Conversion from MPA to Zortress (Everolimus) for GI toxicity post-renal transplant

NCT number: 02974686

Trial was terminated with only 1 participant enrolled. No data is reported here to maintain patient confidentiality.

EVEROLIMUS

Clinical Study Protocol CRAD001AUS209T

Conversion from MPA to Zortress (everolimus) for GI toxicity post-renal transplantation

Authors:	Delos Santos, R, Hagopian, J
Principle or Coordinating Investigator	Delos Santos, R

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
b.i.d.	twice a day
CRF	Case Report/Record Form
CRD	Clinical Research and Development
CPO	Country Pharma Organization
CRO	Contract Research Organization
CSR	Clinical Study Report
ECG	Electrocardiogram
EC-MPS	Enteric-coated mycophenolate sodium
EVR	Everolimus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMS	Integrated Medical Safety
i.v.	intravenous(ly)
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid (Refers to mycophenolate sodium EC or mycophenolate mofetil containing products)
o.d.	once a day
p.o.	oral(ly)
REB	Research Ethics Board
SAE	serious adverse event

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each medication package in studies that dispense medication using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment,, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Protocol synopsis

Title of study: Conversion from MPA to Zortress (everolimus) for GI toxicity post-renal transplantation

This study is a prospective, single-center study to evaluate the effectiveness of conversion from MMF or EC-MPS to EVR during the first year post-renal transplant in patients who experience gastrointestinal adverse effects. The primary outcome will be change in GSRS from baseline (time of conversion) to 30 days post-conversion.

In total, 25 patients will be enrolled and converted from MPA to EVR, at an initial dose of 1 mg PO BID with target everolimus troughs between 3 – 8 ng/mL. Patients who are less than one year from date of transplant with identified GI symptoms who are on immunosuppression with tacrolimus, MPA, and prednisone will be enrolled and followed for 1 year. These patients will be compared to an historical cohort of patients receiving azathioprine for safety outcomes (including rejection and graft/patient survival).

Purpose and rationale: Cellcept® (mycophenolate mofetil, MMF) and Myfortic® (enteric-coated mycophenolate sodium, EC-MPS) are the two formulations of mycophenolic acid (MPA) approved for use as adjunctive immunosuppression post-renal transplantation. Non-infectious gastrointestinal (GI) adverse effects are the main dose-limiting toxicity of MPA therapy, which has been reported in up to 45% of MPA-treated patients. MPA dose reductions, treatment interruptions, discontinuations or withdrawals are common due to GI toxicity from these agents. Studies have demonstrated that patients with GI complications who experienced an MMF dose adjustment or discontinuation had a significantly increased incidence of acute rejections compared with patients without GI complications (30.2% vs. 19.4%, p=0.005). At Barnes-Jewish Hospital/Washington University School of Medicine in St. Louis, it is standard practice to place patients on triple maintenance immunosuppression therapy with MMF or EC-MPS, tacrolimus, and prednisone immediately post-renal transplantation. Patients may be switched from MMF or EC-MPS to azathioprine due to GI symptoms. We feel that everolimus may offer a similar advantage to azathioprine for patients unable to tolerate MMF or EC-MPS in regard to similar incidence of acute rejection, low incidence of GI-related adverse effects, and other patient-oriented outcomes.

Objectives:

Primary objective: To determine if a switch from MMF or EC-MPS to Zortress (everolimus) due to GI intolerance results in improvement of GI symptoms.

Secondary objectives: To determine whether it is safe to switch from MMF or EC-MPS to Zortress (everolimus) due to GI intolerance from MMF/EC-MPS within 12 months post-renal transplantation.

Population:

The population will include adult recipients of living- or deceased-donor renal allografts within the previous 12 months at Washington University/Barnes-Jewish Hospital who are on tacrolimus and prednisone and are experiencing GI toxicity from MPA and have stable renal function with a GFR > 35 mL/min.

