RANDOMIZED CONVERSION OF EBV+ KIDNEY TRANSPLANT RECIPIENTS OF LIVING OR STANDARD CRITERIA DONORS AT THREE MONTHS POST TRANSPLANTATION TO BELATACEPT WITH MPA OR BELATACEPT WITH LOW-DOSE TACROLIMUS (50% OF DOSE) COMPARED TO PATIENTS REMAINING ON CENTER SPECIFIC STANDARD THERAPY OF TACROLIMUS AND MPA

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Division of Organ Transplantation

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Hypothesis

Belatacept-based immunosuppressive therapy will result in improved renal function at 1 year post transplant compared to the combination of tacrolimus & MPA in living donor or deceased donor kidney transplant recipients.

Background and Rationale

Immunosuppressive therapy with the calcineurin inhibitors (CNI) cyclosporine (CsA) and 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 CNI 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. Attempts to minimize CNIs and their known toxicities have been marginally successful due to unacceptable rates of acute rejection and drug toxicity. Patients are converted to alternative immunosuppressive therapy related to CNI side effects including neurotoxicity, nephrotoxicity, cardiovascular (HTN, hyperlipidemia), metabolic (NODAT), and cosmetic side effects. Furthermore, this class of medications is associated also, by blocking IL2 production, with negative impact on regulatory T cells (Tregs) generation (an important subpopulation of T helper cells that has been associated with positive immunomodulation and donor specific hypo-responsiveness).

Until the approval of Belatacept for adult EBV+ renal transplant recipients, there have been limited alternative immunosuppressive agents available to mitigate drug induced renal impairment. The phase III drug trials of Belatacept in combination with MMF and corticosteroids have resulted in significant and sustained improvement in GFR at one year through three years post transplant. The overall safety of belatacept compared to cyclosporine in de novo transplant recipients was similar. However, there was an increased rate and severity of early acute rejection and PTLD of the central nervous system in patients treated with belatacept.

In a phase II switch study conducted by BMS, the incidence of acute rejection at 24 months post conversion was similar in patients remaining on CNI (4%) compared to those converted to belatacept (7%). There were no reported cases of PTLD in this patient population as of two years post randomization. However, one belatacept patient from Mexico developed tuberculosis and there were more non-serious fungal infections in the belatacept treated patients.

Mechanistically, CD28 and CTLA-4 are important for the function of Tregs. Belatacept binds to CD80/CD86 ligands on antigen presenting cells (APCs) preventing CD28 to bind with these ligands and deliver the costimulatory signal to activate the TCell. CTLA-4 is a related receptor expressed on activated T cells that also recognizes CD80/CD86 and is thus termed coinhibitory. It transmits both cell intrinsic and cell extrinsic negative signals that impair activation.

Investigation of the effect of early conversion to Belatacept at month 3 post-transplant on the subpopulations of T cells and B cells and peripheral blood and allograft biopsy-derived gene expression subpopulation profiles are planned. Optimization of the Belatacept immunosuppressive regimen to achieve good long term renal function and improved graft survival requires understanding the relationships of these cell populations to clinical outcomes.

Objectives

The aims of the study are:

1. To assess the incidence of acute rejection and change in renal function by calculated (MDRD) GFR of adult EBV seropositive renal transplant recipients of living or standard criteria donors converted from Tacrolimus to Belatacept or low dose Tacrolimus with Belatacept at three months post-operatively compared to renal transplant recipients randomized to remain on standard dose Tacrolimus and MPA for maintenance therapy at 1 year post-transplantation

2. To evaluate the impact of three different maintenance immunosuppressive regimens (Tacrolimus and MPA, Belatacept and MPA and Low dose Tacrolimus and Belatacept) on subpopulation of T cells including regulatory T cells and B cell subpopulations at baseline(conversion at 3 months post-transplant), 6, 12, & 24 months post-transplant by flow cytometry analysis

3. To evaluate the impact of the maintenance immunosuppressive regimens on allograft immunohistopathology and allograft biopsy-derived gene expression profiles in subpopulations at baseline (conversion at 3 months post-transplant),12 months and 24 months post-transplant to coincide with one year SOC biopsy

