PROTOCOL VERSION DATE: 5/20/2015, Amendment #8

CONCEPT TITLE: A randomized, open label, multicenter study of a belatacept-based early glucocorticoid withdrawal regimen with alemtuzumab or rabbit antithymocyte globulin induction compared to a tacrolimus-based early glucocorticoid withdrawal regimen with rabbit antithymocyte globulin induction in renal transplantation

STUDY PHASE: Phase 4

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STUDY SITE INFORMATION	
Description	▬ Multi-Center (The University Hospital, Cincinnati, OH) (The Christ Hospital, Cincinnati, OH) (California Pacific Medical Center, San Francisco, CA) (University of Wisconsin, Madison, WI) (University of Minnesota, Minneapolis, MN) (University of Colorado, Denver, CO) (University of Illinois, Chicago, IL) (Tampa General Hospital, Tampa, FL)
Competing Studies at Your Institution	▬ Yes ▬ No, this study will take priority enrollment

SUPPORT REQUESTED (Check all that apply)	
Items requested	▬ Drug ▬ Funding Will funding or study drug be provided from other sources? ▬ NO ▬ YES

PROTOCOL ACCEPTANCE FORM

TITLE:	**A randomized, open label, multicenter study of a belatacept-based early glucocorticoid withdrawal regimen with alemtuzumab or rabbit antithymocyte globulin induction compared to a tacrolimus-based early glucocorticoid withdrawal regimen with rabbit antithymocyte globulin induction in renal transplantation**
VERSION:	**Amendment 8 dated 5/20/2015**
STUDY DRUG:	**Belatacept**
IND:	**IND 115, 270**
MEDICAL MONITOR:	**E. Steve Woodle, MD**
SPONSOR:	**University of Cincinnati Medical Center Dept. of Surgery/Division of Transplantation 231 Albert Sabin Way Cincinnati, OH 45267-0629**
DATE FINAL:	**5/202015**

I agree to conduct the study in accordance with the current protocol.

_____

Principal-Investigator's Name (print)

_____ _____

Principal-Investigator's Signature Date

_____

Site

Please return a copy of the form to the University of Cincinnati Transplant Regulatory Office and retain the original for your study files.

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I. Protocol synopsis

Title of study:

A randomized, open label, multicenter study of a belatacept-based early glucocorticoid withdrawal regimen with alemtuzumab or rabbit antithymocyte globulin induction compared to a tacrolimus-based early glucocorticoid withdrawal regimen with rabbit antithymocyte globulin induction in renal transplantation.

Purpose:

The study purpose is to determine the safety and efficacy of a belatacept-based immunosuppressive regimen (calcineurin inhibitor free) with alemtuzumab or rabbit antithymocyte globulin induction and early glucocorticoid withdrawal (CSWD) compared to a tacrolimus-based regimen with rabbit antithymocyte globulin induction and early glucocorticoid withdrawal in renal transplant recipients.

Study Hypotheses:

Belatacept-based immunosuppressive regimen with alemtuzumab induction, MMF(mycophenolate mofetil)/MPA (mycophenolic acid), and early glucocorticoid withdrawal (Group A) in renal transplant recipients will lead to less risk of graft loss, patient death, or reduced renal function at 12 months as compared to a tacrolimus-based immunosuppressive regimen with rabbit antithymocyte globulin, MMF/MPA, and early glucocorticoid withdrawal in renal transplant recipients (Group C).

OR

Belatacept-based immunosuppressive regimen with rabbit antithymocyte globulin induction, MMF/MPA and early glucocorticoid withdrawal (Group B) in renal transplant recipients will lead to less risk of graft loss, patient death, or reduced renal function at 12 months as compared to a tacrolimus-based immunosuppressive regimen with rabbit antithymocyte globulin, MMP/MPA, and early glucocorticoid withdrawal in renal transplant recipients (Group C).

Primary Endpoint:

The primary endpoint is to ascertain the combinatorial endpoint rate at 12 months as defined as

- Patient Death or Graft Loss or estimated GFR (eGFR) (MDRD) < 45 mL/min

Key Secondary Endpoints:

Key secondary endpoints will extensively assess efficacy associated with each regimen at 6, 12, and 24 months to further quantitate these outcomes.

