Project Title: Prospective Study Comparing Brand and Generic Immunosuppression on Transplant Outcomes, Adherence, & Immune Response in Kidney Transplant Recipients

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Prospective Study Comparing Brand and Generic Immunosuppression on Transplant Outcomes, Adherence, & Immune Response in Kidney Transplant Recipients

A Clinical Protocol Submitted in fulfillment of RFA-FD-14-020

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A reliance agreement between UCLA and UCSD, UCI, and UCD will be established so UCSD, UCI, and UCD will rely on UCLA IRB for review and approval to conduct the study.

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SYNOPSIS

Title: Prospective Study Comparing Brand and Generic Immunosuppression on Transplant Outcomes, Adherence, & Immune Response in Kidney Transplant Recipients

Estimated Number of Study Centers: 4

Study Phase: 4

Research Hypothesis: Kidney transplant recipients who received generic tacrolimus will have outcomes that are not inferior to those who received brand tacrolimus during the one-year study period.

Primary Objective: To analyze the effects of use of brand tacrolimus versus generic tacrolimus, on a composite event of either acute rejection, or graft failure, or subject death.

- Acute Rejection will be defined according to the Banff 2007 classification
- Graft failure will be defined as a return to dialysis, re-transplant, or death

Secondary Objectives: To analyze the effects of use of brand tacrolimus versus generic tacrolimus on acute rejection, graft failure, subject death, individual rates of infection, immunologic markers of immunosuppression, subject compliance, and subject acceptance.

Study Design: Phase IV prospective, randomized, open labeled, multicenter, 2-group, parallel, observational study.

Duration of Study: 1 year

Number of Subjects: 200. Study Population: Kidney recipients; no more than 14 days after transplantation and prior to discharge.

Reference Product, Dose, Mode of Administration, and Duration of Treatment: Brand tacrolimus, dosing to be determined by the treating physician and recorded in subjects' study file, to be administered orally (tacrolimus level to be 4-11ng/dL) for a duration of 1 year.

Test Product, Dose, Mode of Administration, and Duration of Treatment: Generic tacrolimus, dosing to be determined by the treating physician and recorded in subjects' study file, to be administered orally (tacrolimus level to be 4-11ng/dL) for a duration of 1 year.

Criteria for Evaluation:

Primary outcome measures:

Time to a composite event, which is defined as the time to first occurrence of acute rejection, failure, death.

Secondary Outcome Measures:

- Graft rejection at 1 year after transplant
- Graft failure at 1 year after transplant
- Incidence of infectious episodes at 1 year after transplant
- Incidence of malignancy at 1 year after transplant
- Death or loss-to-follow-up at 1 year after transplant
- Adherence with medication regimen

Statistical methods: The primary efficacy endpoint will be analyzed as time-to-event, with follow-up time measured in days from the date of transplant to the date of composite endpoint. Statistical testing of time until composite event will be done for the intention-to-treat population, with adjustment for center (Cox regression). Data will also be collected on subjects who are lost to follow up. The intention-to-treat population will consist of all randomized patients who received at least 1 dose of investigational drug (brand or generic tacrolimus).

1 INTRODUCTION

1.1 Research Hypothesis

Primary hypothesis:

Kidney transplant recipients who received generic tacrolimus will have outcomes that are not inferior to those who received brand tacrolimus during the one-year study period.

1.2 Study Rationale

As the patents for brand-name immunosuppressive medications expire, there is increasing interest in using generic immunosuppressive drugs. However, despite pharmacokinetic studies showing bioequivalence, questions remain regarding the clinical impact of use of generic immunosuppression. The most important immunosuppressive agent in the modern transplant era is arguably tacrolimus, a calcineurin-inhibitor with a narrow therapeutic index. This study seeks to answer the question regarding the clinical impact of generic tacrolimus use as measured primarily by acute rejection, loss of graft function, and subject death through a randomized trial of 2 parallel groups: Brand tacrolimus versus Generic tacrolimus. Given that kidney transplantation is the most commonly performed transplant with well-defined measures of rejection and graft failure, this organ will be studied in a four-center study designed to accrue the target number of transplant recipients within the 12-month study period.

1.3 Rationale for Dosing

Because dosing and target tacrolimus levels vary and require customization to subject circumstance, including rejection risk and history of infection, dosing will be decided by each subject's treating physician to approximate a real-world dosing scenario. Please see protocol guidelines for trough level in Section 6.2 study therapy.

1.4 Risks and Benefits

Given that both brand and generic tacrolimus are FDA-approved for use for prevention of rejection after organ transplantation, it is anticipated that trial enrollment will not significantly increase risk for adverse outcomes. Subjects will be monitored closely for adverse events. In addition, in pursuing this study, if increased risk for rejection is found in subjects receiving generic or combination treatment, this information can be used to benefit future transplant recipients.

1.4.1 Overall Risks

All of the medicines used for prevention of rejection can cause unwanted side effects. Side effects may be experienced early or late following a transplant and may be short or long lasting. The study drugs and procedures may have risks and may cause discomfort. The subject must report to the study staff any side effects or symptoms that he/she experiences.

The potential risks and discomforts related to the subject's participation in this study are listed below. There may be other possible risks and discomforts, which are currently unforeseeable.

TACROLIMUS RISKS

Both generic and Prograf contain the same active ingredient, tacrolimus. The most common side effects of tacrolimus are infection, tremor, hypertension, abnormal kidney function, constipation, diarrhea, nausea, headache, abdominal pain, insomnia (difficulty falling asleep), weakness, urinary tract infection, pain, anemia, swelling of the arms, legs, or feet, decreased magnesium levels in the blood, decreased phosphate levels in the blood, increased lipid levels in the blood, and increased potassium levels in the blood.