4. To evaluate the impact of the maintenance immunosuppressive regimens on gene expression profiles in the peripheral blood subpopulations at baseline (conversion at 3 months post-transplant), 6, 12, & 24 months post-transplant

Primary Endpoint

1. Change in eGFR (MDRD) at 1 year post-transplant compared to baseline at month 3 (conversion)

Secondary Endpoints

1. Patient and graft survival
2. Incidence and severity of biopsy proven acute rejection
3. Incidence of new onset post-transplant diabetes mellitus
4. Incidence, timing and severity of bacterial, viral and fungal infections
5. Incidence, timing and severity of malignancies
6. Incidence of hyperlipidemia

Treatments (Group-Specific)

All subjects (N=43) will be randomized (1:1) to one of two treatment arms after enrollment at "Visit 1" (a standard-of-care clinic visit approximately 90 days post-transplant):

1. Conversion from Tacrolimus to Belatacept (Belatacept + MPA) CLOSED TO ENROLLMENT
2. Conversion to low-dose Tacrolimus and Belatacept (Belatacept + Low-Dose Tac)
3. Maintain standard tacrolimus regimen (Tacrolimus + MPA)

Subjects will be randomly assigned to one of the two groups, according to a computer-generated list and block randomization scheme. This method ensures a balance in sample size across groups over time. All possible balanced combinations of assignment within the block (i.e., equal number for all groups within the block) will be calculated. Blocks are then randomly chosen to determine the patients' assignment into the groups.

The lower limit for thee tacrolimus trough will correspond to the lowest level of tacrolimus detectable by the assay run at Northwestern (2 ng/ml per Northwestern's transplant pharmacist).

This a novel evaluation of the belatacept + tacrolimus regimen; as such, we anticipate that the belatecept + tacrolimus combination administered to subjects in Group 2 will provide sufficient immunosuppression in comparison with those receiving standard of care treatment. At the time of conversion (3 months post-transplant) induction therapy from time-of-surgery should still have a protective immunosuppressive effect.

The treatment regimens/group are described below:
Group 1 (belatacept + MPA): subjects continue MPA per SOC, receive bimonthly infusions of belatacept while gradually reducing and then discontinuing tacrolimus-CLOSED TO ENROLLMENT- based on DSMB recommendations-please see letter attached

Belatacept: 5 mg/kg IV on Day 1, 15, 29, 43, and 57 post-conversion, then monthly thereafter.

Tacrolimus tapered over one month as follows:
Days 1- 14: SOC administration
Day 15 (~ 2 weeks into study): 40–60% of the previous dose
Day 21 (~ 3 weeks into study): 20–30% of the previous dose
Day 30 (about 1 month): discontinue

MPA: administered according to SOC

Group 2 (belatacept + Low calcineurin inhibitors (CNI) dose): subjects discontinue MPA, receive bimonthly infusions of belatacept while gradually reducing to a lowered dose of CNI.

Belatacept: 5 mg/kg IV on Day 1, 15, 29, 43, and 57 post-conversion, then monthly thereafter.

CNI tapered over one month as follows:
Days 1- 14: SOC administration
Day 15 (~ 2 weeks into study): 10% of the previous dose
Day 21 (~ 3 weeks into study): 20% of the previous dose
Day 30 (~ 1 month into study): 20% of the previous dose Target trough level ≤ 5 mg per ml of tacrolimus thereafter.

Group 3: (CNI + MPA standard treatment regimen)

CNI: administered to target therapeutic levels per institutional SOC

MPA dose adjustments for gastrointestinal side effects or leukopenia will be made at the discretion of the investigator.

Sample Collection (All Groups)
During this switch subjects will be asked to have weekly labs to monitor bone marrow function and kidney function (routine post-transplant blood tests).

All subjects regardless of the group to which they were randomized (Group 1, Group 2, Group 3) will have the same types of blood, urine and tissue samples collected for research at the same time points as described below and in Table 1. The study is designed so that all sample collection (blood, urine and tissue) corresponds with standard of care visit time points:

Visit 1: ~ 3months after transplant, time of randomization (± 30 Days)
1) A standard of care kidney biopsy will be performed and additional tissue sample will be taken for research in this study if subject has agreed to the procedure.
2) Subjects will have 50 mL of blood taken and 20cc of urine collected as well as vital signs, weight, and medical history taken.