- Composite endpoint at 6 and 24 months (12 months was selected as the time for evaluating the composite endpoint as the primary endpoint, as above)
- Incidence by Banff 2007 criteria of biopsy proven acute rejection (BPAR) stratified by type (ACR, AMR, or Mixed rejection)
- Death-Censored Graft Survival
- Proportion of patients with eGFR (MDRD) < 30 mL/min

- Proportion of patients developing anti-HLA antibodies against the donor (donor specific antibodies) (DSA) after transplantation

Tertiary Endpoints:

Tertiary endpoints will extensively assess additional safety, efficacy and salient endpoints associated with each regimen at 6, 12, and 24 months to further quantitate these outcomes.

- Severity of rejection by Banff 2007 criteria, treatment, and outcome of BPAR stratified by type (ACR, AMR, or Mixed rejection)
- Proportion of patients requiring anti-lymphocyte therapy for BPAR
- Causes of patient and graft loss
- Incidence, severity and treatment of metabolic and cardiovascular comorbidity (new onset diabetes after transplantation [NODAT], exacerbation of preexisting diabetes, hyperlipidemias [total serum cholesterol, HDL, LDL, triglycerides], hypertension, number of anti-hypertensive medications)
- Patient weight change and BMI from pre-transplant
- Change in Framingham Heart Study Coronary Score Heart Disease Risk Point Total
- Cardiovascular events (myocardial infarction, angina, cerebral vascular accident, transient ischemic attack, cardiovascular intervention/procedure or sudden death)
- Incidence of infections and posttransplant malignancies (including PTLD)
- Incidence of leukopenia (White Blood Cell Count < 2000 cells/uL)
- Incidence of anemia (Hg < 7 g/dL)
- Incidence of proteinuria (elevated protein/creatinine ratio >0.8 grams protein per gram creatinine)
- Cumulative total thymoglobulin dosing for induction (mg)
- Renal function assessment by calculated GFR and urine protein creatinine ratio
- Proportion of subjects that remain glucocorticoid-free
- Proportion of subjects on glucocorticoids and mean glucocorticoid dose (mg)
- Patient quality of life (QoL)/Side Effect Assessment
- Incidence of discontinuation of study treatment
- Comparison of immunosuppression-related adverse effects by treatment group.
- To determine the earliest reliable time-point that can be used for prediction of future onset of acute rejection and NODAT

Population:

Inclusion criteria:

1. Male and female patients ≥ 18 years of age.

2. Patient who is receiving a renal transplant from a living or deceased donor.
3. Female patients of child bearing potential must have a negative urine or serum pregnancy test within the past 48 hours prior to study inclusion.
4. The patient has given written informed consent to participate in the study

Exclusion criteria:

Patients meeting any of the following criteria at baseline will be excluded from study participation.

1. Patient has previously received an organ transplant other than a kidney.
2. Patient is receiving an HLA identical living donor transplant.
3. Patient who is a recipient of a multiple organ transplant.
4. Patient has a most recent cytotoxic PRA of >25% or calculated PRA >50% where multiple moderate level HLA antibodies exist and in the opinion of the PI represents substantial HLA sensitization.
5. Patient with a positive T or B cell crossmatch that is due primarily to HLA antibodies.
6. Patient with a donor specific antibody (DSA) as deemed by the local PI to be associated with significant risk of rejection.
7. Patient has received an ABO incompatible donor kidney.
8. The deceased donor and/or deceased donor kidney meet any of the following extended criteria for organ donation (ECD):
    a. Donor age $\geq$ 60 years
    OR
    b. Donor age 50-59 years and 1 of the following:
        i. Cerebrovascular accident (CVA) + hypertension + SCr $>$ 1.5 mg/dL **OR**
        ii. CVA + hypertension **OR**
        iii. CVA + SCr $>$ 1.5 mg/dL **OR**
        iv. Hypertension + SCr $>$ 1.5 mg/dL
    OR
    c. CIT $\geq$ 24 hours, donor age $>$ 10 years
    OR
    d. Donation after cardiac death (DCD)
9. Recipients will be receiving a dual or en bloc kidney transplant.
10. Donor anticipated cold ischemia is > 30hours.
11. Recipient that is seropositive for hepatitis C virus (HCV) with detectable Hepatitis C viral load are excluded. HCV seropositive patients with a negative HCV viral load testing may be included.
12. Recipients who are Hepatitis B core antibody seropositive are eligible if their hepatitis B viral loads are negative. After transplant, their hepatitis B viral loads will be monitored every three months for the first year after transplant. If hepatitis B viral loads become positive, patients will be treated per institutional standard of care.
13. Patients who are Hepatitis B surface antibody seropositive and who receive a kidney from a Hepatitis B core surface antibody positive donor may be included.
14. Recipient or donor is known to be seropositive for human immunodeficiency virus (HIV).
15. Recipient who is seronegative for Epstein Barr virus (EBV).
16. Patient has uncontrolled concomitant infection or any other unstable medical condition that could interfere with the study objectives.
17. Patients with thrombocytopenia (PLT <75,000/mm^3), and/or leucopoenia (WBC < 2,000/mm^3), or anemia (hemoglobin < 6 g/dL) prior to study inclusion.