Mild increases in potassium levels usually don't cause any symptoms but very increased potassium blood levels can cause heart arrhythmias (abnormal heart rhythm). Heart arrhythmias can sometimes cause the heart to stop beating, which may lead to death. The potassium levels in the blood will be monitored during the study and if the level is elevated it can be treated with medications.

Subjects treated with tacrolimus may develop swelling in the brain called posterior reversible encephalopathy (PRES). Symptoms of PRES are headache, confusion, seizures, high blood pressure, and vision changes. PRES can be treated by lowering the blood pressure and reducing the dose of tacrolimus, with improvement of symptoms.

Taking tacrolimus in any form can cause diabetes, even in persons who never had diabetes before. Symptoms of diabetes can be increased thirst, urination and hunger. Diabetes can be treated with medications including insulin and the condition can improve after the tacrolimus is discontinued. The laboratory testing during the study will watch for this, but subjects will be instructed to report to the study staff if they experience frequent urination or increased thirst or hunger.

All anti-rejection medications may result in infections of the blood, body organs, or tissues. These infections may be caused by various types of bacteria, fungi (yeast and molds), or viruses, especially cytomegalovirus (CMV) and herpes viruses. There is an increased risk for opportunistic infections, including activation of latent viral infections, such as BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy. These and other types of infections in patients taking immunosuppressive drugs such as tacrolimus can be severe or fatal. The subject should avoid people with contagious diseases (including colds and flu) and keep cuts and scratches clean. Subjects will be instructed to notify their study doctor right away of any new or unusual symptoms that they may experience.

Immunosuppressive medications also increase the risk of cancer, which could be fatal. The most common cancers in a transplant patient are skin cancers and lymphomas or post-transplant lymphoproliferative disorder (PTLD). Lymphoma and PTLD are disorders of the lymphocytes (one of the body's white blood cells that can cause rejection). The development of lymphomas and cancers appears to be related to the overall extent of immunosuppression, rather than to any specific drug. The overall risk of developing any of these cancers is about 1% in transplant patients.

Tacrolimus may cause other side effects. The subject should call the study doctor if he/she has any unusual problems while taking this medication.

BLOOD DRAW RISKS

Some people have discomfort or pain when blood is collected. Insertion of a needle into the arm can cause some pain, swelling, bruising, and occasionally fainting reactions. Fainting reactions

are usually harmless, of short duration, and typically produce feelings of weakness accompanied by sweating, slowing of the heart rate, and an abnormal decrease in blood pressure. Rarely, there may be a small blood clot or infection at the site of the needle puncture. Very rarely, some people have suffered nerve damage.

POSSIBLE REPRODUCTIVE RISKS

The risks to an unborn human fetus or a nursing child, when a parent is taking tacrolimus, are unknown. Women who are pregnant or nursing a child will be excluded from participating in this study. Female subjects will be asked to confirm to the best of their knowledge that they are not currently pregnant and that they do not intend to become pregnant during the study. Females of non-childbearing potential are defined as women who are postmenopausal (have not had a period in the past 12 months) or surgically sterile. For women who can still have children and who are not abstinent, 2 types of birth control will be required during participation in the study and for 6 weeks after stopping the study drug. If the subject is not abstinent and unable or unwilling to use 2 types of birth control during the study, she will not be allowed to enter the study. Women who use hormonal contraceptives will be informed that the medications used in this study may reduce the levels of the hormones in the blood, which could make that form of birth control not work as well. For this study, acceptable forms of birth control are double-barrier methods (a condom plus a diaphragm or a condom plus a cervical cap, always used with a spermicide), hormonal contraceptives (injected, implanted, or birth control pill) used with another method, or an intrauterine device (Copper T, IUD) used with another method.

Male participants in this study must be willing to use the double-barrier method of birth control with their partners.

Subjects will be instructed to notify their study doctor immediately if they become pregnant or if their female partner becomes pregnant. If a subject becomes pregnant during the study, she will be immediately withdrawn and standard of care will be determined by her treating physician, based on her condition and medical need. The subject or the subject's partner will be asked to sign a new consent form so the sponsor can collect follow-up information. The pregnancy will be monitored by the study doctor until after the birth.

1.4.2. Overall Benefits: Subjects may or may not receive a direct health benefit from participating in this study. They may learn more about what they think and feel about their transplant and medications and be able to track how those feelings and attitudes change over time during the study. Participation in this study will help to gather information about generic tacrolimus, which may be used in the future to improve the care of transplant patients.

2 STUDY OBJECTIVES

2.1 Primary Objectives

Evaluation of time to a composite event, which is defined as the time to first occurrence of acute rejection, or graft failure, or death in brand versus generic arms.

2.2 Secondary Objectives

Will compare in the brand versus generic arms:

- Graft rejection at 1 year after transplant
- Graft failure at 1 year after transplant
- Death at 1 year after transplant
- Loss-to-follow-up at 1 year after transplant
- Incidence of infectious episodes at 1 year after transplant
- Incidence of malignancy at 1 year after transplant
- Adherence with medication regimen

3 STUDY DESIGN AND EVALUATION

3.1 Study Design

A prospective, randomized, open-label, multicenter, parallel, observational study to compare the safety and efficacy of brand versus generic tacrolimus in 200 kidney transplant recipients over a one-year follow up period. All subjects will receive other immunosuppressive medications including induction therapy (thymoglobulin, basiliximab, or no induction) and maintenance, including mycophenolate mofetil and corticosteroid therapy as directed by standard-of-care at each center. Their medication information will be recorded in their study files.

