

  - Donor with a KDPI $\geq$ 70

- Patients who have given written informed consent to participate in the study

5.2 Exclusion Criteria

- Cold ischemic time (CIT) > 30 hours
- Patients who are ABO incompatible, or T, or B cell crossmatch positive
- Patients with a known hypersensitivity to any of the study drugs or to drugs of similar chemical class
- Donor age >70
- Patients with BMI >35 at baseline before surgery
- Pregnant or lactating females
- Females of childbearing potential unwilling to use an effective means of contraception or are planning to become pregnant
- Patients with platelet count <100,000/mm^3 at the evaluation before randomization.
- Patients with an absolute neutrophil count of < 1,500/mm^3 at baseline before surgery or white blood cell count of < 4,500/mm^3
- Patients who are recipients of multiple solid organ transplants
- Patients who have severe hypercholesterolemia (>350 mg/dL) or hypertriglyceridemia (>500 mg/dL). Patients with controlled hyperlipidemia are acceptable
- Patients who have an abnormal liver profile such as ALT, AST, Alk Phos or total bilirubin >3 times the upper normal limit
- Patients who are treated with drugs that are strong inducers or inhibitors of cytochrome P450 3A4, such as terfenadine, astemizole, cisapride, erythromycin, azithromycin, itraconazole, rifampin or lovastatin
- Patients who received an investigational drug or who have been treated with a non-protocol immunosuppressive drug or treatment within 30 days or 5 half-lives prior to randomization
- Patients with a history of malignancy of any organ system, treated or untreated, within the past 2 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin
- Patients who are HIV positive or Hepatitis C (PCR+ only) or Hepatitis B surface antigen positive
- Recipients of organs from donors who test positive for Hepatitis B surface antigen or Hepatitis C (PCR+ only)
- Patients with a history of severe diarrhea, active peptic ulcer disease, or uncontrolled diabetes mellitus (Hgb A1c <7.0 %) at baseline
- Patients who have any surgical or medical condition, which in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism and excretion of study medication, and/or the presence of severe diarrhea or active peptic ulcer
- Patients who have cardiac failure (e.g. resting dyspnea, symptoms with less than ordinary activity, marked limitation of activity) at time of screening or any other severe cardiac disease as determined by the investigator

- Patients with abnormal physical or laboratory findings of clinical significance within 3 months of randomization which would interfere with the objectives of the study
- Patients with any history of coagulopathy or medical condition requiring long-term anticoagulation therapy after transplantation (Low dose aspirin treatment is allowed)
- Patients with known history of focal segmental glomeruloscrelosis
- Presence of psychiatric illness (i.e., schizophrenia, bipolar, major depression) that, in the opinion of the investigator, would interfere with study requirements

6 Treatment

The study is open label. Patients will receive either everolimus or MMF/MPA.

6.1 Investigational and Control Drugs

- Investigational drug: Everolimus (ERL) will be provided as 0.75 mg tablets (10 tablets/blister). Additionally, 0.5 mg tablets (10 tablets/blister) will be supplied for dose adjustments based on blood levels, tolerability, change in co-medications or clinical conditions. Everolimus tablets are white to yellowish, marbled, round, flat with beveled edge.
- Control drug: Mycophenolate Mofetil (MMF)

Investigational or control drug will be administered in combination with tacrolimus (TAC).

6.2 Treatment Arms

Within 24 hours after transplantation, after having met all inclusion/exclusion criteria, patients will be randomized to one of the following treatment groups in a ratio of 1:1:1. All patients will receive Campath or Simulect as induction therapy as well as Solumedrol infusion.

Investigational Drug

Arm 1: Concentration controlled ERL + Low dose TAC + Corticosteroid withdraw

Arm 2: Concentration controlled ERL + Low dose TAC -> MMF/MPA at Month 3 + Corticosteroid withdraw

Control Drug

Arm 3: Standard dose TAC + MMF/MPA + Corticosteroid withdraw

6.3 Treatment Assignment

Once a potential study patient is identified and he/she fulfills the inclusion/exclusion criteria and the informed consent form is signed, the patient will be entered into the study.

The patient will be assigned a patient identification number sequentially (001, 002 etc) Randomization will be performed by the Principal Investigator and/or the clinical research

coordinator using randomization envelopes which each have been randomly assigned a treatment group. A total of 16 patients will be randomized into each treatment group.

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If a patient fulfills the conditions to be randomized, the study team will notify Research Pharmacy staff with the treatment arm and a subject ID number. The Research Pharmacy will then dispense the assigned drug accordingly.

6.4 Treatment Blinding

This is an open-label study. Therefore, after randomization, the investigator, pharmacist and patient will be aware of which treatment is administered to the patient. The investigator should, however, withhold the treatment assignment from the local pathologist interpreting the biopsies. The local pathologist will provide the investigator their interpretation for clinical management of the patient.

6.5 Treating the patient

6.5.1 Patient numbering

Each patient is uniquely identified in the study by a patient number. The center number for this trial will be 01. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. The first patient is assigned patient number 001, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 002, the third patient is assigned patient number 003). Therefore, the first patient is identified as 01-001 (e.g. the second patient is identified as 01-002). A patient number will not be reused. If the patient fails to be randomized for any reason, the reason for not being randomized will be entered on the Screening Log, and the Demography CRF should also be completed.

6.5.2 Dispensing the study drug

Novartis will supply packs of open-label study drug Everolimus.

The study medication packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to the treatment arms, according to the confidential randomization list. The Research Pharmacy will identify the investigational drug to dispense to the patient using the randomization number on the label. Immediately before dispensing the investigational drug to the patient, the Research Pharmacy will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number. The randomization number must also be recorded on the Randomization Number CRF.

6.5.3 Study drug supply, storage and tracking

Study drugs must be received by the Research Pharmacy, handled and stored safely and properly, and kept in a secured location to which only the pharmacy staff and designated assistants have access. All study drugs should be stored according to the instructions specified on the drug labels upon receipt. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in English and comply with the legal requirements of the United States of America. They will include storage conditions for the drug.

The Research Pharmacy will maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger per their SOPs. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will destroy all used and unused study drug, packaging, drug labels, per research pharmacy policy and SOP and a copy of the completed drug accountability log will be retained with study files

6.5.4 Instructions for prescribing and taking the study drug

The investigator should instruct the patient to take the study drug exactly as prescribed. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Study Drug Administration Record CRF.

Everolimus will be provided only as 0.5 mg or 0.75 mg tablets and will be packaged in boxes containing 12 strips of 10 blister packed tablets. The investigator will dispense the appropriate number of blister packed tablets to cover each visit and an additional medication in case of loss, breakage, or scheduling problems.

The investigator/the study team is responsible for instructing the patients regarding the exact dose and dosing schedule to be followed.

Medication labels will comply with the legal requirements of the United States of America and will be in English. The storage conditions for study drug will be described on the medication label.

Investigational drug

Patients will take ERL or MMF/MPA simultaneously with TAC twice daily in 12 hour intervals and on a consistent schedule with regards to time of day and relation to meals. For this study, either MMF 1,000 mg BID or MPA 720 mg BID will be allowed since MMF and MPA are considered to be therapeutically equivalent.

No grapefruit or grapefruit juice should be taken throughout the study.

Arms 1 and 2 (Everolimus Groups)

Initial dosing of ERL will be 1 tablet of 0.75 mg ERL BID (1.5 mg/day) for patients randomized into the either one of ERL groups. Additional medication for dose adjustments will be provided in 0.5 mg or 0.75 mg tablet strengths. The investigator is responsible for instructing the patients regarding the exact dose and dosing schedule to be followed. At Day 7, ERL will be dosed to target trough levels of 3 to 8 ng/ml. At Month 3, ERL will be dosed to target levels of 5 to 8 ng/mL. The ERL trough level should remain less than 8 ng/mL during the whole study duration.

Patients may require dose adjustments based on tolerability, individual response, changes in co-medications, or clinical condition. Dose adjustments can be made at 4-5 day intervals.

Everolimus and tacrolimus should be taken at the same time and consistently either before, during or after meals.