Inclusion/Exclusion criteria:

Key inclusion criteria

1. Kidney transplant recipients at Washington University/Barnes-Jewish Hospital
2. Experiencing GI toxicity from MPA as determined by the treating physician within 12 months post-renal transplant
3. On standard immunosuppression with tacrolimus and prednisone

Key exclusion criteria

1. Dual organ or kidney after another solid organ transplant
2. Presence of a preexisting significant GI condition that does not have a presumed causal relationship with MPA

3. Evidence of any GI disorder induced by an infection, underlying medical condition, or concomitant medication other than MPA
4. eGFR<35 ml/min at time of possible conversion
5. Proteinuria >1 gram/day at time of possible conversion
6. Profound bone marrow suppression at the time of possible conversion as defined as:
    - Hemoglobin <10 g/dL
    - WBC <3 K/cumm
    - Platelets <100 K/cumm
7. Wound healing issues at time of possible conversion (eg, wound dehiscence, wound infection, incisional hernia, lymphocele, seroma)
8. Elevated total cholesterol (>350 mg/dL) and/or triglycerides (>500 ng/dL) at time of possible conversion
9. Hypersensitivity to everolimus, sirolimus, or other rapamycin deriviatives

Investigational and reference therapy:

Investigational therapy

- Everolimus tablets 0.25 mg, 0.5 mg, and/or 0.75 mg

Study design: Patients will be selected if they experience non-infectious GI adverse effects within the first 12 months post transplant. Following selection they will have a baseline screening and enrollment with a complete medical history, medication history, vital signs and labs (including tacrolimus and everolimus levels). In addition, their adverse effects and GSRS and GIQLI will be recorded. After enrollment they will have medication history, vitals, labs (including tacrolimus and everolimus), and GSRS/GIQLI and adverse events recorded at months 1, 3, 6, 9, and 12 (excepting GSRS and GIQLI at month 9).

Efficacy assessments:

- Change in GSRS from baseline to month 3
- Change in GSRS subscores from baseline to month 3
- Changes in GSRS from basline to month 6 and 12
- Change in GIQLI from baseline to month 3
- Change in GIQLI subscores from baseline to month 3
- Changes in GIQLI from baseline to month 6 and 12

Other assessments:

- BPAR rates during study (compared with historical control)
- eGFR by MDRD4 from baseline to month 12 (compared to historical control)
- Death (compared with historical control)
- Graft loss (compared with historical control)

Data analysis:

Data for primary and secondary efficacy will be compared using a paired T-test.

Background

Cellcept® (mycophenolate mofetil, MMF) and Myfortic® (enteric-coated mycophenolate sodium, EC-MPS) are the two formulations of mycophenolic acid (MPA) approved for use as adjunctive immunosuppression post-renal transplantation. Non-infectious gastrointestinal (GI) adverse effects are the main dose-limiting toxicity of MPA therapy, which has been reported in up to 45% of MPA-treated patients. MPA dose reductions, treatment interruptions, discontinuations or withdrawals are common due to GI toxicity from these agents. Studies have demonstrated that patients with GI complications who experienced an MMF dose adjustment or discontinuation had a significantly increased incidence of acute rejections compared with patients without GI complications (30.2% vs. 19.4%, p=0.005). At Barnes-Jewish Hospital/Washington University School of Medicine in St. Louis, it is standard practice to place patients on triple maintenance immunosuppression therapy with MMF or EC-MPS, tacrolimus, and prednisone immediately post-renal transplantation. Patients may be switched from MMF or EC-MPS to azathioprine due to GI symptoms. We feel that everolimus (EVR) may offer a similar advantage to azathioprine for patients unable to tolerate MMF or EC-MPS in regard to similar incidence of acute rejection, low incidence of GI-related adverse effects, and other patient-oriented outcomes.

Purpose and rationale

This study is a prospective, single-center, single-arm study to evaluate the effectiveness of conversion from MMF or EC-MPS to EVR during the first year post-renal transplant in patients who experience gastrointestinal adverse effects. The secondary outcomes will include a comparison of EVR-based immunosuppression to azathioprine (AZA)-based immunosuppression, which is the current standard of practice at this institution. It is felt that EVR-based immunosuppression may offer certain advantages over AZA, including the ability to use lower-exposure tacrolimus maintenance and preserve kidney function as compared to AZA or MPA.

