RANDOMIZED CONVERSION OF CALCINEURIN-INHIBITORS (TACROLIMUS TO SIROLIMUS) AT 6-24 MONTHS POST TRANSPLANT IN A PREDNISONE-FREE IMMUNOSUPPRESSION REGIMEN: IMPACT ON INCIDENCE OF ACUTE CELLULAR REJECTION, RENAL ALLOGRAFT FUNCTION AND LYMPHOCYTES FUNCTION

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Study Product:	*Pfizer Pharmaceuticals* *Calcineurin Inhibitors, tacrolimus/Prograf®, sirolimus/Rapamune® and Cellcept®/mycophenolate mofetil/MMF*

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CONFIDENTIAL

Background

Immunosuppressive therapy with the calcineurin inhibitors (CI) Cyclosporine (CsA) and Prograf®/tacrolimus (Tac), have radically changed the field of organ transplantation. Ironically, although extensively and effectively used for kidney transplantation and other solid organ transplants, CsA and Tac cause important adverse renal side effects: acute and chronic renal dysfunction, hemolytic-uremic syndrome, hypertension, electrolyte disturbances and tubular acidosis.

Chronic nephrotoxicity from CI has been implicated as a principal cause of post-transplant renal dysfunction [1,2] and it is characterized by an irreversible and progressive tubular atrophy, interstitial fibrosis, and focal hyalinosis of small renal arteries and arterioles [3-5]. Early reports in cardiac transplant recipients by Myers et al. [6] clearly demonstrated the risk of chronic nephropathy with interstitial fibrosis in patients receiving CsA. Furthermore, reports by Goldstein et al. [7] and Hornerberger et al. [8] demonstrated that end-stage renal disease developed in 4.3-6.5% of patients receiving heart transplants after 72-82 months of therapy with CsA. Similarly, liver transplant patients maintained on CI have been shown to develop chronic kidney disease.

In a retrospective analysis, Fisher et al. showed a strong association of early (3 months post-transplant) kidney dysfunction and the risk of developing severe CFR post liver transplant [9]. Gonwa et al. [10] reported an18% incidence of severe renal dysfunction at 13 years after orthotopic liver transplant and more important, the development of ESRD was associated with decreased patient survival. The increased mortality in patients with non-renal transplants with chronic renal failure was recently confirmed in a larger population-based cohort analysis [11]. In this study the incidence of chronic renal failure (CRF) in 69,321 patients who received non-renal transplants was 16.5% and CRF was associated with an increase in mortality by a factor of more than four. Risks factors for developing renal failure included: older age, pre-transplant hepatitis C infection, hypertension, diabetes mellitus and chronic exposure to CI.

In renal transplant recipients, complete avoidance of calcineurin inhibitors from the time of renal transplant surgery has been associated with increased incidence of acute cellular rejection. Conflicting data is available regarding the impact of CI avoidance on long term renal allograft function.

We recently completed a retrospective analysis that evaluated renal transplant recipients in which calcineurin inhibitors have been substituted with sirolimus at 1 year post transplant and assessed the risk of rejection, patient and graft loss and renal allograft function. (Please see attached abstract submitted and accepted at the ATC 2007).

From this analysis we concluded that, in a prednisone-free regimen, the conversion from calcineurin inhibitors to sirolimus at 1 yr. post-transplant was not

associated with an increased risk of acute rejection or graft loss. A trend towards a better GFR was noted after conversion from calcineurin inhibitors to sirolimus.

Little is known of the impact of immunosuppressive changes post renal transplant on lymphocytes function.

Research Objective

The aim of the present study is to prospectively investigate the impact of CI conversion (tacrolimus→sirolimus) between 6 and 24 months post-transplant on the incidence of acute cellular rejection, renal allograft function and lymphocytes function.

Primary aim of the study is:

to investigate the impact of CI conversion (tacrolimus→sirolimus) on the incidence of acute cellular rejection.