Arm 3 (MMF/MPA - Control group)

Initial dosing of MMF/MPA will be 1000/720 mg BID (2/1.44 g/day) respectively for patients randomized into the MMF/MPA group. The dose should be adjusted for gastrointestinal intolerance and/or a decrease in WBC. For GI intolerance, the MMF/MPA dose should be reduced to 750 mg BID (1.5 g/day). If the GI intolerance persists, the dose can be reduced to 500 mg BID (1 g/day). MMF/MPA may be administered with antacids containing magnesium and aluminum hydroxides; however it is recommended that MMF/MPA and the antacid not be administered simultaneously. If neutropenia develops, dosing with MMF/MPA should be interrupted or reduced and the patient managed appropriately. The investigator is responsible for instructing the patients regarding the exact dose and dosing schedule to be followed.

MMF/MPA and TAC should be taken at the same time and consistently either before, during or after meals.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

6.5.5 Permitted study drug dose adjustments and interruptions

For patients who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions are permitted in order to keep the patient on study drug. The following guidelines should be followed:

Therapeutic drug monitoring

Blood for ERL trough levels will be obtained from all patients at the time points indicated in Table 7-1. In the ERL group, therapeutic drug monitoring (TDM) will be mandatory throughout the study.

On Day 7 after initiation of Everolimus treatment

For Arm 1 and Arm 2 (ERL groups), the 0.75 mg BID dose will be increased if the ERL trough level is < 3 ng/mL, and reduced if the ERL trough level is > 8 ng/mL until Month 3. Starting at Month 3, ERL will be dosed to target levels of 5 to 8 ng/mL. The dose will be increased if the ERL trough level is < 5 ng/mL, and reduced if the ERL trough level is > 8 ng/mL.

Everolimus dose adjustments should be made on results of the trough levels from the hospital laboratory. Tacrolimus dose adjustments should be made based on the results of the trough levels done at the local laboratory. Tacrolimus trough levels will also be run at the hospital laboratory for purposes of the protocol.

Follow-up ERL and TAC trough levels should be measured 5-7 days after any dose adjustment to ERL or TAC to ensure that the recommended troughs are achieved.

Everolimus and MMF/MPA guidelines for dose reductions for safety reasons:

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. Reasons for study drug dose reductions may be for example, a decrease in the white blood cell count or platelet count, an increase in cholesterol or triglyceride level, gastrointestinal intolerance or other adverse events. Severe and unremitting changes may lead to study drug discontinuation. If study medication (ERL or MMF/MPA) is interrupted for safety reasons for 2 episodes of ≥ 7 consecutive days, or more than 21 consecutive days, discontinuation of study medication should be discussed with the sponsor.

During the course of the trial the study drugs will be administered on a BID regimen. Study medication will not be provided to patients after they have discontinued the study.

- Everolimus 1.5 mg treatment groups
  - It is recommended to reduce the dosing from the standard 0.75 mg BID to 0.5 mg BID The dosing should, however, always follow a BID schedule.
- MMF/MPA 2,000/1,440 mg treatment group
  - MMF/MPA dose can be adjusted for gastrointestinal intolerance or a decrease in WBC. If neutropenia develops (ANC < 1,300/mm^3) dosing with MMF/MPA should be interrupted or reduced, appropriate diagnostic tests performed and the patient managed according to local practice.

Additional information for dose adjustments based on laboratory values or other adverse events may be found in Appendix 3.

All changes in dosing of the investigational and control drug must be recorded on the Study Drug Dosage Administration Record CRF with date and reason.

The TAC dose must be adjusted to get C0-h value within the pre-specified target range: for ERL Arm 1: 4 - 7 ng/mL from Day 1 until Month 3, and 2 - 5 ng/mL starting at the Month 3 Visit; for ERL Arm 2: 4 – 7 ng/mL from Day 1 until Month 3, where the patient will be converted from TAC to MMF/MPA; for SOC arm 3: 8 - 12 ng/mL starting at Day 1 until

Month 12, and 6 – 8 ng/mL from Month 12 until study completion. If TAC is held for > 14 days, study drug should be discontinued and the patient discontinued from the study.

These changes must be recorded on the Dosage Administration Record CRF.

6.5.6 Rescue medication

Treatment of acute rejection episodes

In all suspected rejection episodes, regardless of initiation of anti-rejection treatment, a graft core biopsy must be performed within 48 hours. Biopsies will be read by pathologists at MGTI according to the Banff criteria (Appendix 2). Determination of the need for treatment will be according to our pathologists' findings and the overall clinical presentation of rejection. All episodes of acute rejection should be treated as per institutional standard practice, for example bolus steroids as first line and anti-T-cell antibody for steroid resistant rejections.

The local pathologist will remain blinded to the patient treatment. The results of the biopsy read by the pathologists will be listed on the Kidney Allograft Biopsy CRF and will be used for patient management of acute rejection. A treated BPAR will be defined as a biopsy graded IA, IB, IIA, IIB, or III. The protocol treatment assignment should not be disclosed to the pathologists.

Since patient management is based on local readings, for the analysis of the primary efficacy endpoint the pathologists' biopsy readings will be used. For the analysis of secondary efficacy endpoints and for sensitivity analysis of the primary endpoint, the pathologists' readings will be utilized.

Treatment of patients unable to tolerate oral medication

If a patient develops a short term intolerance of oral medication after the initial dose of study medication, study drug may be temporarily interrupted (Section 6.5.5), alternatively, administration of ERL suspension may be carried out via a nasogastric (NG) tube as described below. Such administration of study drug via NG tube will be recorded on the Immunosuppressive Therapy CRF. If this period is more than 21 consecutive days or more than two episodes of 7 days or longer, study drug discontinuation will be discussed among the study team including the study nephrologists. Patients should be returned to oral medication as soon as possible after such an interruption of administration of study medication by mouth.

Nasogastric administration of Everolimus (Patients randomized to everolimus)

Everolimus may be administered via an NG tube until tablets can be tolerated. In order to guarantee adequate dosing the following handling instructions for the application of everolimus tablets via NG tube should be closely followed:

- Do not use any special crushing equipment.
- Pour the tablets into a small (plastic or glass) medicine beaker which contains 10 ml drinking water and wait about 10 minutes.
- Then crush the tablets gently, using the back of a spoon until only small particles are visible.

- Stir the dispersion gently, pull the dispersion into a syringe and inject into the NG tube.
- Rinse the beaker (and the spoon) 3 times with 5 ml drinking water and inject into the tube.
- Finally flush the tube with 10 ml drinking water.

6.5.7 Other concomitant treatments

6.5.7.1 Background immunosuppressive therapy

Induction Therapy:

Campath (Alemtuzumab) 30 mg or Simulect (basiliximab) 20 mg will be administered at induction of anesthesia along with Solumedrol 500 mg intravenously. Basiliximab 20 mg will also be given intravenously on day 4 post-transplant.

6.5.7.2 Initiation and maintenance of Tacrolimus

It is recommended that the initial dose of TAC be administered according to our standard of care practice within 24 hours after reperfusion of the graft. If patients experience DGF, TAC can be held for up to and including 14 days. However, TAC or study medication (ERL or MMF/MPA) must be started within 24 hours post-transplant. Subsequently, ERL dosing will be adjusted according to trough level results from the reference laboratory. Tacrolimus whole-blood trough concentrations will be determined on on all study visits. Target TAC trough levels will be as follows in Table 6-1. Target therapeutic ranges for TAC C0-h levels in whole blood will be assessed at the hospital laboratory for purposes of this protocol.

If, for any time throughout the study, TAC is held for > 14 days, ERL should be discontinued and the patient discontinued from the study. These patients should be followed throughout the remainder of the study to Month 24 on a follow-up schedule. See Section 7.5, Safety assessments, Follow-up of prematurely discontinued patients.

Table 6-1 Target therapeutic ranges for Tacrolimus C0-h levels in whole blood

Randomization Arm	**Time Post-transplant and Corresponding Levels**		
	0 – 3 months	**3 – 12 months**	**12 – 24 months**
Arm 1 (Everolimus)	4 - 7 ng/mL	2 – 5 ng/mL	2 - 5 ng/mL
Arm 2 (Everolimus)	4 - 7 ng/mL	0 ng/mL	0 ng/mL
Arm 3 (MMF/MPA)	8 - 12 ng/mL	8 - 12 ng/mL	6 - 8 ng/mL

6.5.7.3 Initiation and maintenance of steroids

Intravenous and oral steroids will be administered and withdrawn according to the standard of practice at our institution. For the cases that require maintenance steroid therapy, 5-10 mg/day is allowed per our institutional practice.