Management of GI adverse effects following kidney transplantation has been established as a consistent challenge for transplant centers. Reduction of MPA immunosuppression may lead to adverse outcomes such as rejection or graft failure, and use of AZA has been associated with higher rates of graft loss. Everolimus has been studied in kidney transplant recipients, and has been shown to lead to similar rates of rejection and graft function compared to MPA. Thus, we have proposed this single-arm study to assess improvement in GI adverse effects in renal transplant recipients. If EVR demonstrates a significant benefit with regard to GI adverse effects while maintaining appropriate rejection prophylaxis, it may offer transplant a new option for patients who are experiencing such adverse effects while on MPA therapy.

We will assess patients within the first year post-transplant for signs and symptoms of GI adverse effects, and following ruling out infectious causes, they will be consented and converted to EVR at an initial dose of 1 mg PO BID, which will then be titrated to target trough goals between 3 – 8 ng/mL. Prior to drug initiation, patients will complete the GSRS and GIQLI surveys to assess for intensity of symptoms and associated quality of life. Patients will remain on study therapy for at least 12 months and GSRS and GIQLI will be repeated at 30 days, 3 months, 6 months, and 12 months.

These timelines were chosen to allow enough time to demonstrate a significant change in GSRS scores following conversion to EVR. We have chosen not to include an active control due to the added cost and time that would be required to enroll and follow the additional numbers needed. We will compare data on graft rejection, graft function, graft survival, and patient survival to an historic cohort of patients who were converted to AZA for GI adverse effects. They will be compared on a 2:1 basis to a group of randomly selected patients previously converted to AZA.

Objectives

Primary objectives

To determine if a switch from MMF or EC-MPS to Zortress (everolimus) due to GI intolerance results in improvement of GI symptoms, as measured with the GSRS survey.

Secondary objectives

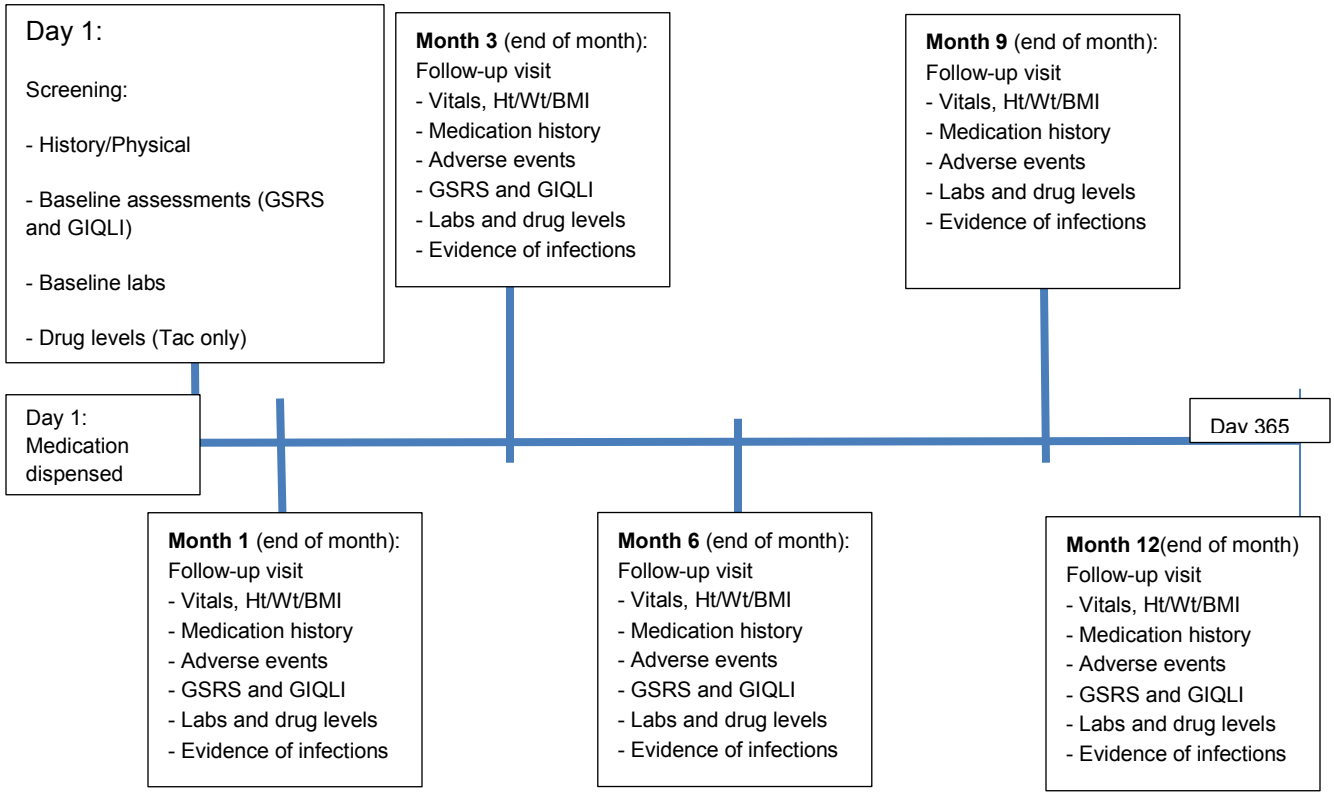
To determine whether it is safe to switch from MMF or EC-MPS to Zortress (everolimus) due to GI intolerance from MMF/EC-MPS within 12 months post-renal transplantation.