Secondary aims of the study are:

i) evaluate whether CI conversion (tacrolimus→sirolimus) contributes positively or negatively on the renal allograft function calculated with e-GFR and proteinuria;

ii) patient and graft survival ;

iii) evaluate if CI conversion impacts on lipid profile, incidence of hypertension, malignancies, and opportunistic infections and post-transplant DM;

iv) evaluate possible modifications of lymphocytes function before and after conversion (tacrolimus→sirolimus)

v) assess tubular toxicity by evaluating urinary biomarkers

Methods

Immediate Post Transplant Period

Patients will receive immunosuppressive therapy as follows:

Induction immunotherapy:

1) Campath®/alemtuzumab (Anti CD52 humanized monoclonal antibody) (30mg IV), on the day of the kidney transplant,
2) methylprednisolone (500 mg IV) on the day of transplant and on day 1 (250 mg IV) and 2 (125 mg IV) post-transplant.

No further steroid will be given post-transplant unless indicated by the following medical conditions: acute renal allograft rejection, renal disease that might require the use of steroids and other systemic diseases such as rheumatoid arthritis (RA), systemic lupus erthematosus (SLE), asthma. Patients

will receive tacrolimus and Cellcept®/mycophenolate mofetil/MMF. The above medication regimen is our standard of care for renal transplant patients, and has been since 2000.

Randomization

For this research study, between 6 and 24 months post-transplant we plan to prospectively randomize 2:1 renal transplant patients to either:

-Continue with tacrolimus and MMF or

-Substitute tacrolimus with sirolimus and continue MMF

A total of 400 pts. are expected to be screened for the randomization and we expect to be able to randomize 275 renal transplant patients into this protocol.

Data Collection

The following data will be collected at the time of randomization:

Recipient demographics- such as age at transplantation, sex and race.

Clinical history- Causes of end-stage renal disease, past medical history

Transplant related information- donor age, cadaveric versus living kidney transplant, histocompatibility and cross match data, viral serology, history of acute rejection and delayed graft function, use of induction therapy and immunosuppressants, use of ACEI and/or ARB, level of renal allograft function- estimated GFR (e-GFR(12) using MDRD formula, proteinuria.

Peripheral blood leukocytes will be obtained from renal transplant recipients for baseline (prior to randomization) lymphocytes functional activity and characterization of lymphocytes subpopulations by flow cytometry analysis.

Peripheral donor leukocytes (from living donor patients) will also be obtained at the time of randomization. These donor leukocytes will be used as stimulator cells to study the functional activity of the recipient's lymphocytes function.

Post randomization

The recipients assigned to continue with tacrolimus and MMF will be routinely followed at our outpatient Transplant center with monthly labs. In addition to the baseline pre-randomization labs, at 6, 12 and 24 months post randomization, peripheral blood leukocytes will be obtained to study lymphocytes functional activity and to characterize lymphocytes subpopulations by flow cytometry analysis.

Post randomization, the recipients assigned to switch from tacrolimus to sirolimus and continue with MMF will be routinely followed at our Transplant center with monthly labs. Furthermore, during the period of conversion from tacrolimus to sirolimus, weekly labs will be obtained to monitor renal function and bone marrow function. In addition to the baseline pre-randomization labs, and labs collected at 6, 12,24, 36, and 48 months post randomization, peripheral blood leukocytes will be obtained to study lymphocytes functional activity to characterize lymphocytes subpopulations by flow cytometry analysis and urine will be collected to assess tubular toxicity by evaluating urinary biomarkers.

Both groups of patients will be followed for 4 years post-randomization. In addition to monitoring renal allograft function, we will evaluate the incidence of acute rejection, patient and graft survival, the impact of CI conversion on the lipid profile, the incidence of hypertension, malignancies, opportunistic infections and post-transplant DM.

Furthermore, with the peripheral leukocytes obtained at baseline prior to randomization and at 6, 12,24, 36, and 48 months post-randomization we will investigate possible modifications of lymphocytes function and of the lymphocytes subpopulations that might have occurred as a consequence of the switch from tacrolimus to sirolimus.