18. Patient is taking or has been taking an investigational drug in the 30 days prior to transplant.
19. Patient who has undergone desensitization therapy within 6 months prior to transplant.
20. Patient has a known hypersensitivity to belatacept, tacrolimus, mycophenolate mofetil, alemtuzumab, rabbit anti-thymocyte globulin, or glucocorticoids.
21. Patient is receiving chronic steroid therapy at the time of transplant.
22. Patients with a history of cancer (other than non-melanoma skin cell cancers cured by local resection) within the last 5 years, unless they have an expected disease free survival of ≥95%.
23. Patient is pregnant, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by positive human Chorionic Gonadotropin (hCG) laboratory test.
24. Women of childbearing potential must use reliable contraception simultaneously, unless they are status post bilateral tubal ligation, bilateral oophorectomy, or hysterectomy.
25. Patient has any form of substance abuse, psychiatric disorder or a condition that, in the opinion of the investigator, may invalidate communication with the investigator.
26. Inability to cooperate or communicate with the investigator.

Study design:

This study is a prospective, randomized, open-label, multicenter safety/efficacy treatment study.

Number of centers & patients:

A total of 315 patients will be consecutively enrolled at eight centers. Patients receiving a renal transplant and meeting enrollment criteria will be randomized 1:1:1 into three groups, with 105 patients in each group. Group C is considered the control group and Groups A and B are considered the Test Groups.

1) **Group A (n = 105):** Alemtuzumab + belatacept + mycophenolate mofetil /Enteric coated mycophenolate sodium + early cessation of steroids
2) **Group B (n = 105):** Rabbit antithymocyte globulin + belatacept + mycophenolate mofetil /Enteric coated (EC) mycophenolate sodium + early cessation of steroids
3) **Group C (n = 105):** Rabbit antithymocyte globulin + tacrolimus + mycophenolate mofetil /Enteric coated (EC) mycophenolate sodium + early cessation of steroids

Study duration:

The active study duration will be approximately 42 months total with an 18 month enrollment period and 24 months of follow-up. The enrollment period will begin with study drug availability.

A 3-6 month period before open enrollment will be required for study activation with an additional 3-6 month period post last follow-up for data analysis.

Immunosuppressive Regimen:

INDUCTION IMMUNOSUPPRESSION

Group A:

Alemtuzumab will be dosed on day of transplant (Study Day 1) at dose of 30 mg given intravenously (IV) over a period of 2 hours after induction of anesthesia. Methylprednisolone IV will be administered 30-60 minutes prior to the administration of alemtuzumab.

Groups B and C:

All patients will receive rabbit antithymocyte globulin.

Rabbit antithymocyte globulin will be dosed post-operatively at a total cumulative dose of 4.0-6.0mg/kg given by days 5-10 post-transplant. It will be administered by local standards of care with the following recommendations. The initial intravenous intra-operative dose will be administered approximately one hour after the methylprednisolone dose. The first dose will be administered so that approximately 25% of the dose is infused prior to revascularization of the graft. Subsequent doses will be administered over a minimum of 4 hours. Premedication with acetaminophen 650mg p.o. and diphenhydramine 25mg p.o. prior to rabbit antithymocyte globulin dose will be given to reduce the incidence of infusion reactions.