Study design

This study will be conducted over a 2-year period, during which patients will be enrolled through the first year, and follow-up of a minimum of 1 year will be collected on each patient. Interim analyses will be conducted at 6-months or upon enrollment of 15 patients (whichever is earliest). The interim analyses will assess the rate of study drug discontinuation due to non-efficacy (as determined by nephrologist). If more than 5 patients (33%) have discontinued drug due to non-efficacy, the study will be terminated. Additionally, any other problems or safety signals will be addressed by the research team at this time.

Subjects meeting criteria will be asked to sign an informed consent, and upon execution of informed consent this will be considered study day 1. They will examined on study day 1 including a medical history, medication history, vital signs, height, weight, and BMI. Subjects will complete GSRS and GIQLI surveys, report adverse effects, and complete laboratory tests, including tacrolimus levels. Subjects will have 5 additional visits during the study period, which will include a medication history, vital signs, height/weight/BMI, adverse effect recording, GSRS and GIQLI (excepting visit 5), laboratory work including tacrolimus and everolimus levels, and reporting of infectious symptoms. These visits will occur at the end of months 1, 3, 6, 9, and 12.

Figure Error! No text of specified style in document.**-1** **Study design**



Population

We intend to include patients who have received kidney transplant at the Washington University/Barnes-Jewish Hospital transplant program in the year prior to enrollment who are exhibiting signs of non-infectious GI toxicity determined by the treating physician to be secondary to MPA. In total, 30 candidates will be enrolled and treated with conversion from MPA to EVR. We anticipate a dropout rate of 20%, and expect that 24 patients will complete a full year of study drug. Severity of GI adverse effects will be assessed using the GSRS and GIQLI scales, but no specific severity threshold will be used to enroll patients. The study will be conducted largely on outpatients, but patients may be initially enrolled during inpatient stays.

Inclusion criteria

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

1. Patients must give written informed consent before any assessment is performed.
2. Adult kidney transplant recipients at Washington University/Barnes-Jewish Hospital
3. Experiencing GI toxicity from MPA as determined by the treating physician within 12 months post-renal transplant
4. On standard immunosuppression with tacrolimus and prednisone

Exclusion criteria

1. Dual organ or kidney after another solid organ transplant
2. Presence of a preexisting significant GI condition that does not have a presumed causal relationship with MPA
3. Evidence of any GI disorder induced by an infection, underlying medical condition, or concomitant medication other than MPA
4. eGFR<35 ml/min at time of possible conversion
5. Proteinuria >1 gram/day at time of possible conversion
6. Profound bone marrow suppression at the time of possible conversion as defined as:
    - Hemoglobin <10 g/dL
    - WBC <3 K/cumm
    - Platelets <100 K/cumm
7. Wound healing issues at time of possible conversion (eg, wound dehiscence, wound infection, incisional hernia, lymphocele, seroma)
8. Elevated total cholesterol (>350 mg/dL) and/or triglycerides (>500 ng/dL) at time of possible conversion
9. Hypersensitivity to everolimus, sirolimus, or other rapamycin deriviatives

Treatment

Investigational and control drugs

Patients enrolled in the trial will receive everolimus tablets at a starting dose of 1 mg PO BID, which will be dispensed in 0.5 mg tablets in blister-packages of 60-each.