The Phase 1 portion of this study consist of 2 Arms:

Arm 1: Brand Tacrolimus (Prograf) for entire study duration (12 months)

Arm 2: Generic Tacrolimus for entire study duration (12 months)

Additionally, the study consists of 2 Phases:

Phase 1: Subjects have been randomized into either Arm 1 or Arm 2 medication. Once 40 subjects have been enrolled onto Phase 1, Phase 2 will commence.

Phase 2: Subjects will no longer be randomized. All subjects will be enrolled onto generic tacrolimus because they have elected to receive generic tacrolimus (standard of care from the subject's insurance).

3.2 Study Population

The study population includes recipients of kidney allografts, no more than 14 days after transplantation and prior to discharge.

3.3 Criteria for Evaluation

Primary efficacy endpoints:

The primary endpoint of this study will be the time to a composite event, which is defined as the time to first occurrence of acute rejection, or graft failure, or death. The definition of graft failure includes re-transplant, return to dialysis, and/or death. The definition of acute rejection will be based on the Banff 2007 classification. For power considerations, it is assumed that overall 13% of subjects will experience this endpoint by one year post-transplant.

Secondary efficacy endpoints:

Secondary efficacy endpoints will include individual analyses of graft rejection, failure, death, or loss-to-follow-up at 1 year after transplantation. The cause of graft failure and death will also be analyzed. In addition, these individual endpoints and the composite endpoint will be evaluated by age group (adult and elderly (>65) and ethnicity. Other endpoints will include, rejection severity, death due to organ failure, and medication adherence. Adherence will be measured with daily medication diaries, and with the coefficient of variation of tacrolimus in subjects' blood.

Secondary safety endpoints:
Secondary safety endpoints will include the need for hospitalization, infectious episodes (bacterial, fungal, and viral), development of malignancy, and development of new-onset diabetes after transplantation.

3.4 Sample Size Determination

The total number of subjects (200) is based on statistical calculation to have more than 80% power to detect a non-inferiority margin of 26 percentage points of the composite endpoint of acute rejection, graft loss and death over the baseline of 13% in the brand tacrolimus at one year post-transplantation. (See details in next paragraph.)

For power considerations regarding the primary objective, the following assumptions are made:

1. Subjects will be uniformly enrolled over 1-year accrual period
2. Primary analysis will be done via non-inferiority, log-rank tests on an intention-to-treat basis comparing generic recipients (Arm 2) with brand recipients (Arm 1)
3. Data will be also collected from standard-of-care records on subjects who are lost to follow-up
4. Overall, 13% of subjects are expected to experience the primary endpoint by 1 year post-transplant, yielding a yearly hazard rate for the reference group of –log (0.87) = 0.14

Given these assumptions, 200 subjects (if 50 and 150 in brand and generic groups, respectively) are needed to observe 25 events (6 and 19 in brand and generic groups, respectively). These numbers achieve >80% power at a 0.05 significance level to detect a non-inferiority hazard ratio of 3.54 when the actual hazard ratio is 1.0. PASS statistical software (version 13.0) was used for calculation. For completeness, we acknowledge that the study has 80% power only for the specific set of conditions listed above and may lack canonical power when analyzing hypotheses involving secondary endpoints.

Table 1 - Via PASS

Power >= 80% (alpha = 0.05, 5% dropout, 12 mo. study time**)**

Scenario	Sample Size (N)	Brand Surv% (Haz rate/mo)	Equiv HR	Generic Non-inferior Surv% (hrate/mo)	1-year Margin of inferiority

Kidney only	200	87% (0.0116)	3.54	61% (0.0411)	Δ=26%pts

Source: PASS 13 Power Analysis and Sample Size Software (2014). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass. (Non-inferiority logrank test.)

A descriptive analysis will be incorporated of generic supplied within the analysis.

3.5 Data Safety and Monitoring Board Review Responsibilities

A Data and Safety Monitoring Board (DSMB) will be convened for only Phase 1 of the study trial, to act in an advisory capacity to monitor participant safety, evaluate the progress of the study, review procedures for maintaining the confidentiality of data, and review the quality of data collection, management, and analyses. The DSMB will include 3 people with no interest or participation in research activities associated with this trial. DSMB members will not have any direct involvement with the study investigators or intervention. Each DSMB member will sign a Conflict of Interest Statement which includes current affiliations, if any, with pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationships that could be perceived as a conflict of interest related to the study objectives. Members of the Board will include experts in subject education, cultural tailoring, randomized controlled trials, and kidney transplantation.

The Board will be instructed to review the study and its educational components to look for any component of the design or education that could result in harm of study participants. Data will be presented in a blinded manner during the open sessions of the DSMB. At DSMB meetings, data and discussion are confidential. There will be no DSMB for Phase 2 of the study. This is because the Phase 2 part of the study is open label, where standard of care procedures are being performed. There will be no use of any investigational drug. The Principal investigator will continue to monitor participant safety per study site standard of care guidelines.

3.6 Interim Analyses

There will be no interim analysis on the primary endpoint. Safety analyses of secondary safety endpoints will be performed monthly and reviewed by The Data and Safety Monitoring Board (DSMB) for Phase 1 of the study. Safety endpoints and SAEs will be monitored on a continuous basis.