Visit 2: 6 months after transplant (± 30 Days)
1) Blood, urine and vitals will be collected as in Visit 1

Visit 3: 12 months after transplant (± 45 Days)
1) A standard of care kidney biopsy will again be performed, and a tissue sample will be taken for research in this study if subject has agreed to the procedure.

2) Blood, urine and vitals will be collected as in Visit 1.

Visit 4: 24 months after transplant (± 60 Days)

1) A standard of care kidney biopsy will be performed and additional tissue sample will be taken for research in this study if subject has agreed to the procedure.
2) Blood, urine and vitals will be collected as in Visit 1.

Table 1: Schedule of Sample Collection and Analyses (All Groups)

SAMPLES AND INFORMATION COLLECTED AT TRANSPLANT AND POST-TRANSPLANT TIME-POINTS	Study "Baseline"= Randomization at 3 Months Post-transplant SOC visit	6 Months Post - Transplant	12 Months Post Transplant	24 months Post Transplant
Renal Bx. (SOC))	X		X	X
MDRD for eGFR (SOC)	X	X	X	X
HLA antibodies (SOC)	X		X	X
Clinical Data (SOC)	X	X	X	X
Urine Protein/creatinine ratio (SOC)	X	X	X	X
Gene expression blood*	X	X	X	X
Gene expression Biopsy*	X		X	
Cellular Assays for T and B cells.*	X	X	X	X
Flow Cytometry*	X	X	X	X

*Indicates monitoring and testing completed for this study's immunobiology research.

The PI and fellow transplant nephrologists will determine how standard of care blood and serum samples are utilized and analyzed (routine laboratory tests, tacrolimus trough levels, etc.) at each specific visit according to routine transplant protocols.

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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

Rejection will be treated at the discretion of the investigator.

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 Medicine/Northwestern University and subjects will be recruited from the patients seen in the Division of Solid Organ Transplantation. We expect that 43 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.

Sample Size and Sample Size Justification

43 adult (18 years old or >), *de novo*, EBV seropositive recipients of living or standard criteria deceased donor renal transplants will be randomized to one of two treatment arms.17 subjects/arm will be randomized into Group 2 and Group 3 (Group 1 is now closed to enrollment at 9 subjects) to evaluate the efficacy of conversion at three months post-transplantation from Tacrolimus to either:

(1) Belatacept and MPA (closed to enrollment at 9 subjects) or
(2) low-dose Tacrolimus with Belatacept as compared with
(3) standard-dose Tacrolimus and MPA as assessed by the following primary endpoint:

1. Change in eGFR (MDRD) at 1 year post-transplant compared to baseline at month 3 (conversion)

Sample size was calculated based upon a hypothetical 20% improvement in renal function at one year and beyond in the Belatacept + MPA group vs. standard of care Tacrolimus + MPA group (accounting for 10% attrition). This is based upon our experience in a pilot study of CNI and steroid avoidance in de novo living donor transplant recipients (ATC, 2012).

Recipient Inclusion Criteria

1. Adult ≥ 18 years of age
2. Male or Female
3. EBV seropositive
4. Recipient of renal transplant from living or deceased donor

Recipient Exclusion Criteria

1. Recipients with EBV serostatus negative or unknown
2. History of acute rejection (AR) within 3 months prior to randomization
3. History of antibody mediated rejection
4. Positive T-cell lymphocytotoxic cross match
5. Proteinuria >1 g/day or > 0.5 g/day if diabetic in two weeks prior to randomization
6. Rejection on 3 month post-transplant screening biopsy

7. BK nephropathy at 3months post-transplant screening biopsy
8. Positive pregnancy test at the time of randomization in female of child bearing potential
9. History of previous transplant
10. History of positive human immunodeficiency virus test
11. History of positive HCV infection
12. End Stage Renal Disease (ESRD) secondary to primary FSGS (focal segmental glomerulonephritis)
13. Currently participating in or has participated in an investigational drug or medical device study within 30 days or five drug half-lives, whichever is longer, prior to enrollment into this study. Patients cannot be given another investigational agent during the course of this study (through 24 months +/- 60 Days). Patients may participate in another concurrent study only if that study is a non-interventional, observational investigation

Donor Inclusion/Exclusion Criteria
Any donor who provides consent and is accepted per institutional requirements as a donor will meet donor inclusion/exclusion criteria for purposes of this protocol.