Biopsy

Chronic nephrotoxicity from calcineurin-inhibitors (CI) has been implicated as a principal cause of post-transplant renal dysfunction and it is characterized by an irreversible and progressive tubular atrophy, interstitial fibrosis, and focal hyalinosis of small renal arteries and arterioles. Furthermore, chronic nephrotoxicity from CI has been documented in all non-renal transplants and the chronic renal failure secondary to the use of CI has been associated with an increase in mortality by a factor of more than four.

The present proposal is to identify those subjects already participating in this study who are willing to undergo a kidney biopsy with the aim of evaluating renal allograft pathology and renal allograft tissue gene expression profiles of the two groups of patients maintained on Tacrolimus/ MMF or switched to SRL/MMF. Performing kidney biopsies on the subjects who consent for the procedure will allow us to address the effect of immunosuppressive modifications on renal allograft pathology at 24 months post randomization. We also plan to obtain renal allograft biopsies at 12 months post-transplant (standard of care) in order to establish a baseline parameter for to compare the 24 month sample. An additional biopsy at 48 months will allow us to examine long term results of graft function. We also plan to obtain renal allograft biopsies to be stored in RNA later to further extend our knowledge on the effect of CI free immunosuppression on gene expression profiles.

Obtaining renal allograft tissue samples at 24 and 48 months post randomization can have potential important ramifications to help explain the mechanisms of fibrosis and tubular atrophy typically associated with CI and the role of CI elimination with the substitution of SRL. All data will then be analyzed comparing gene expression profiles of peripheral blood (Paxgene tubes are routinely collected at the different time points as part of the original study). Based on power analysis, we will perform 24 and 48 months post randomization biopsies in 70% of the total subjects enrolled in the study (approximately 46 subjects from the tacrolimus/MMF group and approximately 93 subjects from the sirolimus/MMF group).

Donors

Donor cells are essential in our study to evaluate the effect of different immunosuppressive agents alone or in combination on the process of allo-recognition. Donor cells from living donors have been being collected (there is a specific informed consent form for donors) and will continue to be collected when possible. Approximately 275 donors will be recruited for this study.

While the process of obtaining donor cells from living donors is easy, recipients of a deceased donor kidney have, by definition, no living donor. Consequently, we cannot fully study their immune system. Instead, we would like to utilize already stored deceased donor cells to perform the experiments originally proposed in our ongoing project. We will use only donor cells from deceased donors whose families have consented to research.

Primary Safety Endpoints

The primary safety endpoints will be assessed on the adverse events (AEs) and serious adverse events (SAEs) that are observed throughout the trial.

Treatment of Acute Renal Allograft Rejection

Initial treatment for biopsy-confirmed acute rejection for all subjects will be pulse corticosteroids (methylprednisolone 500 mg IV x 3 days), tapered to a dose of 20 mg prednisone by day 7, unless the severity of the initial episode warrants use of anti-T-lymphocyte antibody (OKT3 or Thymoglobulin). Recurrent rejection will be treated with anti-T-lymphocyte antibody (OKT3 or Thymoglobulin).

Subject Selection and Withdrawal

The study will be conducted at Northwestern Medical Faculty Foundation/Northwestern Memorial Hospital/ Northwestern University and subjects will be recruited from the patients seen in the Division of Solid Organ Transplantation. A total of 400 recipient subjects will be screened and we expect that 275 recipients will be prospectively studied. The study will be conducted in recipients of living donor kidneys and deceased donor kidneys. Patients who satisfy the following inclusion/exclusion criteria will be eligible for the study.

Inclusion Criteria

1) Subjects should be adults ≥ 18- ≤ 70 years of age
2) Subjects can be either gender or of any ethnic background
3) Subjects should be single organ recipients (kidney only)
4) Subjects must be able to understand the protocol and provide informed consent.