4 STATISTICAL METHODOLOGY

4.1 Dataset descriptions

For all subjects enrolled in the study, data sets will be generated and updated at each study visit based on information collected during routine clinical care visits. Data to be collected from routine clinical care will include:

Donor variables: Age, sex, race, ethnicity, Human Leukocyte Antigen (HLA) data, Blood type, Cause of death (if applicable), Cold ischemic time, Donor crossmatch results, Donor serologies (CMV, EBV Hepatitis B and C), DCD and ECD donor status, Cadaveric or living (related or unrelated) donor

Recipient variables: Age, sex, race, ethnicity, HLA data, Blood type, Transplant date, Recipient serologies (CMV, EBV Hepatitis B and C), Medical history including presence of diabetes mellitus, PRA, single antigen testing, and generic drug supplier.

Medications: induction immunosuppression, maintenance immunosuppression, treatment for rejection and concomitant medications.

Post-transplant follow-up: Rejection diagnosis (grade and method of confirmation) and date, Graft status and date of failure (if applicable), Cause of graft failure (if applicable), Death and Cause of death (if applicable), Dates of hospitalizations, Biopsy results and dates, Single antigen testing results and dates, as well as Episodes of infection, including type of infection, type of organism, treatment, and response to treatment..

4.2 Statistical Analyses (Aim 1 only)

The primary research hypothesis states that subjects receiving generic tacrolimus (Arm 2) would exhibit a 1-year survival rate non-inferior at a 26% margin to the rate among subjects receiving brand tacrolimus (Arm 1). The primary efficacy endpoint will be analyzed as time-to-event, with follow-up time measured in days, from the date of transplant to the date of composite endpoint. Statistical testing of time until composite event will be done for the intention-to-treat population. A Cox regression analysis (adjusting for transplant center via indicator variables) will be used to test the null hypothesis that H0: $HR \geq HR_0$ versus the alternative hypothesis H1: $HR < HR_0$ where HR_0 is hazard ratio of the generic group over the brand group at the margin set at 3.54 (i.e., a 26% non-inferiority margin). The null hypothesis will be rejected if the upper bound of the 90% 2-sided confidence interval (corresponding to a 5% one-sided significance level) for HR is less than 3.54.

Secondary analyses are described next but all are considered exploratory since formal testing of hypotheses is considered dubious given the small sample sizes of stratified subjects. Additional Cox models that include indicator functions for the generic arm (with brand serving as baseline) and/or stratification based on age/race covariates will be used to estimate specific hazard ratios with 95% confidence intervals to evaluate differences among recipients in Arm 2 and risk groups. Also, individual analyses of single endpoint hazard ratios (graft rejection, failure, death) as well as point and interval estimates of group-specific survival rates at 1-year (via Kaplan-Meier and Greenwood methods) are planned without adjustment for multiple comparisons.

Standard descriptive summaries will also be used to report and compare adherence (as measured with daily medication diaries, and with the coefficient of variation of tacrolimus in subjects' blood) and immunologic endpoints (measured by the production of donor specific HLA antibodies).

5.0 SUBJECT SELECTION CRITERIA

Recruitment: No recruitment flyers will be used in the study, as subjects will be recruited in person during their primary hospitalization after transplant or during their pre-transplant visit. For entry into the study, all subjects must meet the following criteria.

5.1 Inclusion Criteria

1. Signed informed consent and/or assent
2. Between the ages of 18 and 70 years, inclusive

3. Current or future kidney transplant recipients, no more than 14 days after transplant and prior to hospital discharge. Inclusion of future kidney transplant recipients cannot exceed 30-days pre-transplant.
4. Able to swallow tablets and capsules at the time of randomization
5. Subjects must be receiving a primary or secondary kidney allograft from a deceased donor or from a non- HLA identical living donor
6. Negative cross match test, and compatible (A, B, AB or O) blood type
7. Subjects must have no known contraindications to tacrolimus
8. Women of childbearing potential (WOCBP) must have a negative pregnancy test and be willing to use 2 methods of contraception during the study and for 6 weeks after stopping the study drug.

WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy with documented serum follicle stimulating hormone level > 35 mIU/cc). Women who are using oral, implanted, or injectable contraceptive hormones (intrauterine device), mechanical products or barrier methods (diaphragm, condoms, spermicides), are practicing abstinence, or have a sterile partner (e.g., vasectomy), will be considered of child bearing potential.

In addition, WOCBP who are taking MMF must use methods of birth control as stipulated in the package insert, namely:
Either intrauterine device, or partner with vasectomy, or one hormone (oral contraceptive pill, transdermal patch, vaginal ring, or progesterone injection or implant) and one barrier method (diaphragm or cervical cap with spermicide, contraceptive sponge, or male or female condom), or two barrier methods as described above.

WOCBP must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) at the time of transplant.

5.2 Exclusion Criteria

1. Those who receive simultaneous combined organ transplants
2. Subjects with clinically significant active infections (for example, those requiring hospitalization, or as judged by the Investigator) or malignancies
3. Recipients who are concurrently receiving belatacept or anticipate to receive belatacept as part of their immunosuppressive regimen
4. Subjects currently enrolled in another investigational device or drug study
5. WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for 6 weeks after stopping the study drug
6. Women who are breast-feeding or pregnant with a positive pregnancy test on enrollment or prior to study drug administration
7. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled into this study.
8. Any psychiatric or medical condition that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.

6 STUDY CONDUCT

6.1 Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki, and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

Freely given written informed consent must be obtained from every subject or their legally authorized representative prior to clinical trial participation, including informed consent for any screening procedures conducted to establish subject eligibility for the trial.

For further details on informed consent, see Section 10.2.

The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s).

This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

Systems with procedures that assure the quality of every aspect of the study will be implemented.