Subject Recruitment and Screening
The study will be conducted at Northwestern Medicine/ Northwestern University and subjects will be recruited from the patients seen in the Division of Solid Organ Transplantation. We expect that 43 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 infections that require modification or withdrawal of maintenance immunosuppression will be withdrawn from the study.

Subjects who withdraw early will be given the option to consent to the study team following and recording their SOC data from EMR after they have withdrawn.

Data Collection and Follow-up for Withdrawn Subjects

When subjects have been withdrawn prematurely from the study, an attempt will be made to collect at least survival data on these 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 during the follow-up period of the protocol.

Donors

Blood samples from donor subjects, using a separate donor ICR, will also be obtained during standard-of-care follow-up appointments. These donor leukocytes will be used as stimulator cells in studies of functional activity of recipient T-cells. These samples will be processed in the principal investigator's research laboratory.

We aim to obtain samples from all living donors (up to 43 from recipients who end up enrolling and participating in the research study.

<u>Study Drugs</u>

Belatacept (Nulojix®)

Belatacept will initially be infused intraveneously at a dose of 5 mg/kg over a 30 minute period. This medication will be given in an open label fashion, according to package insert recommendations. The first dose of belatacept will be given at the time of randomization to those patients assigned to have tacrolimus switched to belatacept.

More than 1000 kidney transplant patients have received belatacept in clinical trials. Patients in these trials received belatacept or cyclosporine (a marketed drug for comparison), in addition to basiliximab, MMF and steroids to prevent transplant rejection. In general, patients treated with belatacept had the same overall rate of side-effects, including infections and cancers, as patients who received cyclosporine. In the first 36 months of follow-up in the three clinical trials done in kidney transplant patients, the frequency of side-effects was similar comparing belatacept and cyclosporine. The most commonly reported side-effects (in ≥ 20 % of subjects) among belatacept subjects were urinary tract infection, diarrhea, constipation, nausea, swelling, decrease in transplanted kidney function, fever, cough, high blood pressure, and low white blood cells count.

<u>Other previously reported side-effects included</u>**:** Low levels of phosphorus, calcium, low or high levels of potassium in blood; high levels of creatinine, glucose and cholesterol; vomiting, abdominal pain, operation-site complications and pain, low red blood cells count, blood or protein leaks in the urine, low blood pressure; graft dysfunction, headache, back pain, and trouble sleeping. Some side effects were serious and required hospitalization. Some were fatal.

Post-transplant lymphoproliferative disorder (PTLD), a tumor of white blood cells that can occur after kidney transplantation, developed more frequently in patients who received belatacept (14 cases out of 949; 1.5% of subjects) than those who received cyclosporine (3 cases out of 476; 0.6%). In addition, more than half of the PTLD cases in belatacept patients involved the brain (9 cases out of 14; 65% of belatacept patient), which is a higher proportion than expected. A total of 11 of 17 subjects with PTLD died; 8 out of 14 in the belatacept group and 3 out of 3 in the cyclosporine group.

PTLD is almost always associated with the Epstein Barr virus (EBV). EBV is the same virus that causes infectious mononucleosis or "the kissing disease." Most patients who receive a transplant have been exposed to EBV in the past and have antibodies that can fight the virus. These patients have a lower risk of PTLD than patients who don’t have antibodies to EBV. The risk of developing PTLD may also increase if subject is treated with certain potent immune suppressing therapies or have another type of infection called Cytomegalovirus (CMV).

Progressive multifocal leukoencephalopathy (PML), a rare, often fatal, infection of the brain has occurred in 1 kidney transplant recipient and it was fatal.

Neurological examinations will be performed to monitor the risk of developing PTLD and PML.

Some patients in the kidney transplant study have received belatacept for up to 5 years. In general, the rate of side effects decreases over time.