Exclusion Criteria

1) Subjects with ESRD secondary to primary FSGS (focal segmental glomerulonephritis).
2) Inability to comply with study procedures
3) Inability to sign the informed consent
4) Subjects with a significant or active infection
5) Subjects who are pregnant or nursing females
6) Subjects with a history of severe hyperlipidemia not controlled with statins, patients with at total cholesterol of > 400 mg/dl
7) Subjects with a platelet count <100,000mm^3 WBC< 2,000mm^3
8) Subjects with severe proteinuria at the time of randomization (>2gm/day)
9) Subjects with more than 2 episodes of acute cellular rejection post transplantation will be excluded from this study
10) An estimated GFR<40 cc/min (This will be calculated by MDRD or by Cockcroft-Gault formulas, which are both are commonly used formulas for estimated GFR.)
11) A history of malignancy during the post-transplant period (other than treated basal cell cancer and/or squamous cell cancer)
12) Subjects, who, due to the existence of a surgical, medical or psychiatric condition, other than the current transplant, which in the opinion of the investigator, precludes enrollment into this trial
13) A history of ACR during the most recent previous 3 months prior to randomization

**Other: prior to approaching any individual who has undergone desensitization procedures prior to transplant, we must first check with Dr. J. Friedewald

Subject Recruitment and Screening

The study will be conducted at Northwestern Medical Faculty Foundation/Northwestern Memorial Hospital/ Northwestern University and subjects will be recruited from the patients seen in the Division of Solid Organ Transplantation. A total of 400 recipient subjects will be screened and we expect that 275 recipient patients to be prospectively studied.

Early Withdrawal of Subjects

When and How to Withdraw Subjects

Subjects may withdraw from the clinical trial at any time for any reason with no prejudice to their medical care. Subjects may also be stopped in the study without their consent if their medical care requires they be. Also, the Institutional Review Board (IRB) may stop the study at any time and all subjects will be returned to taking tacrolimus and followed for safety. Subjects will be informed of why they are being stopped.

Subjects non-compliant with medications and clinic follow-ups will be withdrawn from the study.

Subjects with post-transplant complications such as malignancy or infections that require modification or withdrawal of maintenance immunosuppression will be withdrawn from the study.

Data Collection and Follow-up for Withdrawn Subjects

Even though subjects may be withdrawn prematurely from the study, an attempt will be made to collect at least survival data on such subjects throughout the protocol defined follow-up period. Such data is important to the integrity of the final study analysis, since early withdrawal could possibly be related to the safety profile of the study. If a subject withdraws consent to participate in the study, attempts will be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period.

Study drugs

Sirolimus (Rapamune®)

Sirolimus will initially be given at a dose of 2-4 mg orally (PO) daily. The dose will be modified to achieve 24 hours trough concentrations of 6-10 ng/ml by HPLC assay. This medication will be given in an open label fashion. The first dose of sirolimus will be given at the time of randomization to those patients assigned to have tacrolimus switched to sirolimus.

Mycophenolate Mofetil (Cellcept ®)

Cellcept® will be given at a dose of between 750 to 1000 mg PO twice daily. The first dose will be given on Day 0 (day of kidney transplant surgery). This medication will be given in an open label fashion. There will not be any change in the dose of Cellcept® at the time of randomization unless indicated by medical reasons (i.e. Neutropenia, GI side effects.)

Tacrolimus (Prograf®)

Tacrolimus will be given 1-2 mg PO twice daily, beginning Day 1 (post-operative Day 1). The dose will be modified to achieve 12 hour trough concentrations of 6-10 ng/ml. This medication will be given in an open label fashion.

Alemtuzumab (Campath®)

The first dose of Campath® will be 30 mg given IV, and administered intra-operatively during renal transplantation. This medication will be given in an open label fashion and will only be administered while the patient is in the hospital in the immediate post-transplant period.

Corticosteroids (methylprednisolone)

Time:	**Dose**
Preop (Intraop/Day 0)	500 mg
POD#1 (Day1)	250 mg
POD#2 (Day2)	125mg
POD#3(Day 3)	0 mg

Statistical Analysis

Once the 2 groups of renal transplant patients are identified, two sample t tests will be used to compare differences in continuous variables between groups; chi square tests will be used to compare differences in discrete variables. Multivariable logistic regression analysis will be also performed to identify the combination of clinical variable that are significantly associated with the development of acute rejection and renal allograft function after conversion from tacrolimus →sirolimus.

Safety and Adverse Events

For the purpose of this clinical trial, the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE), dated December 12, 2003 will be used to grade all adverse events.

Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

The investigator will notify the drug manufacturer, IRB, and FDA of any death or adverse event occurring at any time after a subject has discontinued or

terminated study participation that may reasonably be related to this study. The drug manufacturer, IRB, and FDA will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery will ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Recording of Adverse Events

At each contact with the subject, the investigator/member of investigator's team will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 25 days of the investigator/sponsor's knowledge of the event if this event meets UPIRSO criteria. Copies of each report and documentation of IRB notification and receipt will be kept in the regulatory binder for the clinical trial.

FDA Notification by Sponsor

The principal investigator/sponsor shall notify the FDA and study drug manufacturer by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug within 24 hours of the investigator/sponsor's knowledge of the event.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the principal investigator/sponsor will submit the adverse event in a written report to the FDA and study drug manufacturer as soon as possible, but no later than 15 calendar days from the time the determination is made.

Stopping Rules

Subjects diagnosed with two acute renal allograft rejection episodes post conversion from tacrolimus to sirolimus will be stopped from participating in the study and will be switched back to tacrolimus.

Subjects that develop significant side effects secondary to sirolimus (severe thrombocytopenia (platelets count <50, 000); severe hyperlipidemia not controlled by the use of statins or other cholesterol lowering agents; worsening proteinuria or severe de-novo proteinuria will have sirolimus stopped and patients will be switched back to tacrolimus

Subjects developing post-transplant infections (i.e., UTI, CMV,HSV, EBV, HCV, HBV, HIV,PCP), that in the opinion of the investigator are detrimental to the subject and their participation in this research trial, will be stopped from participating in this study.

Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 Study Monitoring, Auditing and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Internal Data and Safety Monitoring Plan

An Internal Data and Safety Monitoring Plan, is based on the GCRC and some NIH guidelines for Data Safety Monitoring. All physicians associated with the Solid Organ Transplant Department are listed as either the PI or Sub-I's with this study. The plan approved by the IRB would utilize the statistical analyst along with the current QA committee to review the research SAE's and AE's.

Data Handling and Record Keeping

Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or

magnetic media, x-rays, biopsy slides, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" is placed in the space. If the item is not applicable to the individual case, "N/A" is written in the space. All entries should be printed legibly in black ink. If any entry error has been made, forensic correction is made by drawing a single straight line through the incorrect entry and the correct data is entered above it. All such changes must be initialed and dated. Errors are not to be erased or covered with "white-out". For clarification of illegible or uncertain entries, the clarification is written above or next to the item, then initialed and dated.

Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), (Northwestern University Institutional Review Board), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the investigator/sponsor before commencement of this study. The investigator will place a list of IRB members and their affiliate in the regulatory binder for the clinical trial.

All subjects for this study will be provided with a copy of the consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, will be obtained before the subject is submitted to any study procedures. This consent

form will be signed by the subject and the investigator-designated research professional obtaining the consent. The subject will be given a signed copy of the informed consent for their records.

Study Finances

This study is financed through Northwestern Memorial Foundation, divisional funding, and Pfizer Pharmaceuticals (as of March 2008).

Conflict of Interest

Any investigator who has a conflict of interest with the study (patent ownership, royalties, or financial gain greater than the minimum allowable by Northwestern University) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee- sanctioned conflict management plan prior to participation in this study. All Northwestern University investigators will follow the University conflict of interest policy. The investigators will sign conflict of interest document number ORSP-100, as per Northwestern University IRB guidelines.

Subject Stipends or Payments

All study related laboratory tests (flow cytometry analysis of peripheral lymphocyte and functional assays of lymphocytes will be provided to the subject free of charge). Subjects will be provided with reimbursement for parking on study related visits.

In addition, because most of the recipients' donors do not usually need to return to this center's transplant clinic beyond one-year post-transplant, a $25 stipend will be paid to donors who come to this center solely to consent for this research study and allow the collection of the one-time blood sample necessary for the study.

Publication Plan

Findings from this study will be presented at scientific meetings as an abstract, a poster or oral presentation. The findings may also be published in peer reviewed professional journals. No subjects will be identified in any manner regardless of the way the results are presented to the scientific community and/or public.

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