6.2 Study Therapy

6.2.1 Clinical Sites: Kidney recipients will be enrolled at UCLA, UCSD, UCI, UC Davis Medical Centers. Mechanistic studies will be performed utilizing specimens collected from all sites. Adherence will be measured with daily medication diaries, and with the coefficient of variation of tacrolimus in subjects' blood.

6.2.2 References and comparator arms: During phase 1 of study, following consent and randomization, the control group were prescribed brand tacrolimus and the comparator group was prescribed generic tacrolimus. The study drugs were prescribed upon discharge, but no later than 14 days after transplant. Subjects continued to receive study drug for up to one year post-transplant. During phase 2 of study, generic tacrolimus will only be prescribed as part of their regular care upon discharge but no later than 14 days after transplant.

6.2.3 Provision of investigational drugs: We anticipate that brand and generic tacrolimus will be provided for the entire study period for Phase 1 of the study. Generic tacrolimus will be obtained by the subject through their insurance for Phase 2 only. (See letters from Astellas - Appendix 5)

6.2.4 Number of subjects and sample size justification: We plan to enroll a total of 200 subjects between the four sites. Of the 200 kidney recipients at least 20 will be African American recipients. 40 randomized subjects will be on Brand and 160 subjects will be on generic.

6.2.5 Eligible Subjects: In Phase 1, eligible subjects will be initially randomized using a ratio of 2:1 (Brand:Generic) until 40 subjects have been enrolled into the brand medication arm (Arm 1) and 20 have been enrolled into the generic medication arm (Arm 2). In Phase 2, 140 additional eligible subjects will be enrolled without randomization onto generic tacrolimus only as part of their regular care. All subjects will be followed for 1-year post-transplant. (A split-phase randomization process is necessary due to a limited supply and narrow expiration-time window associated with the Brand medication product.)

6.2.6 Screening, recruiting and eligibility: All Kidney recipients that are 1) less than 30 days pre-transplantation or 2) up to 14 days post-transplantation, but prior to discharge, who are deemed a candidate for a tacrolimus immunosuppression regimens and meet the inclusion and exclusion criteria above, are eligible for the study. They will be invited to participate and given written informed consent for enrollment. We will attempt to enroll all subjects in a 12-month time period.

6.2.7 Study enrollment and randomization: This randomized, prospective, open-labeled, 2-group, parallel observational study will enroll a total of 200 subjects across 4 clinical sites. During phase 1 of the study, randomization was done after the informed consent process, using a block system pre-generated by a computer and stratified by site, ethnic group, and age cohort. During phase 2 of the study, no randomization will occur, and all subjects will be placed onto standard of care generic tacrolimus.

Table 2- Projected Enrollment is Shown Below According the Study Site

Site	UCLA	UCSD	UCI	UC Davis			Total
Kidney	130	20	30	20			200

Table 3 - Adult Transplant Subjects – Trough Levels:

*Based on individual subject therapeutic level.

		1 mo.	2mo.	3mo.	6mo.	9mo.	12mo.
UCLA/UCSD/UCI/UC DAVIS		8-11	8-11	8-11	4-11	4-11	4-11

The tacrolimus level ranges listed in Table 3 are target ranges. The adjustment of trough level should be based on the clinical judgment of the Principal Investigator and the subject's primary physician. The product insert recommends a trough level of 4-11. If the trough level falls outside the 4-11 range the Investigator must provide a justification. Trough levels will be monitored

throughout the study. For more details see Table 5 Study Schedule. All adjustments will be recorded in the subject's study file.

6.2.8 Study regimens:

Eligible and consented subjects will be randomized into the 2 groups below:

Arm 1 (n=40) will receive brand tacrolimus for the entire study

Arm 2 (n=160) will receive generic tacrolimus for the entire study

According to their standard practice and attending physician and surgeon recommendation, subjects should also be on a maintenance regimen consisting of any of the following medications: mycophenolate mofetil, mycophenolate sodium, corticosteroids, azathioprine. Concomitant belatacept administration is not permitted. To minimize confounding factors, efforts will be made between UCSD, UCI, UC Davis, and UCLA to synchronize a similar organ specific maintenance immunosuppressive regimen across the four sites. However, each subject's maintenance regimen will ultimately be at the discretion of the treating physician. The tacrolimus level will be maintained between 4-11 ng/dL during the duration of the study.

6.2.9 Study Visits and Post randomization follow-up

A total of 7 visits, over a 12-month period, are planned as follows. All subjects will continue to receive routine labs as part of their standard of care from their treating physician. For detailed information about the study labs schedule see Table 5 Study Schedule. Safety labs are done as part of their standard of care from their treating physician.

Subjects on Phase 1 who need more study drug medication before his or her next study visit, will receive a new supply from clinic. Subjects on Phase 2 will receive drug from their pharmacy/hospital.

First (Baseline) Visit (up to 14 days after transplant but before the study subject is discharged from the hospital):

- Subject reviews and signs consent form
- Review of subject's medical history
- Review of subject's current medications
- Review of subject's physical exam including vital signs (blood pressure, temperature, pulse and respiration rate), height and weight
- Review of clinical labs
- Randomization of subject in Phase 1 only
- Subject will receive drug at discharge.