Treatment arms

This will be a single-arm study. All patients enrolled with be assigned to the everolimus arm. We will include an observational retrospective analysis of those on AZA-based immunosuppression for comparison of risk of acute rejection, chronic rejection, graft-loss, and death, but these patients have already been allocated treatment and completed follow-up.

Treatment assignment

This will be a single-arm study. All patients enrolled with be assigned to the everolimus arm.

Treatment blinding

This will be an open-label study. All participants including researchers, subjects, and analysts will be aware of treatment allocation.

Treating the patient

Patient numbering

Patients will be numbered sequentially from 1 through 30 based on the order they complete consent and enrol in the study

Dispensing the study drug

Study drug will be dispensed by the Barnes-Jewish Hospital Investigational New Drug (BJH IND) pharmacy, 216 S. Kingshighway Blvd. They will receive a supply of 360 tablets of the 0.5 mg strength during their first study visit with a prescription label as outlined below.

Study drug supply, storage and tracking

Study drug supply with be shipped to the IND pharmacy, and it will be stored within an automated dispensing cabinet system (PYXIS), accessible only to the BJH IND pharmacy staff. Dispensing logs will be maintained by the BJH IND pharmacy staff, and the study team will track doses assigned for each patient during and following the titration period.

Instructions for prescribing and taking the study drug

Upon enrollment, patients will be instructed to begin taking 2 tablets by mouth twice daily beginning the evening following enrollment. Patients will continue taking everolimus twice daily through the study duration until the morning of the final visit (visit 6- end of month 12). The dose will be adjusted based on everolimus trough levels (as measured in whole blood using liquid chromatography and mass spectrophotometry methods) to target an everolimus level between 3 and 8 ng/mL. These assessments of everolimus levels will be made on a q2week schedule initially.

Permitted study drug dose adjustments and interruptions

As above, patients will have regular assessments of their everolimus levels. The first level assessment will be taken no sooner than 3 days following administration of the first dose. Any dose changes will lead to follow-up levels no sooner than 3 days following dose adjustment. The trough goal for EVR for the study is between 3 and 8 ng/mL. Levels below 3 ng/mL should result in a dose adjustment equaling double the previous dose. Levels above 8 ng/mL should result in a decrease in dose by 0.25 mg per dose. Changes to dose may also be made at treating physician discretion.

Additionally, tacrolimus levels will be assessed and doses adjusted upon these levels, targeting a trough level between 2 and 5 ng/mL. Adjustments to TAC doses may be made at treating physician discretion.

Drug interruptions may occur at the discretion of treating physician for severe or opportunistic infection, evidence of adverse effects requiring interruption (such as pulmonary infiltrates), or during periods of severe illness where oral route is unavailable.

Other concomitant treatment

Stong inducers or inhibitors of CYP3A4/3A5 are prohibited.

Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an “x” the visits when they are performed. The day of enrollment will be considered to be study Day 1. Subjects will make scheduled study visits on Day 1, at the end of Months 1, 3, 6, and 12. Subjects who discontinue their study treatment regimen should be treated according to standard of care immunosuppression and return for the assessments indicated by X in Table 6-1. 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 to determine the subject and graft status.