MAINTENANCE IMMUNOSUPPRESSION

Groups A and B will receive belatacept in combination with mycophenolate mofetil/EC mycophenolate sodium/early glucocorticoid withdrawal.

Belatacept will be administered via intravenous (IV) infusion according to the FDA approved dosage recommendations. Subjects randomized to belatacept arms will receive the first dose of IV belatacept (10 mg/kg) within 12-24 hours post reperfusion. The second dose will be given between post-transplant days 4 -6 (Study Days 5-7), and then study days 14, 28, 56, and 84 (12 weeks) and then subjects will receive belatacept at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial at 24 months (104 weeks). Study Day 1 is defined as the day of transplant.

Group C will receive tacrolimus in combination with mycophenolate mofetil/EC mycophenolate sodium/early glucocorticoid withdrawal

Tacrolimus will be administered orally twice daily (BID). The recommended total initial dose of tacrolimus is 0.1 mg/kg/day in two divided doses orally. Tacrolimus should be started post-transplant within 48 hours or when serum creatinine drops lower than 4mg/dL, whichever comes

first. The initial targeted trough level of tacrolimus will be 8 - 12 ng/mL for Days 1 through 30, with dose reduction to achieve a 12-hour trough target of 5 - 10 ng/mL thereafter.

Groups A, **B and C** will receive mycophenolate mofetil/EC mycophenolate sodium and early glucocorticoid withdrawal.

The first dose of mycophenolate mofetil/EC mycophenolate sodium will be administered pre-operatively. Patients receiving mycophenolate mofetil will be dosed 1000 mg twice daily (2000mg/day). Patients receiving EC mycophenolate sodium will be dosed 720 mg twice daily (1440 mg/day). Dose may be increased for African American transplant recipients to mycophenolate mofetil 1500 mg twice daily (3000mg/day) or EC mycophenolate sodium 1080 mg twice daily (2160 mg/day).

These doses of mycophenolate mofetil and EC mycophenolate sodium have shown efficacy, pharmacokinetic and pharmacodynamic equivalence.

Subsequent dosage adjustments based on physician discretion are permitted due to toxicity only.

Glucocorticoid therapy will be administered as described. Methylprednisolone will be administered on Days 1 through 3. Additional tapering doses of glucocorticoids will continue to be given until Day 5 as below:
Day 1 (day of transplant): 500mg IV prior to alemtuzumab (Group A) or rabbit antithymocyte globulin (Groups B and C)
Day 2: 250mg IV
Day 3: 125mg IV
Day 4: 80mg p.o.
Day 5: 60mg p.o.
No further steroids

Monitoring of DSA:

DSA will be monitored in all arms of the study at baseline, 3 months, 6 months, 12 months and 24 months, and at times of suspected rejection at the central lab. Local prospective DSA monitoring is discouraged if results will impact renal biopsy rate in the absence of renal dysfunction. The remaining serum sample will be utilized for ELISA signature for NODAT.

QPCR assessment for acute rejection signature will be monitored in all arms of the study at baseline, 3 months, 6 months, 12 months and 24 months, and at times of suspected rejection at the central lab.

Recommended Treatment of Biopsy proven Acute Cellular Rejection (BPACR) Banff Grade 1a-1b

Continue current regimen of belatacept or tacrolimus, Solumedrol 7mg/kg (Max 500mg) IV daily X 3 days. If improving trend in Scr, then initiate oral Prednisone recycle (Prednisone 200mg X 1, Prednisone 160mg X 1, Prednisone 120mg X 1, Prednisone 80mg X 1, Prednisone 40mg X 1, Prednisone 20mg X 1, Prednisone 10mg X 1, then discontinue steroids). If no improving trend in Scr after 3-5 days of treatment initiation, then repeat biopsy. If Banff grade is the same or worse, then initiate or increase tacrolimus to a goal trough of 10-15 ng/mL or initiate rabbit antithymocyte globulin for 7-14 days of CD3 suppression. If Banff grade is improving or minimal persistent rejection, continue oral prednisone recycle.