Dosing and changes of steroid dosing will be recorded in the Immunosuppressive Therapies CRF.

6.5.7.4 Cytomegalovirus prophylaxis for viremia or viruria

CMV prophylaxis with Valcyte for a minimum of 90 days is mandatory for all cases at our institution. Treatment with ganciclovir, cytomegalovirus hyperimmune globulin, acyclovir or valacyclovir will be administered according to our standard practice. All cases of CMV positive donors to CMV negative recipients will be treated with Valcyte for 6 months according to our standard practice. CMV prophylaxis may also be given following any antibody treatment of acute rejection episodes.

6.5.7.5 BK viremia or viruria

Patients with BK viremia or viruria should be treated according to our institutional practice. Patients whose BKV treatment includes a reduction of immunosuppression can remain in the study if the ERL trough level remains between 3 ng/mL and 8 ng/mL or the MMF/MPA dose remains stable. Patients treated with antiviral therapy can remain in the study.

6.5.7.6 *Pneumocystis carinii* pneumonia prophylaxis

All patients will be started on trimethoprim-sulfamethoxazole, starting when oral medication can be tolerated and continuing for the 3 to 6 months post-transplant, in accordance with MGTI standard practice. Aerosolized pentamidine or dapsone may be administered to patients unable to tolerate trimethoprim-sulfamethoxazole.

6.5.7.7 Treatment of oral Candida

For oral thrush (Candida) Nystatin may be used in a swish and swallow regimen, alternatively clotrimazole (Mycelex) lozenges/troches may be used. Routine use of systemic agents (i.e. itraconazole, voriconazole and fluconazole) will not be allowed unless patients are systemically infected. Administration of azoles may increase blood concentrations of everolimus; therefore their use should be minimized. Particular attention to side effects is required (see Appendix 4).

6.5.7.8 Lipid lowering medications

HMG CoA reductase inhibitors (e.g., fluvastatin) are to be administered according to our standard practice for the management of hyperlipidemia. Patients requiring treatment with this class of medication (especially lovastatin) should be monitored closely for signs of rhabdomyolysis, such as, dark-colored urine, fever, muscle cramps, pain, spasm, or stiffness, unusual tiredness or weakness. Lipid lowering therapy should be optimized before dosage reduction of study medication is considered (see Appendix 4).

6.5.7.9 Other medications

The investigator and the study team will instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant Medications/Significant Non-Drug Therapies after Start of Study Drug CRF. If administered for an adverse event (AE), it should be appropriately cross-referenced on the AE CRF.

All other immunosuppressive drugs other than those specified in the protocol are disallowed except those needed to treat rejection.

6.5.8 Study drug discontinuation and premature patient withdrawal

Study drug must be discontinued and the patient withdrawn from the trial if the investigator determines that continuing it would result in a significant safety risk for that patient. The following circumstances require study drug discontinuation:

- Withdrawal of informed consent
- Pregnancy
- Use of immunosuppressive drugs other than those specified by protocol except those needed to treat acute rejection.
- If the everolimus trough level is ≤ 3ng/mL and cannot be maintained.
- If tacrolimus is held for more than 14 days.
- Any other protocol deviation that results in a significant risk to the patient's safety

If study drug (ERL or MMF/MPA) is interrupted for longer than 21 consecutive days or more than 2 episodes of 7 days or longer, discontinuation of study drug should be considered and discussed with the sponsor.

For patients prematurely discontinuing ERL, a post-study follow-up contact will be made at Month 3, 6, 12, 18 and 24 after transplantation, except in patients who prematurely discontinue ERL due to death, lost to follow up or patient withdrew consent. Information will be collected on serum creatinine levels, urea, rejection episodes, graft loss/ re-transplant, malignancies, opportunistic infections, patient survival and current immunosuppressive therapy.

Patients who prematurely discontinued ERL will be followed for any serious adverse event (SAE) occurring within 30 days following the last dose of ERL. These SAEs should be reported to appropriate regulatory authorities.

In addition to these requirements for study drug discontinuation, the investigator should discontinue study drug for a given patient if, on balance, he thinks that continuation would be detrimental to the patient's well-being.

A Study Drug Discontinuation form should be completed, giving the date and primary reason for stopping the study drug.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason. If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF.

Patients who discontinue study drug prior to the 24 month treatment period will be contacted at scheduled months 6, 12, 18 and 24 visits to obtain follow-up information and should not be considered withdrawn from the study. Information will be collected on vital signs, hospitalizations, rejection episodes, lab results (proteinuria and serum creatinine),

graft loss/re-transplant, SAEs, malignancies, opportunistic infections, patient survival, CMV infections and immunosuppressive therapy. In addition, major adverse cardiac events (MACE) will be reported during the follow-up period as a Serious Adverse Event (SAE). These include acute myocardial infarction, congestive heart failure, percutaneous coronary intervention (PCI), automatic implanted cardiac defibrillator (AICD), coronary artery bypass graft surgery (CABG), cerebral vascular accident, and peripheral vascular disease.

Biopsies will be obtained at 3, 12 and 24 months post-transplantation for all patients who agree to have this procedure done. Biopsies will be obtained at 3 months and 1-year post-transplantation biopsies are performed as a part of standard institutional protocol.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the information on survival status, graft loss/re-transplant, rejection episodes, malignancies, opportunistic infections and immunosuppressive therapies. Since patients will be followed even after discontinuation of study medication, the Study Completion CRF page should only be completed at Month 24 or earlier if the patient can no longer be followed, e.g, death, lost to follow-up, withdrawal of consent.

No study drug will be provided for patients who discontinue study medication prior to study completion at 24 months.

See Section 7 for the required assessments of these patients after study drug discontinuation.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator /the study team will show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

6.5.9 Study completion and post-study treatment

As study completion CRF page should be completed at Month 24. The investigator/the study team also will provide follow-up medical care for all patients who are prematurely withdrawn from the study, or will refer them for appropriate ongoing care. No drug will be provided after study completion at Month 24.

6.5.10 Early study termination

The study can be terminated at any time for any reason by the investigator. Should this be necessary, the patient should be contacted and seen as soon as possible and treated as described in Section 7 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to assure that adequate consideration is given to the protection of the patient’s interests. The investigator will be responsible for informing IRB of the early termination of the trial.

7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an “x” the visits when they are performed.

Patients should be encouraged to attend all visits on the designated day. However visit windows will be allowed of ± 1 day for Days 5 and 7, ± 3 days for Days 14, 21, and 28 visits, ± 1 week for Months 2 – 12 visits, and ± 2 weeks for Months 15 – 24 visits.

Patients who discontinue study drug before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

Patients who discontinue study drug should also return for the assessments indicated in Table 7-1, including a blood sample for serum creatinine. If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone when they refuse to return, and at 6, 12, and 24 months to determine the information on survival status, graft loss/re-transplant, rejection episodes, malignancies, opportunistic infections and immunosuppressive therapies. Since patients will be followed even after discontinuation of study medication, the Study Completion CRF page should only be completed at Month 24 or earlier if the patient can no longer be followed, e.g. death, lost to follow-up, or withdrawal of consent.

All patients will be contacted 30 days after the last dose of study medication regarding Serious Adverse Event information. Graft loss, death and malignancy are considered to be SAEs and should be entered on a SAE form and reported to the relevant regulatory authorities during the follow-up period (beyond 30 days after the last dose). Other Serious Adverse Events that are related to study medication as assessed by the investigator should also be entered on a SAE form and reported to the relevant regulatory authorities during the follow-up period.

Patients who prematurely discontinue study medication due to death, lost to follow up or patient withdrew consent will not have any post-study follow up evaluations.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last dose of study drug or last completed visit (whichever is later), including final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the patient record.