Table Error! No text of specified style in document.**-1** **Assessment schedule**

	Screening And Enrollment	Treatment period (post-switch)				Final study visit
		Month 1	Month 3	Month 6	Month 9	Month 12
Visit	1	2	3	4	5	6
Medical history	X					
Medication history	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Height, weight, BMI	X	X	X	X	X	X
Informed consent	X					
Dispense medication and/or instruct subject regarding use	X					
Record adverse events	X	X	X	X	X	X
GSRS and GIQLI instruments	X	X	X	X		X
Clinical laboratory tests	X	X	X	X	X	X
Tacrolimus/everolimus trough levels **Trough concentrations to be drawn twice weekly upon initiation and/or dosage change until therapeutic goal level is obtained	X	X	X	X	X	X
Evidence of bacterial, viral, and fungal infection **At the following visits and at any point such infection is reported to a physician, transplant coordinator, or study coordinator	X	X	X	X	X	X

Patient demographics/other baseline characteristics

After informed consent has been signed and the subject's eligibility to participate in the study has been determined, baseline subject information will be obtained in accordance with local regulations, including date of birth, age, sex (with child bearing status for females), race and ethnicity. In addition, relevant medical history (including CKD and ESRD history) and current medical conditions at screening, a full physical examination, vital signs and a pregnancy test (for females of child-bearing potential) will also be performed (or documented if recently performed). At Baseline/Transplantation information on the renal transplant procedure, recipient and donor transplant background, recipient and donor viral serology and recipient/donor HLA testing results will be recorded. Post-transplant, when all Inclusion/Exclusion criteria are met, the subject may begin receiving drug.

Treatment exposure and compliance

All pre-transplant immunosuppression administered, such as basiliximab, rATG and any other agents (CNI, MPA and/or corticosteroids) administered pre-enrollment will be recorded. All post-enrollment doses of everolimus and tacrolimus administered during the course of the study will be recorded in the data monitoring sheets. For all these immunosuppressive drugs the start date, total dose, stop date and reason for dose administration or dose change are to be provided. Tacrolimus trough levels will be determined locally and recorded on the data monitoring sheets. The local trough values will be used to adjust the tacrolimus dosing. Everolimus trough levels will be determined by the local laboratory and recorded on the data monitoring sheets.

Efficacy

Gastrointestinal Symptom Rating Scale (GSRS)

At each study visit, with the exception of study visit #5, the will be administered by a member of the study team. Subjects will be interviewed by one of the investigators, and their responses will be recorded at each time point. The interviewer will be provided a sheet with each of the symptom areas, the associated questions, and the rating scale to conduct the interview. They will ask each question and read each potential response to the patient and circle the associated answer. These scores will be used to calculate their overall GSRS score, as well as the 5 sub-scores. The GSRS has been validated in numerous studies, including the initial study of the GSRS (Svelund J. *Dig Dis Sci.* 1988) which demonstrated validity and strong interrater reliability. It has subsequently been studied in the setting of kidney transplant recipients experiencing non-infectious GI adverse effects (Bolin P. *Transplantation 2007*). The scores in each of the domains (indigestion, diarrhea, constipation, abdominal pain, and reflux) will be recorded following the interview and will be compared longitudinally.

Gatrointestinal Quality of Life Index (GIQLI)

Following completion of the GSRS, the interviewer will then provide a paper copy of the GIQLI for the patient to complete. This is a 36-question survey containing 5 domains (Core symptoms, physical items, psychological items, social items, social items, and disease items) which each question contains 5 possible answers (which are rated from 0 – 4). Subjects will be asked to review the survey and each question, and circle the associated answer and return the survey to the interviewer. The interviewer will record the responses to each question and scores will be calculated and tracked for each patient longitudinally. The utility of this survey has been demonstrated by an initial assessment of reliability (Eypasch E. *Br J Surgery.* 1995) and has been used in multiple studies to assess any gastrointestinal symptoms and has demonstrated reproducibility.

Safety

Treated Biopsy Proven Acute Rejection (tBPAR)

A treated BPAR is any condition where the subject received anti-rejection treatment and was histologically diagnosed as acute rejection. Renal biopsies will be collected for all cases of suspected acute rejection.

Kidney allograft biopsy

For all suspected rejection episodes, regardless of initiation of anti-rejection treatment, an allograft biopsy must be performed within 48 hrs. Biopsies will be read by the pathologist according to the updated Banff 2009 criteria. The results of the biopsy read by the pathologist will be recorded in the research database. The results will be used for subject management for acute rejection. The local pathologist will remain blinded to treatment. Any biopsies performed according to local practice (e.g. not for cause) should also be recorded.