Recommended Treatment of BPACR Banff Grade ≥2a

Continue current regimen of belatacept or tacrolimus, initiate antithymocyte globulin for 7-14 days of CD3 suppression. If no improving trend in Scr after 7 days of treatment initiation, then repeat biopsy. If Banff grade is the same or worse, continue antithymocyte globulin, initiate or increase tacrolimus therapy to a goal trough of 10-15 ng/mL and initiate or add corticosteroid therapy. If Banff grade is improving or minimal persistent rejection, continue antithymocyte globulin.

Recommended Treatment of Biopsy proven Antibody mediated rejection (BPAMR) or biopsy proven Mixed acute rejection (BPMAR)

May treat BPAMR or BPMAR with a bortezomib-based or IVIG-based protocol.

The following schematic is a guideline for the treatment of BPAMR and BPMAR with bortezomib-based treatment with rituximab:

Treatment Day	PRE	1	4	7	10
PLASMAPHERESIS 1.5 PV		X	X	X	X
Methylprednisolone 100 mg IVP or PO		X	X		
Methylprednisolone 50 mg IVP or PO				X	X
BORTEZOMIB 1.3 mg/m_2 IVP or SC		X	X	X	X
RITUXIMAB 375 mg/m_2 IV		X			

Statistical Methods:

Populations for Analysis

Intent-to-Treat (ITT) Analysis - This study will be analyzed as an intent-to-treat analysis at 12 and 24 months. All patients who were randomized and transplanted (graft is reperfused) will be included in the intent to treat population for analysis.

Following the ITT principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The safety analysis set will consist of all patients who received at least one dose of belatacept in Groups A and B and at least one dose of tacrolimus in Group C. Patients will be analyzed according to the treatment they have received.

The per protocol (PP) analysis set will consist of all randomized patients without major protocol deviations (PDs) as defined in full protocol.

Statistical Analyses

The following statistical methods will be used dependent on the type of outcome variable. For continuous variables an Analysis of Variance (ANOVA) will be performed with terms for treatment and investigative site. For time-to-event variables, the Kaplan Meier (KM) survival curves will be estimated and the Log Rank test with site as a stratification variable will be performed. For categorical variables, a Cochran-Mantel-Haenzel (CMH) test will be performed with site as the stratification variable. If the cell sizes are sparse, a Fisher's Exact test will be used. The Hochberg (for KM, CMH) or Tukey-HSD (for ANOVA) adjustment will be used for each endpoint to control the alpha level at 5% for comparing the three treatment groups.

Sample Size Assessment

The primary endpoint for this trial is the percentage of patients in each treatment group that meet the composite endpoint at 12 months as defined as patient death or graft loss or estimated GFR < 45 mL/min. It is assumed that the percentage of patients in the Control Group (i.e. Thymo/FK/MMF/CSWD) meeting the primary endpoint is 50%. Each of the test groups will be tested against the control group using Kaplan-Meier methodology and the Log-Rank test. To control the overall experiment-wise error rate at 5%, the Hochberg method for multiple comparisons will be used. In this procedure, the p-values for the two comparisons will be ordered from largest to smallest. If the largest p-value is less than $\alpha=0.05$, then both comparisons can be tested at $\alpha=0.05$. If the largest p-value is greater than $\alpha=0.05$, then we cannot reject the null hypothesis for that comparison. We then compare the second largest p-value to $\alpha=0.025$ and reject the null hypothesis if the p-value is less than $\alpha=0.025$. A sample size of 105 completed patients per group will provide at least 80% power to detect an absolute difference of 21% between two groups at the two-sided $\alpha=0.025$ if the percentage of patients meeting the primary endpoint in the control group is assumed to be 50%.

II. Clinical Section

1. Background and Rationale

Glucocorticoids have been a cornerstone of immunosuppressive therapy for six decades (1). Although glucocorticoids provide potent suppression of allo-immune responses in humans, their adverse effects including infection, diabetes, weight gain, hypertension, hyperlipidemia, bone disease, dermal thinning, collagen loss in multiple tissues, and cataracts, combined with a lack of available therapeutic monitoring all argue against their continued use in transplantation.