Table 7-1 Evaluation schedule

	SCR	OR	Day							Month										
	-21- 0	0	1	3	5	7	14	21	28	2	3	4	6	8	10	12	15	18	21	24
Informed consent	X																			
Randomization	X																			
Background information	X																			
Inclusion/exclusion	X	X																		
Medical History	X	X																		
Transplant information		X																		
Viral serology	X										X		X			X		X		X
Pregnancy test	X												X			X				X
EKG		X																		
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam		X														X				
Laboratory tests		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Renal Biopsy	X[1]										X[2]					X[2]				X
Study medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Campath dosage		X																		
Everolimus trough level					x	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tacrolimus trough			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36						X			X				X			X				X
Steroid	Per hospital protocol																			
Adverse events	As needed																			
Allograft rejection	As needed																			
Graft loss record	As needed																			
Dialysis log	As needed																			
Infection log	As needed																			
End of treatment	As needed																			
Comments	As needed																			
Follow-up record	Completed at 3, 6, 12, 18 and 24 months after the first dose of study medication for patients who prematurely discontinued study medication prior to Month 24.																			
Renal Biopsies	The study renal biopsy to be performed at 24 months. If clinically indicated biopsies were done prior to the scheduled biopsies at month 3, 12 and 24, repeat biopsy may not be performed.																			

OR: Day of transplant

Windows: Day 5, 7: ±1 day, Day 14, 21, 28: ±3 days, Month 2-12: ± 1 week, Month 15-24: ± 2 weeks

Biopsy windows: ± 4 weeks

1. Pre-transplant biopsy
2. 3-month and 1-year post-transplantation biopsies are performed as part of standard institutional protocol.

7.1 Information to be collected on screening failures

Patients discontinuing prior to randomization are considered screening failures. If a patient discontinues before entering the treatment period, only the Demographic information and

Screening Log entry with the primary reason for discontinuation should be completed on the CRF.

7.2 Patient demographics/other baseline characteristics

After informed consent has been signed and the patient's eligibility to participate in the study has been determined, baseline patient information will be obtained, such as date of birth, age, sex, race, full relevant medical history/current medical conditions, information on renal transplantation background of recipient and donor and on transplantation procedure.

Baseline assessments will occur in the time period starting 30 days pre-transplantation and ending at the time of transplant. Results of a physical examination at a baseline, include pregnancy test (within 48 hours prior to transplantation), vital signs, blood chemistry and hematology, urinalysis, including a quantitative protein/creatinine ratio.

7.3 Treatment exposure and compliance

All doses of study medication administered during the course of the study will be recorded on the appropriate Study Drug Dosage Administration CRF. Everolimus trough levels will be determined by the designated hospital laboratory.

Tacrolimus dosing will be entered on a separate TAC Dosage Administration CRF. Tacrolimus trough levels will be locally determined and recorded on the relevant CRF. Dose adjustments will be made based on local assay results.

Immunosuppressive therapies will be recorded on a separate Immunosuppressive Therapies CRF. Steroids will be recorded until steroid withdrawal occurs in accordance with MGTI's standard practice.

For all immunosuppressants, the start date, total dose, stop date and reason for administration or change are to be provided. If study drug is interrupted due to inability to tolerate oral medication and rescue therapy via an NG tube is administered the non-study drug immunosuppressive (i.e. crushed ERL suspension) should be recorded on the Immunosuppressive medications CRF. For anti-hypertensive medications,

Other drugs administered prior to and continuing at start of study medication will be entered on the 'Concomitant medications' CRF.

Immunosuppressive drugs administered prior to and continuing at start of study medication will be entered on the 'Immunosuppressive Medications' CRF.

Compliance will be assessed by the investigator and/or study personnel using pill counts (will be obtained from Investigational Drug Service pharmacy) and information provided by the patient. This information should be captured in the source document.

7.4 Efficacy

7.4.1 Acute Rejection

All suspected acute rejection episodes must be entered on the Kidney Allograft Rejection CRF. Suspected rejection episodes ultimately determined to be other conditions should also be entered on the Adverse Event CRF.

7.4.2 Treated Biopsy Proven Acute Rejection

Renal biopsies will be collected for all cases of suspected acute rejection. For all suspected rejection episodes, regardless of initiation of anti-rejection treatment, a graft core biopsy must be performed within 48 hours. Biopsies will be read by hospital pathologists in accordance with institutional practice. The results of the biopsy will be listed on the Kidney Allograft Biopsy CRF. The results will be used for patient management for acute rejection and for the efficacy analysis. A treated BPAR will be defined as a biopsy graded IA, IB, IIA, IIB, or III and which is treated with anti-rejection therapy.

Reference to acute rejection reporting:

Report any acute rejection episode on the Kidney Allograft Rejection CRF. No SAE form will be completed. However, if the episode is unusual in appearance or clinical course, and/or graft threatening, an Adverse Events CRF must be completed. In this particular case, a SAE form will be completed when appropriate and submitted according to procedure outline in Section 8.2.

7.4.3 Kidney Biopsy

Baseline biopsies will be obtained on all patients. 3, 12, and 24 month biopsies will be obtained for all patients. The Month 3 and Month 12 biopsies will be performed as a part of the standard of care. In addition, biopsies should also be collected for any patients with suspected viral infection, renal dysfunction, or in all cases of suspected acute rejection. Any biopsy result should be recorded on the Kidney Allograft Biopsy CRF.

7.4.4 Graft Loss

The allograft will be presumed to be lost on the day the patient starts dialysis and is not able to subsequently be removed from dialysis. If the patient undergoes a graft nephrectomy, then the day of nephrectomy is the day of graft loss. This will be reported on the premature discontinuation of study medication CRF, if medication is discontinued prematurely. The reason for graft loss will be recorded on the Graft Loss CRF. If graft loss occurs after the patient has discontinued study medication, the appropriate Follow-Up CRF should be completed. Graft loss is considered a Serious Adverse Event and should be reported on the Serious Adverse Event CRF and the SAE form must be reported to the relevant regulatory authorities within 24 hours.

7.4.5 Death

In the event of patient death, an SAE form should be completed and reported to the relevant regulatory authorities within 24 hours. The events leading to the death should be entered on the Adverse Event CRF and the death should be indicated on the premature discontinuation of study medication CRF (if death occurs while on treatment) and the Study Completion CRF.

7.4.6 Renal function

Renal function will be assessed by measuring serum creatinine, by calculated GFR using the MDRD formula, and proteinuria as determined by a spot urine protein/creatinine ratio.

7.4.7 Premature study treatment discontinuation

This will be captured on the Premature Discontinuation of Treatment CRF. Dates and reasons must be provided.

7.4.8 Premature study discontinuation

This will be captured on the Study Completion CRF. Reason must be provided.

7.4.9 Appropriateness of efficacy measurements

The efficacy variables selected are standard for this indication/patient population.

7.5 Safety

7.5.1 Physical examination

A through physical examination will be performed during the baseline period and at the Month 12 and 24 visits.

Information for all physical examinations must be included in the source documentation. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's CRF. Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's CRF.

7.5.2 Vital signs / Weight

Vital signs (radial pulse rate, blood pressure and weight (to the nearest 0.1 kilogram [kg] in indoor clothing) will be recorded at baseline, prior to the first morning administration of study medication, and at each subsequent visit. Systolic and diastolic blood pressure will be measured in accordance with MGTI's standard practice. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

7.5.3 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study (See Section 8.1)

7.5.4 Infections

Infections should be recorded with the start and end date, type of infection, and medications used on infection log CRF. If medications are used to treat the infection, the name of the medication must be entered on the Concomitant Medications CRF. If the patient is hospitalized, an SAE form must be reported.

7.5.5 Major Adverse Cardiac Events

Major Adverse Cardiac Events will be considered an SAE and will be entered in the adverse events CRF. These include acute myocardial infarction, congestive heart failure, percutaneous coronary intervention (PCI), automatic implanted cardiac defibrillator (AICD), coronary artery bypass graft surgery (CABG), cerebral vascular accident, and peripheral vascular disease

7.5.6 Laboratory evaluations

All laboratory tests will be done at the hospital affiliated laboratory. Laboratory samples should be drawn prior to administration of the morning dose of both TAC and study medication. All samples will be drawn with the patient in the fasting state (more than eight hours after the last meal) if possible. Non-fasting blood samples will be clearly identified.