Graft Loss

The allograft will be presumed to be lost on the day the subject starts dialysis and is not able to subsequently be removed from dialysis. If the subject undergoes allograft nephrectomy prior to starting permanent dialysis, then the day of nephrectomy is the day of graft loss.

Death
In the event of subject death, the SAE leading to Death should be reported to the sponsor DS&E within 24 hr.

Renal Function
Renal function by calculated eGFR using the MDRD4 formula (Coresh, 2003) from enrollment to Month 12 is a primary variable for assessment of renal function in this study. This will also be the primary method of assessment of renal function with respect to other renal endpoints.

Physical examination
A thorough physical assessment will be performed at Screening, Months 3, 6 and 12. Information about the physical examination will be recorded in the visit history document. Significant findings that are present prior to the start of the study must be included.

Vital signs

Vital signs (radial pulse rate and blood pressure) will be recorded at each study visit in the visit history document. Blood pressure and pulse rate will be assessed at the same arm each time of determination and after the subject has rested in the sitting position (may be supine if during hospitalization) for at least five minutes. Systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1-2 minute intervals and the mean of the three measurements will be recorded on the Vital Signs CRF. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Height and weight
Height will be recorded at Screening only, weight will be recorded at Screening and at each subsequent visit. Results will be recorded in the visit history form.

Laboratory evaluations

All lab work will be conducted at local laboratories, with the exception of study visit laboratories, which will be conducted on-site.

Pregnancy and assessments of fertility

Pregnancy testing (serum) must be carried out for all females of child-bearing potential. A negative serum pregnancy test must be recorded within 30 days of enrollment.

Other assessments

As above

Health-related Quality of Life

As above

Safety monitoring

Adverse events

Definition of an AE: Any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational medicinal product.

Investigational Medicinal Product (IMP) includes the drug under evaluation and the comparator drug(s) if specified as part of the research objective, given at any time during the study. Medical conditions/diseases present before starting the drug of interest are only considered adverse events if they worsen after starting the drug of interest.

The occurrence of adverse events will 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 will be recorded in the study database including the following information:

1. the severity grade (mild, moderate, severe) or (grade 1-4) (delete 1 of the 2 options)
2. its relationship to the drug(s) of interest (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)

Serious adverse event reporting

A SAE is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is otherwise a significant medical event.

This includes any SAEs likely to arise from the trial indication or progression of underlying/concomitant illness (es) (e.g. progression of cancer in oncology trials), unless specified in the protocol as study specific exemptions.

Any SAE, irrespective of causality, occurring after the subject has provided informed consent and until four weeks after the subject has stopped study participation must be reported unless otherwise stated in the protocol. SAEs occurring after four weeks from ending study participation should only be reported if considered by the Investigator attributable to the exposure to the investigational drug(s) during the trial period. This includes the period in which the study protocol interferes with the standard medical treatment given to a subject, even if study treatment has not yet started (e.g. withdrawal of previous treatment during washout period, change in treatment to a fixed dose of concomitant medication).

Timelines: All serious adverse events (SAEs) from interventional clinical trials must be reported by the sites to Sponsor within 24 hours of occurrence of the SAE. The timelines for investigator initiated trials reporting to the sponsor will be done as per Third Party Study/Investigator Initiated Trial Agreement.

Follow-up reports:

SAEs will be followed until resolution or until it is judged to be permanent, and an assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

The Sponsor shall support in the following-up of all SAEs so that complete information is available to maintain patient safety and also as part of any commitments by the sponsor to any Health authority OR specific Health authority follow-up requests for the product under investigation.

Pregnancies

To ensure patient safety, each pregnancy in a patient (or a patients partner) on study drug must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy will 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.

Data review and database management

Data collection

Data collection will occur via the RedCap system. All local staff have received training on RedCap. Multiple forms will be created, including a baseline/screening form, and visit-specific forms. Only investigators will have access and the ability to download data.

Database management and quality control

The principal investigator will take responsibility for assessing quality data entry by overseeing all data entry into the RedCap system.