Month 1 Visit:

- Review of subject's current medications
- Review of subject's physical exam including vital signs (blood pressure, temperature, pulse and respiration rate), height and weight
- Review of any changes in subject's health and any reactions to the study medication will be recorded
- Review of routine standard of care clinical labs

- Subject returns completed dosing diary and receives new dosing diary
- Subject will receive drug if applicable

Month 2/3 Visit:

- Review of subject's current medications
- Review of subject's physical exam including vital signs (blood pressure, temperature, pulse and respiration rate), height and weight
- Review of any changes in subject's health and any reactions to the study medication will be recorded
- Subject returns completed dosing diary and receives unfilled dosing diary
- Subject will receive drug if applicable

Month 6/9/Visit:

- Review of subject's current medications
- Review of subject's physical exam including vital signs (blood pressure, temperature, pulse and respiration rate), height and weight
- Review of any changes in subject's health and any reactions to the study medication will be recorded
- Review of routine standard of care clinical labs
- Subject returns completed dosing diary and receives unfilled dosing diary
- Subject will receive drug if applicable.

Month 12 Visit (End of Study Visit):

- Review of subject's current medications
- Review of any changes in subject's health and any reactions to the study medication will be recorded
- Review of routine standard of care clinical labs
- Subject returns final completed dosing diary
- Subject returns any drug remaining in his or her possession to the study team if applicable (Phase 1 only).

A safety follow-up phone call will be made at month 13 (+/- I week) to record patient's wellbeing and graft survival. This call will serve as the last AE follow-up if any was reported at month 12.

Routine Standard of Care Clinical Labs

All subjects will continue to have routine blood and urine collection to monitor kidney function as part of their standard of care treatment at UCLA or UCSD, UCI, and UC Davis. These routine blood collections are not included in the total blood for the study discussed above. The schedule for these routine blood and urine collections will depend on the subject's condition and will be at their treating physician's discretion.

6.3 Adherence

Adherence will be measured with daily medication diaries, and with the coefficient of variation of tacrolimus in subjects' blood.

6.4 Blinding/Unblinding

As this is an open label study, no arrangements need to be made for blinding or potential unblinding.

6.5 Prohibited and Restricted Therapies During the Study

Use of experimental drugs and the immunosuppressive medication belatacept are prohibited for study participants.

DRUG INTERACTIONS

- Mycophenolic Acid Products: Can increase MPA exposure after crossover from cyclosporine to Prograf; monitor for MPA-related adverse reactions and adjust MMF or MPA-dose as needed
- Nelfinavir and Grapefruit Juice: Increased tacrolimus concentrations via CYP3A inhibition; avoid concomitant use
- CYP3A Inhibitors: Increased tacrolimus concentrations; monitor concentrations and adjust tacrolimus dose as needed with concomitant use as per routine clinical care.
- CYP3A4 Inducers: Decreased tacrolimus concentrations; monitor concentrations and adjust tacrolimus dose as needed with concomitant use as per routine clinical care.

Limitations of Use:

- Do not use simultaneously with cyclosporine
- Intravenous use reserved for subjects who cannot tolerate capsules orally
- Use with sirolimus in kidney transplant has not been established

CONTRAINDICATIONS

- Hypersensitivity to tacrolimus or HCO-60 (polyoxyl 60 hydrogenated castor oil)

6.6 Non-therapy Precautions and Restrictions

Subjects should not eat grapefruit or drink grapefruit juice in combination with Prograf or generic tacrolimus. Subjects will be instructed to avoid eating grapefruit and drinking grapefruit juice during the study.

6.7 Withdrawal of Subjects from Study

All efforts should be made to follow all subjects for the entire duration of the study.
Withdrawal of a subject from study medication does not imply that the subject is withdrawn from the study. Subjects MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:

• Withdrawal of informed consent (subject's decision to withdraw for any reason)
• Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy and further participation in the study (including obtaining vital status of the subject and allograft) is not in the best interest of the subject.
• If the subject's physician switches them from tacrolimus to another immunosuppressant medication for their safety
• Termination of the study
• Subjects who become prisoners or become involuntary incarcerated for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

EARLY WITHDRAWAL:

Subject participation in this study will last for approximately 1 year. If the subject withdraws at any time early from the study, for any reason, the subject will be interviewed 30 days after leaving the study to check on how the subject is doing after coming off the study drug. This follow-up is to evaluate their safety.

7.0 STUDY PROCEDURES AND OBSERVATION

7.1 Time and Events Schedule

The following windows are permitted for subsequent doses:

Visit	Visit Window
Month 1-3	Target date ± 3 days
Month 6 -12	Target date ± 7 days

7.2 Study Visits

Baseline Visit

At the baseline visit, 2-14 days after transplantation, subjects will undergo screening for eligibility by review of inclusion and exclusion factors and informed consent as administered by study personnel. Subjects will be consented in the privacy of their own rooms. The PI will review the informed consent with the patients and the subjects will have ample time to ask questions. Once the subject has signed the consent form then they will be given a copy of the signed consent form. After subjects have been consented, the following steps will be taken: Randomization to Arm 1 or 2 (for Phase 1 only), review of medical history and concomitant medications, review of labs, vital sign evaluation, and physical examination. Subjects will receive a study diary to record the name of the drug, dates, and times of taking tacrolimus (see Appendix 2 for Subject Diary).

Visits 1,2,3,6,9, and 12

At each additional study visit (Month 1, 2, 3, 6, 9, and 12 (End of Study Visit), (see Schedule of Events below), subjects will undergo a review of medical history and concomitant medications, review of labs, vital sign evaluation and physical examination. For more details see Table 5 Study Schedule. At the 12-month visit, subjects will return the study diary, any remaining study drug, and any related study materials. The study dosing diary will be reviewed at each study visit when available.