Therapeutic drug monitoring (TDM) will be mandatory throughout the study. The transplant team will be alerted when ERL trough levels are < 3 ng/mL or > 8 ng/mL to adjust the dose of ERL. All ERL dose adjustments will be made based on these results.

Blood samples for TAC trough levels from the hospital affiliated laboratory will be used to obtain tacrolimus through levels. Adjustments should be made for TAC using the trough levels from the laboratory.

Extreme values will be reported to the investigator and/or the study team for immediate action as per standard of care. The Investigator is asked to comment on these abnormalities if they are clinically significant in the CRF.

7.5.7 Hematology

Hematology will include platelets, hemoglobin, red blood cell count, white blood cell count, and absolute neutrophil count with differential to be measured at Baseline, on Day 1, 3, and 5; Weeks 1, 2, and 4; Months 2, 3, 4, 6, 8, 10, 12, 15, 18, 21, and 24.

7.5.8 Clinical chemistry

Sodium, potassium, chloride, calcium, magnesium, inorganic phosphate, blood urea nitrogen, creatinine, glucose, uric acid, AST, ALT, alkaline phosphatase, total bilirubin, total cholesterol, HDL, LDL, triglycerides, CPK, lipase, and amylase will be assessed at hospital affiliated laboratory. The blood chemistry will be measured at Baseline, on Day 1, 3, and 5; Weeks 1, 2, and 4; Months 2, 3, 4, 6, 8, 10, 12, 15, 18, 21, and 24. LDL and HDL will be measured only at Baseline, Week 4, Months 6 and 12.

Random or fasting plasma glucose values as needed to rule out or confirm suspected new onset of diabetes.

If the CPK level is above the upper limit of normal, CK-MB fraction will be measured.

If the total bilirubin concentration is greater than 1.5 times the upper limit of normal, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

7.5.9 Urine measurements

Measurements will be taken for glucose, protein and quantitative protein/creatinine ratio by a mid-stream urine sample at Baseline, Day 1, 3, and 5; Weeks 1, 2, and 4; Months 2, 3, 4, 6, 8, 10, 12, 15, 18, 21, and 24.

7.5.10 Pregnancy and assessments of fertility

Any pregnancy that occurs during study participation should be reported to the relevant regulatory authorities and the drug manufacturer. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Any female patient that becomes pregnant after the start of study medication should be discontinued and the patient switched to standard treatment. All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at screening, and a urine pregnancy test if suspect, and at the end of study visit. Pre-menopausal women will also undergo pregnancy tests at 6 months, 12 months and the 24 months. A positive urine pregnancy test requires immediate interruption of study medication until a pregnancy is confirmed. If confirmed, the patient must be discontinued from the trial.

7.5.11 Viral serology

Viral serology will be assessed at screening and Months 3, 6, 12, 18, 24. All patients will be tested for hepatitis B surface antigen (HBsAg), Hepatitis C, CMV, BKV and HIV at baseline per standard of care. Earlier tests $\leq$ 12 months, are acceptable. Any patients with a positive HBsAg, positive hepatitis C serology, or HIV will be excluded. If results are not available prior to randomization, the patient may be included. If results are later found to be positive, the patient will subsequently be dropped from the study and administered the standard care at MGTI.

Premature discontinuation from study medication

For those patients who prematurely discontinue study medication prior to Month 24, the Premature Discontinuation of Treatment CRF should be completed. The date of last dose and reason for discontinuation of study medication should be clearly documented and all subsequent post-study follow-up evaluation forms should be completed at the appropriate time points. Patients who prematurely discontinue study medication due to death, lost to follow up or patient withdrew consent will not have any post-study follow up evaluations.

Premature study discontinuation and follow-up

For all patients prematurely discontinuing study medication, a post-study follow-up contact will be made at 6, 12, and 24 months after transplantation, except in patients who prematurely discontinue study medication due to death, lost to follow up or patient withdrew consent. Information on allograft and patient survival, malignancies, rejection episodes, and current immunosuppressive regimen will be collected. A blood sample will also be collected for serum creatinine. All patients will be contacted 30 days after the last dose of study medication regarding Serious Adverse Event information. Graft loss, death and malignancy are Serious Adverse Events and should be entered on a SAE form and

reported to the relevant authorities during the follow-up period (beyond 30 days after the last dose). Other Serious Adverse Events that are related to study medication as assessed by the investigator should also be entered on a SAE form and reported to the IRB and other relevant authorities during the follow-up period.

Clinically notable laboratory abnormalities present at the time of discontinuation will be followed until the abnormality is no longer considered clinically significant.

This will be captured on the Study Completion CRF. Reason must be provided.

7.5.12 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

7.6 Other assessments

7.6.1 Resource utilization

For resource utilization, all relevant information about initial hospitalization for initial transplantation and all follow-up hospitalizations post transplantation (in the transplant study center or all other centers, if any) will be recorded. The hospitalization data will include the main reason for admission, duration of hospitalization and number of days by level of care. All attempts should be made to collect RU variables in all patients throughout the duration of the study in order to avoid selection bias. There may also be circumstances when the collection of such data after completion of the study may be warranted. These data will be collected in the Hospitalization CRF and will be presented in a separate report.

7.6.2 Health-related Quality of Life

The SF-36 is a widely used instrument to measure generic health status. It is a 36-item questionnaire that yields an 8-scale health profile as well as summary measures of individual patients. It has proven useful in monitoring generic and specific populations, comparing the relative burden of different diseases, differentiating the health benefits produced by different treatments, and in screening individual patients. The purpose collecting SF-36 data in this study is to compare the final health status of those on the ERL and low dose TAC arm of the trial to those on the ERL and low dose TAC which converts to MMF/MPA arm and to those on the MMF/MPA and standard dose TAC arm of the trial.

The eight profiles (scales) are: bodily pain, general health, vitality, mental health, physical functioning, role-physical, role-emotional and social functioning. The two summary measures are physical health and mental health.

Patients must complete the questionnaire before other clinical assessments at any given visit. The SF-36 can be administered in 5 to 10 minutes with a high degree of acceptability and quality. An appropriate person should be designated to facilitate self-administration. The administrator should not influence but can answer questions and address concerns and ensure that the questionnaire is filled out correctly and completely.

Completed questionnaires will be reviewed and examined by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. The

investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient.

If the occurrence of AEs or SAEs is confirmed, the physician must record the events as per instructions given in Section 7.5.1 of the protocol. Investigators should not encourage the patients to change the responses reported.

8 Safety monitoring

8.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

Protocol exempted events: Unusually severe rejection episodes

Acute rejections are considered protocol exempted events. They should not be reported simply because they result in hospitalization thus meeting the criteria for SAEs. Acute rejection episodes will therefore not be routinely expedited to health authorities. However, acute rejections should be reported as SAEs if they are unusual in appearance, clinical course and/or are graft threatening.

Graft loss, death and malignancy are serious adverse events and should be entered on a SAE form for 30 days after last dose of study medication, including patients that prematurely discontinue from the study.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the adverse event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the package inserts. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient begins taking study drug and until 30 days after the patient has stopped study participation must be reported to relevant regulatory authorities and IRB within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

The investigator must assess the relationship to study drug, complete and submit the SAE report forms. The original copy of the SAE reports and submission confirmation must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

8.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to relevant regulatory authorities and drug manufacturers within 7 days of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.4 Data Monitoring Committee

A data monitoring committee (DMC) will be instituted to review safety and efficacy. The DMC will be comprised of at least 2 physicians, a pharmacist and a statistician not affiliated with the study. They will be selected based on their scientific and clinical background and have expertise in kidney transplantation.

The DMC will meet to review the available safety data after 12, 24, 36 and 48 patients enrollment to the study. Following the completion of the enrollment, the DMC will meet bi-annually and/or at the request of PI. The DMC will review the clinical and laboratory safety data and make recommendations regarding the further conduct of the study with respect to safety. If a safety concern is identified, the DMC will determine whether or not dosing should be continued or modified depending on the event and occurrence of other adverse events.