It is unknown if these side-effects are caused by belatacept, as some of these side-effects were reported by patients who received cyclosporine, and all patients received other immunosuppressive drugs. Similarly, there may be other side effects if belatacept that are unknown.

There is limited information available regarding the effectiveness of vaccines in non-human primates and humans that have been treated with belatacept. No data are available on the effect of therapeutic vaccinations in subjects receiving belatacept. Due to the risk of infection, subjects should not receive any live vaccinations during the course of the study. Similarly, neither the varicella (chicken pox) nor the live oral polio vaccine should be given to anyone living in subject’s home due to the rare risk of transmitting the infection.

Mycophenolic Acid (MPA/MMF) (Myfortic®)
MPA will be given at a dose of between 540mg to 1080 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 MPA at the time of randomization unless indicated by medical reasons (i.e. Neutropenia, GI side effects.)

Common side-effects are diarrhea, vomiting, and decrease in the number of red and/or white blood cell. Rarely, subjects may experience gastrointestinal bleeding. Cases of progressive multifocal leukoencephalopathy, a rare, often fatal, infection of the brain have been reported in patients taking MPA.

Tacrolimus (Prograf®)
Tacrolimus will be administered to target therapeutic TAC level per institutional SOC, beginning Day 1 (post-operative Day 1). The dose will be modified to achieve 12 hour trough concentrations of 5-10 ng/ml. This medication will be given in an open label fashion. The dose may be modified for Group 2 subjects to maintain trough level of ≤ 5 ng/mL.

Common side-effects are decrease in kidney function, high blood pressure, diabetes, tremor (shaking of a body part), headache, nausea, vomiting, diarrhea, tingling in hand or feet and decrease in the number of red and/or white blood cells, increase in blood potassium levels and decrease in blood magnesium levels.

Safety and Adverse Events

For the purpose of this clinical trial, the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (CTCAE), dated June 14, 2012, will be used to grade all adverse events.

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.

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.

Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.

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 investigation product, action taken, and treatment required. If treatment for the event was administered, it should be recorded in the medical record. The investigator must supply BMS and the IRB/IEC with any additional information requested, notably for reported deaths of subjects.

Serious Adverse Event Collecting and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

All SAEs, whether related or unrelated to belatacept, and all pregnancies must be reported to BMS (by the investigator or designee) within 24 hours.

All SAEs should be reported via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

> **SAE Email Address**: Worldwide.Safety@BMS.com
>
> **SAE Fax Number**: <<609-818-3804>>

For studies conducted under an **<u>Investigator IND</u>**, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible **and no later than 7 days** (for a death or life-threatening event) **or 15 days** (for all other SAEs) **after the investigator's or institution's initial receipt of the information.** BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:

> **MEDWATCH**
> **5600 Fishers Lane**
> **Rockville, MD 20852-9787**
> **Fax: 1-800-FDA-0178 (1-800-332-0178)**
> **http://www.accessdata.fda.gov/scripts/medwatch/**

All SAEs should simultaneously be faxed or e-mailed to BMS at:

> **Global Pharmacovigilance & Epidemiology**
> **Bristol-Myers Squibb Company**
> **Fax Number: 609-818-3804**
> **Email: Worldwide.safety@bms.com**

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 within 24 hours to the BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

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.

IRB Notification by Investigator
Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 10 days of the investigator'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 Investigator
The principal investigator 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'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 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 belatacept will be stopped from participating in the study and will be switched back to tacrolimus. Subjects may be stopped from participating in the study and will be switched back to tacrolimus after a single episode of acute renal allograft rejection when appropriate.

A subject's ongoing immunosuppressive therapy will be determined by the PI and fellow transplant nephrologists if that subject develops significant side effects secondary to belatacept such as severe thrombocytopenia (platelets count <50, 000), post-transplant lymphoproliferative disorder (PTLD) or progressive multifocal leukoencephalopathy (PML)..

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.

Patient Authorization: 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 the Northwestern University Institutional Review Board (IRB), 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 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 printed 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.

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. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

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 for 90 days 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 within one year 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.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any serious laboratory abnormality that required the subject to receive specific corrective therapy.