Trough levels will be monitored throughout the study (see Table 3 for Trough Level schedule). Subjects will continue to have routine blood and urine collection to monitor kidney function as part of their standard of care treatment at UCLA, UCSD, UCI, or UC Davis. The results of a few of these labs will be collected as part of study safety labs. For more details see Appendix 1.

Table 5 - Study Schedule

	Baseline	1 mo.	2 mo.	3 mo.	6 mo.	9 mo.	12 mo.
Obtain informed consent	x						
Confirm inclusion/exclusion	x						
Review medical history	x	x	x	x	x	x	x
Review physical exam	x	x	x	x	x	x	x
Review concomitant medications	x	x	x	x	x	x	x
AE monitoring (Safety labs)		x	x	x	x	x	x
Review of labs	x	x	x	x	x	x	x
Randomization *	x						
Tacrolimus dispensation (if applicable)	x	x	x	x	x	x	
Tacrolimus level from routine clinical labs		x	x	x	x	x	x
Review dosing diary		x	x	x	x	x	x

*Randomization for Phase 1 only, no randomization will occur during Phase 2 as all subjects will be placed on generic drug.

7.3 Details of Procedures

Study Drug Dispensing:

Drug Supply

The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. Drug supply will be received at the sites from Astellas in the form of bulk bottles, with the pharmacist or designated study staff allocating the necessary units to standard 30, 40, 60 gram pill bottle vials. Phase 2 generic medication will be supplied and obtained through subject's insurance from their local pharmacy or hospital.

Compliance

The diary will be used to verify compliance. If subjects demonstrate continued noncompliance of study drug dosing, despite educational efforts, the investigator may withdraw the subject from the study.

Local Labs:
Local laboratories at each study site will be used for all standard-of-care (including tacrolimus trough levels).

Safety Assessments:
Safety assessments include AEs, clinically significant changes in vital signs, physical examination, and laboratory test abnormalities. The investigator will determine the severity of each AE as mild, moderate, severe, or very severe in accordance to the Common Terminology Criteria for Adverse Events (CTCAE)[1]. In addition, the investigator will determine the relationship of the AE to the administration of the study drug.

Urine or serum pregnancy tests will be performed prior to the first dose for all WOCBP. If any female subject becomes pregnant, she will be immediately discontinued from study medication. Standard of care for a pregnant woman will be determined by her treating physician based on her condition and medical need. In addition, for women who become pregnant while using MMF or within 6 weeks of discontinuing therapy, study personnel or the subject's healthcare practitioner will report the pregnancy to the Mycophenolate Pregnancy Reference Registry (1-800-617-8191) and will strongly encourage the subject to enroll in the pregnancy registry. The subject will also be apprised of the potential hazard of mycophenolate products to the fetus. The risks and benefits of MMF will be discussed with the subject. In certain situations, the subject and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus.

Trough level Monitoring:
In case of study dose adjustments, transplant coordinators and study coordinator will collect and record subjects' trough levels and dose adjustments from their medical records. Subjects will sign a separate HIPAA (*Health Insurance Portability and Accountability Act of 1996)* Form to allow access to their medical record information.

8 DRUG PRODUCT

8.1 Reference product
Astellas will supply brand tacrolimus:
Oblong, hard capsule for oral administration contains anhydrous tacrolimus USP as follows:

- 0.5 mg, light-yellow color, imprinted in red "0.5 mg" on the capsule cap and "logo607"* on capsule body
- 1 mg, white color, imprinted in red "1 mg" on the capsule cap and "logo617"* on capsule body
- 5 mg, grayish-red color, imprinted with white "5mg" on the capsule cap and "logo657"* on capsule body

8.2 Test products
Phase 2 generic medication will be supplied and obtained through their insurance from their local pharmacy or hospital during transplant admission, clinic, hospitalizations, and non-scheduled study visits.

8.3 Drug Product Records at Site
It is the responsibility of the investigator to ensure that a current record of drug product disposition is maintained at each study site where drug product is inventoried and disposed.

9 ADVERSE EVENT REPORTING IN CLINICAL TRIALS

[1] http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

9.1 Importance of Adverse Event Reporting

Timely and complete reporting of safety information assists in identifying any untoward medical occurrence, thereby allowing: (1) protection of the safety of study subjects; (2) a greater understanding of the overall safety profile of the drug products; (3) recognition of dose-related toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to worldwide regulatory requirements.

9.2 Adverse Events: Adverse events will be recorded using the current definition of National Cancer Institute common terminology criteria for adverse events (CTCAE).

Definitions:
Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Adverse Event (21 CFR 312.32(a): An *adverse event* (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Serious Adverse Event:

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-Threatening Adverse Event:
An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

9.3 Collection of Safety Information

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre -existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. Subjects will be asked to report any AEs to the study team.

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

An important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs (See Section 9.4 for reporting pregnancies).

NOTE: The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an “important medical event” or a life threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. If known, the diagnosis of the underlying illness or

disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the event was administered, it should be recorded in the study file. The investigator must supply the IRB with any additional information requested, notably for reported deaths of subjects.

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent using the same procedure used for transmitting the initial SAE report. All SAEs and AEs should be followed to resolution or stabilization.

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. NSAE information should also be collected from the start of period or other observational period intended to establish a baseline status for the subjects. NSAEs and AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow up is also required for NSAEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified NSAEs must be documented appropriately.

Adverse Events will be reported to Institutional Review Boards (IRBs) according to regulations.