Decisions based on the recommendations of the Board will take into account the potential risks and benefits associated with continuing enrollment of patients in the study. The final decision with respect to the modification of the protocol will be made by the PI after having discussion with a selected group of experts. In the event of study termination, all health authorities, IRB and DMC would be notified of the termination within one business day.

9 Data review and database management

9.1 Data collection

The study staff will enter the study-related patient data required by the protocol into the study-specific electronic Case Report Forms (CRFs) that conforms to 21 CFR 312.62 requirements. Once the content of the electronic CRFs are reviewed for accuracy against the patient record, the data will be entered into a Georgetown University hosted HIPAA compliant electronic Web-based database (REDCap).

9.2 Database management and quality control

A designated study staff member will act as a data manager, will check for data discrepancies and, by generating appropriate queries, allow the data to be confirmed or corrected. The Investigator must certify that the data entered into the CRFs are complete and accurate.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed at the hospital affiliated laboratory and the results will be available via the hospital and clinic information systems electronically.

At the conclusion of the study, unused study drugs will be returned to Novartis and the occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis (Section 10). Any changes to the database after that time can only be made by joint written agreement between the investigator and a contracted statistician.

10 Data analysis

A contracted statistician at the Georgetown-Howard Center for Clinical and Translational Research will perform the statistical analysis.

10.1 Populations for analysis

Full Analysis Set (FAS; intent-to-treat) consists of all randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

Safety Set (SS) consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Patients will be analyzed according to treatment received. Of note, the statement that a patient had no adverse events also constitutes a safety assessment.

Per Protocol Set (PPS) consists of all FAS patients without a major protocol violation and/or deviation, and who have completed the study. Analysis will be conducted in this set as well.

Efficacy analysis will be performed on the FAS, as defined above, with patient data analyzed according to the treatment groups to which they were randomized. It will also be done on the SS and PPS with patient assignment as treatment actually received.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline characteristics will be recapitulated by treatment group. Unless otherwise specified, continuous variables will be summarized with the number of non-missing observations, mean, median, standard deviation, minimum and maximum. Discrete and categorical variables will be summarized by frequencies and percentages.

10.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

The average daily dose of ERL, MMF/MPA, and TAC will be recapitulated within the defined period by treatment group.

On calculating dosage averages over a time period, zero doses will be used for periods of study medication interruption regardless of the reason (i.e. suspected drug toxicity, adverse events, non-compliance, etc).

The reasons for ERL, MMF/MPA, or TAC dose adjustment will be assessed at certain periods and summarized by treatment group.

The duration of exposure for ERL, MMF/MPA and TAC, measured in days since the first administration of the study medication, will be summarized. Note that duration of exposure includes periods of temporary interruption of respective medication.

Summary statistics will be presented for total daily dose of corticosteroids, expressed in doses equivalent to prednisone. These calculations will include any steroids used for the treatment of rejection episodes.

Other immunosuppressive therapies will be summarized by WHO drug names by treatment group. The tables will show the number of patients receiving these drugs at any time, and percentages.

All non-immunosuppressive medications or non-drug therapies will be grouped into prior and concomitant medications and summarized separately by treatment group.

All of the analysis will be performed on the SS.

10.4 Analysis of the primary objective(s)

Patients' data will be summarized with respect to demography and baseline characteristics, including information on donor and recipient and on transplant procedures, for SS as 1 group, for FAS and PPS by the randomized treatment groups.

Efficacy will be analyzed on the pooled SS, and on FAS and PPS comparing the 3 treatment groups. Efficacy variables include BPAR, graft loss, death and combinations thereof.

Safety and tolerability will be assessed in terms of treatment-emergent adverse events, laboratory tests and vital signs measurements. Safety analyses will be conducted on the SS, and on FAS comparing the 3 treatment groups.

10.4.1 Variable

The primary efficacy variable is the composite efficacy failure rate (treated BPAR, graft loss, death or loss to follow-up) at 6, 12 and 24 months post-transplant. The secondary variable is renal function assessed as eGFR during the first 24 months post-transplantation, determined by the MDRD formula. Other secondary variables include the incidences of CMV and BKV, new onset diabetes mellitus, chronic kidney disease with associated proteinuria, adverse events, serious adverse events and tacrolimus associated adverse events.

10.4.2 Statistical model, and method of analysis

The primary analysis will be the comparison of ERL with TAC based on FAS using an analysis of variance (ANOVA) model. Stratification factors applied at randomization will be included as binary factors in the ANOVA model in addition to treatment group.

10.4.3 Handling of missing values/censoring/discontinuations

All efforts will be made to complete data except for cases of loss to follow-up, graft loss or death. Loss to follow-up, graft loss or death is defined as one whose last day of contact is prior to Month 24 and who did not experience graft loss or death. The missing data will be assumed to be missing at random except for above cases. The sensitivity analysis based on a complete case analysis and a missing data analysis will be conducted if imputed data exceeds 5 % of total data.

The modified last observation carried forward (LOCF) will be applied if eGFR has not been obtained at study visits. Only in cases where the observed measurement was obtained within 6 weeks of the expected study visit, modified LOCF will be employed to impute missing data. In other words, missing data will be replaced with data from out-of-window visit occur within 6 weeks of scheduled visit. None of data will be carried forward beyond 6 weeks, and will not be imputed by other methods. For the FAS analysis, this will be done regardless of whether a patient discontinued study medication or not. For patients experiencing graft loss, the last value before dialysis or re-transplantation will be used.

10.4.4 Supportive analyses

Event rates will be compared between treatment groups using the Cochran-Mantel-Haenszel test, stratified by induction therapy.

A logistic regression analysis of the primary efficacy variable will be performed. The odds ratio for treatments, 95% confidence interval for the odds ratio, and p-values (if applicable) will be reported based on the fitted model.

A Kaplan-Meier survival analysis will be performed where all treated BPARs, graft losses, deaths of losses to follow-up that occur up to month 24 will be considered efficacy failures. The incidence of the composite efficacy failure (treated BPAR, graft loss, death of loss to follow-up) within 24 months will be compared between the two treatment groups using Kaplan-Meier probability estimates of efficacy failure and the associated 95% CI obtained

using the standard error derived by applying Greenwood's formula. The differences between the curves will be tested using the log-rank test.

10.5 Analysis of secondary objectives

10.5.1 Efficacy (secondary)

Secondary efficacy variables include:
• The incidence of treated BPAR at 24 months
• The incidence of graft loss at 24 months
• The incidence of death or loss to follow-up at 24 months

The incidence of treated BPAR, graft loss, and death or loss to follow-up will be analyzed using a Cochran-Mantel-Haenszel test stratified by induction therapy.
A Kaplan-Meier survival analysis will be performed for each time to treated BPAR, time to graft loss and time to death or loss to follow-up. The incidences will be compared among the three treatment groups using Kaplan-Meier probability estimates of efficacy failure and the associated 95 % CI obtained using the standard error derived by applying Greenwood's formula. The differences between the curves will be tested using the log-rank test.

FAS will be used for analyses of the secondary efficacy variables.

10.5.2 Safety

Safety variables to be assessed include discontinuation from study, discontinuation from treatment, renal function, AE/infection, SAE, notable events, laboratory tests, and vital signs.

Comparison of calculated GFR using an analysis of covariance (ANCOVA) with baseline (Month 1) GFR as a covariate, and treatment and induction therapy as main effects, will be performed. Month 24 GFRs will be divided into three categories (<30, 30-60, >60) to classify chronic kidney disease. The proportion of patients in certain categories will be compared between treatment groups using the Cochran-Mantel-Haenszel test controlling for the Month 1 category.

Other safety variables include incidences of AEs, SAEs, new onset diabetes mellitus, CMV, BKV and proteinuria. These incidences will be compared between treatment groups using a Cochran-Mantel-Haenszel test, stratified by induction therapy. Urine protein/creatinine ratios will be compared between treatment groups using the Wilcoxon Rank-Sum test.

Additional assessments of safety will be based on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined notable ranges. Other safety data (e.g. vital signs and special tests) will be considered as appropriate. The data collected will be presented in listings, summary tables and graphs. All analyses will be performed on the SS.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. The same type of summaries will be provided for serious adverse events and for events suspected to be related to the study medication. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Laboratory data will be summarized by presenting shift tables using notable ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by the flagging of notable values in data listings.