Overdose

In case of over dosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted. Limited data suggest that plasmapheresis may accelerate removal of belatacept from systemic circulation.

Potential Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 7.2.1 for reporting details).

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

   AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

   AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

<u>Non-Serious Adverse Events (NSAEs)</u>

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

The following hospitalizations are not considered SAEs in BMS clinical studies:

1. 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)
2. Elective surgery planned before signing consent
3. Admissions as per protocol for a planned medical/surgical procedure
4. Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
5. Medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
6. Admission encountered for another life circumstance that carries no bearing on health status and requires no medical-surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

Non-Serious Adverse Events (NSAEs) Collecting and Reporting

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 a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. NSAEs 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.

<u>Data Handling and Record Keeping</u>

Data and Statistical Plan

Sample size calculation of 43 subjects (17 subjects in Group 2 and Group 3, 9 subjects in Group 1, now closed to enrollment) has been conducted based upon a hypothetical 20% improved renal function at one year and beyond in the Belatacept + MPA group vs. standard dose Tacrolimus and MPA and a hypothetical 10% improvement in renal function in the Low dose Tacrolimus + Belatacept vs. standard of care Tacrolimus + MPA group accounting for 10% attrition . This is based upon our experience in a recently completed pilot study of CNI and steroid avoidance in de novo living donor transplant recipients where iodothalamate GFR at one year was 53.6 +/- 12.5 cc/min in the CNI group vs. 65.7 +/- 9.2* in the CNI avoidance cohort. The anticipated incidence of acute rejection will be ≤ 7% in the belatacept treatment arm as reported in the Phase II belatacept switch study. We expect to recruit 17 subjects per study arm (9 subjects in Group 1, now closed to enrollment) to acquire a total of at least 15 subjects per study arm at the end of the study with a power of 90% and a two-sided tests at a significance level of 0.05. Reducing sample size will have no impact as the two remaining groups will still reach original target enrollment number and Group 1, which is now closed, will be analyzed with the number of patients so far enrolled (n = 9). Based upon our transplant center volume of approximately 160 living donor kidney transplants per year, we estimate that patient accrual for the study can be completed within 18 months. Pt follow-up in this study will be for 21 months post-conversion (24 months post-transplantation).

The normality of primary endpoint will be examined and when needed, appropriate transformations will be applied. The primary analysis to compare the mean change in eGFR from month 3 to 1 year and 24 months post-transplant between the two Belatacept arms and the standard care arm will be performed using the mixed effects model accounting for the correlations among repeated measures. We will include time, baseline eGFR, group indicators for the treatment and control arms, and their interaction term as covariates. The difference between the two treatment arms and the control arm in the change of eGFR will be examined by estimating the regression coefficients of the interaction between the group indicators and time. Dunnett tests will be used for investigating contrasts between each of the two belatacept arms and the standard of care control arm. This will reduce the chance of a false positive.

Secondary binary endpoints including the incidence of acute rejection will be compared between two Belatacept arms and standard arm using the Fisher's exact test due to the sparse cells expected. Secondary continuous endpoints including maintenance immunosuppressive regimens on allograft immunohistopathology and allograft biopsy-derived gene expression profiles will be analyzed by mixed effects model described above to detect changes at 6, 12, and 24 months post-transplant.

Due to the huge number of hypothesis testings (comparisons between treatment arms, between peripheral blood subpopulations, and over different time points) for all the endpoints, we will control the false discovery rate (FDR) to be less than 0.125 to account for multiple comparisons using q-values (Storey, 2002).

The relationship between patient and graft survival and treatment and standard arms will be studied with Kaplan-Meier estimation and a log-rank test.

Recognizing that missing data due to dropout over time could bias study findings, we will compare outcomes between study completers and non-completers. If differences suggest selective dropout, adjusted analyses described by Robins et al [*Robins JM, Rotnitzky A, Zhao LP. Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. Journal of the American Statistical Association. 1995;90:106-21*] will be applied.

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. The primary data collection instrument for this study will be OTTR electronic notes.

Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years on site 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. After two years of on-site storage, all files relating to this project will be sent offsite for an additional 13 years.

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 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 by Bristol-Myers Squibb.

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

Subjects will be provided with parking voucher on study related visits.

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.