Data analysis (Any or all sections may be included based on type of study)

Statistical analysis and report writing will be performed when the last subject has completed 12 months on study.

Populations for analysis

Subjects completing three months of therapy and returning for study visit #2 will be included in the primary analysis. All subjects receiving at least one dose of everolimus will be included in all outcomes related to safety.

Patient demographics/other baseline characteristics

Demographic and background information for the population will be summarized using frequency distribution (for categorical variables) and descriptive statistics of mean, median, maximum, minimum and standard deviation (for continuous variables).

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

The number of patients remaining on study medication at each study visit will be recorded. Additionally, mean tacrolimus and everolimus levels will be reported at each study visit.

Analysis of the primary objective(s)

Variable

The primary variable is the resultant score derived from the GSRS, which ranges from 0 – 45, compared at enrollment and at visit 2 (end of month 3).

Statistical hypothesis, model, and method of analysis

The null hypothesis: Conversion from MPA-based immunosuppression to EVR-based immunosuppression will result in similar GSRS scores at 3 months compared to baseline.

We will analyze changes in the GSRS using a paired T-test.

Handling of missing values/censoring/discontinuations

We will not include patients in the primary analysis and subsequent analyses of efficacy if they drop out of the study. We will analyze safety endpoints from a modified ITT approach, whereby patients receiving at least one dose of everolimus are considered on therapy until the end of their study period (12 months).

Supportive analyses

A per-protocol set will be analyzed as a secondary endpoint with regards to safety endpoints, including BPAR, graft loss, and death.

Analysis of secondary objectives

Efficacy (secondary)

We will conduct analysis of GIQLI scores at visit 2, 3, 4, and 6 compared with baseline assessment, as well as inter-visit comparisons. Additionally, we will conduct subscore analyses of the GSRS and GIQLI at each of these timepoints. The pre-specified domains of the GSRS to be analyzed will be the abdominal pain, diarrhea and reflux scores. The GIQLI subscores will be analyzed for all domains.

Safety

Safety variables to be assessed include BPAR, graft loss, death, graft function at each study visit, discontinuation from study, discontinuation from treatment, infection, SAE, notable events, laboratory tests, and vital signs. All safety analyses will be done on the safety set. Selected variables will be analyzed using all available data including data assessed.

Health-related Quality of Life

As above.

Sample size calculation

- The sample size was calculated based on the myTIME study. Sample size calculation showed that a minimum sample size of 25 patients will be required to provided 80% power to detect a change from baseline of 12 points in the total GSRS score (15-105 scale) considering a 0.05 significance level and a standard deviation of 18 and allowing for a 20% dropout. A paired t test will be utilized to compare the overall GSRS score, the GSRS subscale scores, and the GIQLI from baseline.

- Assuming a 5% 1-year rate of acute rejection, we plan to evaluate 60 historical control patients to compare differences in the secondary endpoints of acute rejection, graft survival, patient survival, and infections. The historical control group will be randomly selected from a consecutive list of patients who received a renal transplant during the same study period and were maintained on MMF 500mg-1gram BID or EC-MPS 360-720mg BID, tacrolimus, and prednisone and met stated inclusion and exclusion criteria as listed below. 30 conversion patients will be enrolled and compared 1:2 with historical controls.
- Statistical analysis for the historical control comparison will utilize the Chi-squared test for events, ANOVA for renal function outcome differences and other continuous variables, and Kaplan-Meier estimates for patient and graft survival

Ethical considerations

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 applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. 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.

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 adhere to the contraception requirement 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.

Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to the sponsor before study initiation.

Publication of study protocol and results

Type here

Protocol adherence

Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. 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.

References

1. Behrend M. Adverse GI effects of mycophenolate mofetil: aetiology, incidence and management. Drug Saf 2001; 24:645.

2. European Mycophenolate Mofetil Study Group. Placebocontrolled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute

rejection. Lancet 1995; 345:1321.

3. Tierce JC, Porterfield-Baxa J, Petrilla AA, et al. Impact of mycophenolate mofietil (MMF)-related gastrointestinal complications and MMF dose alerations on transplant outcomes and healthcare costs in renal transplant recipients. Clin Transplant. 2005; 19(6):779.