Data from other tests (e.g. vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration. The data collected will be presented in listings, summary tables and graphs. All analyses will be performed on the SS.

10.5.3 Health-related Quality of Life (HQOL)

The SF-36 will be employed to assess HQOL in study subjects at Day 7, 28, Month 6, 12 and 24 post-operation. The mean scores of SF-36 will be summarized by visits according to treatment group. The change from baseline in the summary scores will be compared using an ANOVA with treatment as a factor. If the assumptions of the model are not met, the analysis will be done using Kruskal-Wallis tests.

10.6 Sample size calculation

Since this is a pilot study, the sample size estimation method proposed by Julious was considered in order to minimize the sample size (14). Julious proposes to employ sample size of 12 per group for a pilot study (14). Assuming the drop out rate of 20% along with the ease of blocked randomization, we propose the sample size of 16 per arm, totaling 48 patients. The estimated effect size, α, and β corresponding to this sample size are 0.9, 0.05 (two-sided), and 0.2 respectively (15). A block size of 12 along with an allocation ratio of 1:1:1 will be employed as a randomization scheme.

10.7 Power for analysis of critical secondary variables

Correlation between laboratories will be checked periodically throughout the study period. eGFR will be calculated using MDRD formula for each visit following the kidney transplantation. All data will be analyzed using the intent-to-treat approach as well as on-treatment based approach. Comparisons between treatment groups experiencing composite efficacy failure and each component will be analyzed with Fisher's exact test. The Chi-square and/or one-way analysis of variance (ANOVA) will be used for acute rejection episodes and creatinine levels respectively.

10.8 Interim analysis

No interim analysis is planned.

11 Ethical considerations

11.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with US Code of Federal Regulations Title 21, and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board (IRB)-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

The investigator and the study team will prepare the informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must avoid pregnancy for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.3 Responsibilities of the investigator and IRB

The protocol and the proposed informed consent form must be reviewed and approved by IRB before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to designated agents of Novartis, IRBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

11.4 Publication of study protocol and results

The study team assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB it cannot be implemented. All major protocol deviations will be recorded and reported to the IRB.

12.1 Protocol Amendment

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the IRB. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis and IRB should be notified of this action within 10 working days.

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Appendix 1: Clinically notable laboratory values and vital signs

Table 13-1 Criteria for notable abnormalities

Chemistry parameters	Standard units	SI units
Liver function and related variables		
AST (SGOT)	≥3 × ULN	≥3 × ULN
ALT (SGPT)	≥3 × ULN	≥3 × ULN
Bilirubin	≥3 × ULN	≥3 × ULN
Alkaline phosphatase	≥3 × ULN	≥3 × ULN
Renal function, metabolic and electrolyte variables		
Urea	None	None
Creatinine	30% above baseline	30% above baseline
Uric acid	M ≥12 mg/dL	M ≥714 µmol/L
	F ≥9 mg/dL	F ≥535 µmol/L
Glucose	<45 mg/dL or >250 mg/dL	<2.5 mmol/L or >13.9 mmol/L
Cholesterol	≥350 mg/dL	≥9.1 mmol/L
Triglycerides	≥750 mg/dL	≥8.5 mmol/L
CPK (MB)	None	None
Potassium	≤3.0 mEq/L	≤3 mmol/L
	≥6.0 mEq/L	≥6 mmol/L
Magnesium	<0.97 mg/dL or >3.65 mg/dL	<0.4 mmol/L or >1.5 mmol/L
Calcium	≤6 mg/dL or ≥13 mg/dL	≤1.5 mmol/L or ≥3.2 mmol/L
Phosphate	None	None
Amylase	≥2 × ULN	≥2 × ULN
Lipase	≥2 × ULN	≥2 × ULN

Hematology parameters	Standard units	SI units
Hemoglobin	<7 g/dL	<4.39 mmol/L
Platelets (thrombocytes)	<50 k/mm^3	<50 × 10^9/L
	≥700 k/mm^3	≥700 ×10^9/L
Leukocytes (WBCs)	≤2.0 k/mm^3 or ≥16 k/mm^3	≤2.0 × 10^9/L or ≥16 × 10^9/L
Granulocytes (neutrophils)	≤1,000/mm^3	≤1 × 10^9/L
Eosinophils	≥12%	≥12%
Lymphocytes	≤1,000/mm^3	≤1 × 10^9/L
Urinalysis		
Protein/creatinine	<200 mg/g	<22.7 mg/mmol

Vital sign variables	Notable criteria
Pulse (beats/min.)	None
Systolic BP (mm/Hg)	Either an increase of ≥30 that results in ≥180 or >200(mm/Hg) or Either a decrease of ≥30 that results in ≤90 or <75 (mm/Hg)

Diastolic BP (mm/Hg)	Either an increase of ≥20 that results in ≥105 or >115 (mm/Hg) or Either a decrease of ≥20 that results in ≤50 or <40 (mm/Hg)

Appendix 2: Banff '97 Classification of renal allograft rejection

Banff '97 diagnostic categories for renal allograft biopsies[1]

1. Normal
2. Antibody-mediated rejection - Rejection demonstrated to be due, at least in part, to documented anti-donor antibody ("suspicious for" if antibody not demonstrated)
   - Type I – ATN – like – C4d+, minimal inflammation
   - Type II – Capillary–margination and/or thromboses, Ig and/or C4d+
   - Type III – Arterial – v3, C4d+
3. Borderline changes ("suspicious" for acute cellular rejection). This category is used when no intimal arteritis is present, but there are foci of mild tubulitis (1 to 4 mononuclear cells/tubular cross section) and at least i1.
4. Acute/active rejection
   - TYPE IA - Cases with significant interstitial infiltration (> 25% of parenchyma affected) and foci of moderate tubulitis (> 4 mononuclear cells/tubular cross section or group of 10 tubular cells).
   - TYPE IB - Cases with significant interstitial infiltration (> 25% of parenchyma affected) and foci of severe tabulitis (> 10 mononuclear cells/tubular cross section or group of 10 tubular cells).
   - TYPE IIA - Cases with mild to moderate intimal arteritis (v1).
   - TYPE IIB - Cases with severe intimal arteritis comprising > 25% of the luminal area (v2).
   - TYPE III - Cases with "transmural" arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells (v3 with accompanying lymphocytic inflammation).
5. Chronic/sclerosing allograft nephropathy**
   - GRADE I (Mild) Mild interstitial fibrosis and tubular atrophy without (a) or with (b) specific changes suggesting chronic rejection.
   - GRADE II (Moderate) Moderate interstitial fibrosis and tubular atrophy (a) or (b).
   - GRADE III (Severe) Severe interstitial fibrosis and tubular atrophy and tubular loss (a) or (b).
6. Other, specify (changes not considered to be due to rejection, i.e., post-transplant lymphoproliferative disorder, nonspecific changes, acute tubular necrosis, etc.)

*The recommended format of report is a descriptive narrative signet followed by numerical codes (Banff 97) in parentheses. Categorization should in the first instance be based solely on pathologic changes, and then integrated with clinical data as a second step. More than one diagnostic category may be used if appropriate.

**Glomerular and vascular lesions help define type of chronic nephropathy; chronic/recurrent rejection can be diagnosed if typical vascular lesions are seen.

[1] Racusen LC, Colvin RB, Solez K, et al (2003) Antibody-mediated rejection criteria - an addition to the Banff '97 classification of renal allograft rejection. American Journal of Transplantation; 3(6):708-714

Appendix 3: Guidelines for Everolimus and MMF/MPA dose reduction

An investigator may interrupt temporarily or reduce, the dosage of study medication (Everolimus or MMF/MPA), if in his/her opinion this is clinically warranted, in response to any causally associated AE (e.g., neutropenia, thrombocytopenia, leukocytopenia, hyperlipidemia, hypertriglyceridemia or gastrointestinal intolerance). The following guidelines should be followed:

1- PLATELETS

Platelet count < 75,000/mm^3

Step 1: dose reduction should be considered and may be instituted at the discretion of the Investigator.