Adverse Event Reporting to the Food and Drug Administration (FDA)

- Adverse Event Reporting
    - Within 10 working days of discovery: PI will report these types of AE/SAE to the FDA Project Officer (PO) (Murewa Oguntimein)
        - Not expected, i.e. not listed in the informed consent document or the investigator's brochure/protocol;
        - An expected adverse event that occurs at a greater frequency or duration than expected;
        - Requires modification of the protocol and/or informed consent document
    - Serious Adverse Events: within 10 days after discovery. PI will report these types of SAEs to the FDA PO and Medical Officer.

SAEs will be reported to Murewa Oguntimein from the FDA within 10 working days of discovery using the investigator adverse event reporting form.

The quarterly progress reports will include an aggregate analysis of SAEs in the Safety report section of the documents.

9.4 Pregnancy Reporting

Any pregnancy that occurs during study participation should be reported using a Pregnancy Form. To ensure subject safety, each pregnancy must also be reported to the FDA's PO within 24 hours of learning of its occurrence. 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, congenital abnormalities, or maternal and newborn complications. For additional instructions for rapid notification of pregnancies please see Section 9.5.

9.5 Instructions for Rapid Notification of Pregnancies

Each pregnancy that started during the study must be reported by the investigator to the FDA within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up should be

reported on the Study Pregnancy Form, but any SAE experienced during pregnancy must be reported on the AE/SAE CRF (refer to Section 9.4).Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their relations to the study drug.

10 ADMINISTRATIVE SECTION

10.1 Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

• IRB for review and approval/favorable opinion
• Regulatory authority (ies), if required by local regulations.

10.2 Informed Consent

Investigators must ensure that subjects or their legally authorized representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate.

10.2.1 Informed Consent Procedures

Preparation of the consent form is the responsibility of the investigator, and will include all elements required by ICH, GCP, applicable regulatory requirements, and the ethical principles that have their origin in the Declaration of Helsinki. The consent form will also include a statement that regulatory authorities have direct access to subject records. Prior to the beginning of the study, the investigator will have the IRBs written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The investigator will provide the subject or legally authorized representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language will be non-technical and easily understood. The investigator will allow time necessary for the subject or the subject's legally authorized representative to inquire about the details of the study. The informed consent will be signed and personally dated by the subject or the subject's legally authorized representative and by the person who conducted the informed consent discussion. The subject or legally authorized representative will receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the trial.

10.2.2 Illiterate Subjects

If the subject or legally authorized representative is unable to read, a reliable and independent witness will be present during the entire informed consent discussion. The choice of the witness must not breach the subject’s rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. Family members or acquaintances are appropriate independent witnesses. After the subject or legally authorized

representative orally consents and has signed, if capable, the witness will be instructed to sign and personally date the consent form, attesting that the information is accurate and that the subject or legally authorized representative has fully understood the content of the informed consent agreement and is giving true informed consent.

10.2.3 Update of Informed Consent

If important new information becomes available that is relevant to the subject's consent, the informed consent, and any other information provided to subjects or their legally authorized representatives, will be revised and approved by the IRB prior to use. The investigator, or a person designated by the investigator, will fully inform the subject or the subject's legally authorized representative of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication will be documented.

During a subject's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the subject.

10.3 Records and Reports

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug product. Designated investigator staff will enter the data required by the protocol into Case Report Forms (CRFs). The confidentiality of records that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

10.4 Institutional Review Board (IRB)

Before study initiation, the investigator will have written and dated approval/favorable opinion from the IRB for the protocol, consent form, product labeling, and any other written information to be provided to subjects. The investigator will provide the IRB with reports, updates, and other information (e.g., amendments, administrative letters) according to regulatory requirements or institution procedures.

10.5 Records Retention

The investigator must retain drug product disposition records, copies of case report forms (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB).

The study records will be retained at least three years and records relating to research which is conducted shall be retained for at least 3 years after completion of the research per policy 45 CFR 46.115 Protection of Human Subjects 21 CFR 56.115 IRB Records. The study records will be stored with Iron Mountain in a secure location and will l be destroyed according to regulations.

References

1. Solez K, Colvin RB, Racusen LC, Haas M, Sis B, Mengel M, Halloran PF, Baldwin W, Banfi G, Collins AB, Cosio F, David DS, Drachenberg C, Einecke G, Fogo AB, Gibson IW, Glotz D, Iskandar SS, Kraus E, Lerut E, Mannon RB, Mihatsch M, Nankivell BJ,

Nickeleit V, Papadimitriou JC, Randhawa P, Regele H, Renaudin K, Roberts I, Seron D, Smith RN, Valente M. Banff 07 Classification of Renal Allograft Pathology: Updates and Future Directions. *American Journal of Transplantation*. 2008 Apr; 8(4):753-60.

Appendix 1

The following safety labs in these tables are done as part of the standard of care. These are not additional labs required for the study.

Study Safety labs for Kidney Transplant Subjects

	Baseline	1 mo.	2 mo.	3 mo.	6 mo.	9 mo.	12 mo.
Comprehensive metabolic panel	x	x	x	x	x	x	x
Calcium	x	x	x	x	x	x	x
Magnesium	x	x	x	x	x	x	x
Phosphorus	x	x	x	x	x	x	x
CBC with differential	x	x	x	x	x	x	x
Urinalysis	x						

Appendix 2

Subject Dosing Diary:

1U01FD-14-020 Study Diary **IRB: 14-001423** **Diary of:**			Month
Site Number: Subject ID: Previous Tacrolimus Daily Dose: mg		New Daily Dose: mg Dispensing Visit Number: Next Expected Dispensing Visit Number: Next Expected Dispensing Visit Date:	
Day	Date	Morning Dose mg	Evening Dose mg
1			
2			
3			
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