Step 2: if the platelet count remains below 75,000/mm^3 despite the initial dose reduction, a further dose reduction may be implemented per the table below:

Platelet count < 50,000/mm^3 Dose interruption should be considered.

Platelet count < 30,000/mm^3 Dose interruption will be mandatory.

If the platelet count returns to 30,000/mm^3 for 3 days, study medications may be restarted at lowest reduced dose. If the platelet count is stable at the reduced dose for 3 days, study medications may be increased to the next higher dose. If the platelet count remains stable at greater than 75,000/mm^3 for 7 days, the full dose of study medications may be restarted.

2- WHITE BLOOD CELLS

WBC < 3,000/mm^3 or absolute neutrophil count < 1,300/mm^3

Step 1: dose reduction should be considered and the first dose reduction may be instituted at the discretion of the Investigator.

Step 2: if the white count remains less than 3,000/mm^3 despite the intial dose reduction, a further dose reduction may be implemented per the table below:

If the WBC is less than 2,000/mm^3, dose interruption will be mandatory.

Once WBC returns to 2,000/mm^3 for 3 consecutive days, study medication may be restarted at the lowest level. If the WBC is stable at the reduced dose for 3 days, study medication may be increased to the next higher dose level. Once WBC returns to levels > 3,000/mm^3 for 7 days, study medication may be increased to the full dose.

3- CHOLESTEROL

If cholesterol and/or triglycerides are found to be elevated, dosing should be reconsidered and optimized as appropriate, in addition to provided dietary advice. If the elevation is confirmed by a second measurement within 2 weeks under fasting conditions (last meal ≥ 8 hours prior to sampling) the following guidelines are recommended.

Cholesterol > 250 - 450 mg/dL or > 6.5 -11.6 mmol/L:

Dietary instruction is strongly recommended and statin therapy, e.g. fluvastatin, should be considered (see Appendix 4)

If the abnormality persists, the dosing of study medication will be adjusted as follows:

Cholesterol ≥ 450 mg/dL or 11.6 mmol/L: Dose reduction should be considered

Cholesterol > 750 mg/dL or > 19.4 mmol/L: Study medication should be interrupted

4- TRIGLYCERIDES

Triglycerides > 250 mg/dL or > 2.9 mmol/L:

Dietary instruction is strongly recommended and statin therapy should be considered

If the abnormality persists, the dosing of study medication will be adjusted as follows:

Triglycerides ≥ 600 mg/dL or ≥ 6.9 mmol/L: Dose reduction should be considered

Triglycerides > 1000 mg/dL or 11.4 mmol/L: Study medication should be interrupted

Table 13-2 **National cholesterol education program guidelines**

Total cholesterol	
Under 200 mg/dL	Desirable
200-239 mg/dL	Borderline-high
240 and over	High
HDL cholesterol	
Under 35 mg/dL	Low

Table 13-3 **Treatment based on LDL cholesterol**

Diet therapy	**Initiation level**	**LDL goal**
Without CHD and without 2 risk factors	160 mg/dL or over	Under 160 mg/dL
Without CHD and with 2 or more risk factors	Over 130 mg/dL	Under 130 mg/dL
With CHD	Over 100 mg/dL	100 mg/dL or under
Drug treatment	**Initiation level**	**LDL goal**
Without CHD and without 2 risk factors	190 mg/dL or over	Under 160 mg/dL
Without CHD and with 2 or more risk factors	160 mg/dL or over	Under 130 mg/dL
With CHD	130 mg/dL or over	100 mg/dL or under

(Data from Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults: Summary of the second report of the National Cholesterol in Adults [Adult Treatment Panel II] JAMA 269[23]:3015-3023, 1993)

Appendix 4: Possible Everolimus drug-drug interactions

During treatment with immunosuppressive agents, such as everolimus, steroids and tacrolimus, vaccination may be less effective. The use of live vaccines should be avoided.

Table 13-4 Everolimus Drug Interactions

Drugs not allowed	Sirolimus	Patients to be discontinued from everolimus if given
	Terfenadine Astemizole Cisapride	Inhibitors of P-450 (CYP), in particular CYP3A (as everolimus) have the potential to increase the exposure of these drugs resulting in prolongation of QT intervals on

		ECGs
	Ketoconazole* Clarithromycin Telithromycin Ritonavir	Strong inhibitors of P-450 (CYP) have the potential to increase the exposure of everolimus
	Rifampicin Rifabutin	Strong inducers of P-450 (CYP) have the potential to decrease the exposure of everolimus
Drugs strongly discouraged	Lovastatin** Simvastatin**	Confirmed interaction between everolimus and this drug
	Cerivastatin** Rosuvastatin**	Insufficient data available to make recommendations regarding concomitant use of the newer statins and everolimus
	Quinidine Fluoxetine Paroxetine	Potential interaction of everolimus with CYP 2D6 substrates
	Itraconazole* Voriconazole*	Strong inhibitors of P-450 (CYP) have the potential to increase the exposure of everolimus
Drugs necessitating close monitoring	Digoxin	Potential interaction with everolimus has not been evaluated, patients on digoxin should have periodic measurements of digoxin levels
	Fluconazole*	Strong inhibitors of P-450 (CYP) have the potential to increase the exposure of everolimus

* The concomitant administration of the antifungal agent ketoconazole, is prohibited in patients who are taking everolimus. If ketoconazole must be administered, everolimus must be discontinued. If –azole antifungal agents must be administered to patients, everolimus blood levels must be monitored closely. The investigator should anticipate the need to reduce or withhold the dose of everolimus. Fluconazole may pose the smallest risk for drug-drug interactions.

** Patients requiring treatment with this class of medication (especially lovastatin) should be monitored closely for signs of rhabdomyolysis, such as dark-colored urine, fever, muscle cramps, pain, spasm, or stiffness, unusual tiredness or weakness.

Appendix 5: Possible tacrolimus drug-drug interactions

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering tacrolimus with drugs that may be associated with renal

dysfunction. These include, but are not limited to: aminoglycosides, amphotericin B and cisplatin. Since tacrolimus is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism of tacrolimus with resultant increases in whole blood or plasma concentrations. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus and decreased whole blood or plasma concentrations. Monitoring of blood concentrations and appropriate dosage adjustments are essential when such drugs are used concomitantly.

Table 13-5 **Drugs that may affect Tacrolimus blood concentrations**

Calcium channel blockers	Antifungal agents	Gastrointestinal prokinetic agents
Diltiazem Nicardipine Nifedipine Verapamil	Clotrimazole Ketoconazole Fluconazole Itraconazole	Cisapride Metoclopramide
Macrolide antibiotics	**Other drugs**	
Clarithromycin Erythromycin Troleandomycin	Bromocriptine Cimetidine Cyclosporine Danazol Methylprednisolone Protease inhibitors	
Drugs that may decrease tacrolimus blood concentrations		
Anticonvulsants	Antibiotics	
Carbamazepine Phenobarbital Phenytoin	Rifabutin Rifampin	

Interaction studies with drugs used in HIV therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir) or that are metabolized by CYP3A (e.g., ritonavir) are administered concomitantly with tacrolimus. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided.

Immunosuppressants may affect vaccination. Therefore, during treatment with tacrolimus, vaccination may be less effective. The use of live vaccines should be avoided.

Appendix 6: Possible MMF/MPA drug-drug interactions

The use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective. Influenza vaccinations may be of value.

Table 13-6 Possible MMF/MPA Drug-Drug Interaction

Drugs not allowed	Cholestyramine	Patients to be discontinued from CellCept, if given
Drugs strongly discouraged or not to be administered simultaneously	Acyclovir or prodrug-Valacyclovir	Competition for tubular secretion may increase the concentration of CellCept
	Sevelamer CA^{2+}free phosphate binders	CA^{2+}free phosphate binders to be given 2 hours after CellCept to minimize impact on absorption
	Norfloxin together with Metronidazole	Not recommended to be given concomitantly with the combination of both drugs
	Antacids with magnesium and aluminum hydroxides	Do not take simultaneously, administer alone under fasting conditions
Drugs necessitating close monitoring	Ganciclovir or prodrug-Valganciclovir	Competition for tubular secretion may increase the concentration of CellCept