Initial Efforts with Late Glucocorticoid Withdrawal Under Tacrolimus-based Immunosuppression

Initial experiences with tacrolimus (2-10) indicated that this agent possessed unique and potent immunosuppressive properties, which made it a promising agent on which a glucocorticoid free immunosuppressive regimen could be developed. Early reports of glucocorticoid withdrawal (CSWD) with tacrolimus involved late CSWD (defined as three months or later post-transplant) (11), which was performed following tacrolimus therapy for refractory rejection. Prior to this experience, glucocorticoids could not be withdrawn in patients who were considered to be high immunologic risk. Yet this experience demonstrated that CSWD could be achieved even in patients with the most refractory acute renal allograft rejections. The Pittsburgh experience with late CSWD under tacrolimus therapy was later confirmed with experience at another center (12).

Early Glucocorticoid Withdrawal: Initial Experience

Successes with CSWD tacrolimus rescue therapy led to design and conduct of a number of tacrolimus-based *de novo* CSWD trials dating back to 1995. Strategies in designing CSWD regimens were based on a set of paradigms gleaned from the existing literature and included: 1) acute rejection risk is higher the earlier CSWD is attempted following transplantation and also to how rapidly CSWD is completed, 2) induction therapy reduces acute rejection risk; 3) the magnitude of maintenance immunosuppression reduces acute rejection risk; and 4) historical acute-rejection risk factors—particularly recipient African American race have similar effects in CSWD (13).

An important feature of these initial tacrolimus-based CSWD immunosuppressive regimens was the replacement of azathioprine with mycophenolate mofetil as an antiproliferative agent. When these early CSWD protocols were implemented (14), mycophenolate mofetil had not been used in combination with tacrolimus because mycophenolate mofetil pivotal trials were conducted in combination with cyclosporine. In the mycophenolate mofetil pivotal trials, mycophenolate mofetil therapy was associated with reduction in acute rejection rates by approximately a third. Therefore, it was hypothesized that the tacrolimus/ mycophenolate mofetil maintenance immunosuppressive regimen would provide optimal immunosuppression for developing new CSWD regimens.

In December 1995 early CSWD under tacrolimus/ mycophenolate mofetil based immunosuppression was implemented as primary therapy for de novo kidney transplant recipients. The initial experience with early CSWD under tacrolimus/ mycophenolate mofetil was reported in 1998 with demonstration of very low acute rejection rates at that time (21%, which was lower than UNOS reported rates at the time) and also with good patient and graft survival (14). Subsequently longer term experience was reported with three-year data that demonstrated that early results were maintained without significant reduction in allograft survival over time (15). This data provided the first experience demonstrating that excellent three year allograft survival could be obtained with early CSWD, which suggested that the problems previously documented in the Canadian multicenter trial (increased allograft loss with CSWD), could possibly be

overcome when potent maintenance immunosuppressive therapy was employed for early CSWD (16).

These initial experiences with early CSWD protocol were remarkable for several reasons. First, it was the first early CSWD regimen using tacrolimus as the CNI, and also was the first early CSWD regimen that employed the tacrolimus/ mycophenolate mofetil combination. Of note, today, sixteen years later, the tacrolimus/ mycophenolate mofetil regimen is currently the most common maintenance immunosuppressive regimen for early CSWD in renal transplantation. It is important to note that these initial early CSWD protocol represented the first to employ the concept of aggressive loading of maintenance immunosuppressive agents in the pre and early post-transplant period. Third, these studies deliberately included African Americans, as they were previously excluded from glucocorticoid withdrawal regimens because of their known high risk for acute rejection. Despite this, excellent rejection rates were achieved in African Americans. Of note, our initial trial subsequently became the basis for the design of the first and double blind, randomized clinical trial of early CSWD in renal transplantation. This study will be described in detail below.

Simultaneous CSWD and CNI Minimization

An important step in the evolution of CSWD studies was to combine CNI minimization and early CSWD. Before this could be achieved, however, additional experiences had to accumulate with early CSWD, particularly with potent T cell depleting induction therapy, so that the potential for increased acute rejection rates could be minimized. By 1999, a substantial experience had been accumulated with early CSWD that was adequate to design and conduct the first combined early CSWD and CNI minimization regimens.

Combined Early CSWD and Calcineurin inhibitor (CNI) Minimization

The initial CSWD/CNI minimization trial was designed in 2000 and included induction therapy with a T-cell-depleting agent that was included to reduce acute rejection risk. Maintenance immunosuppression consisted of low dose cyclosporine, mycophenolate mofetil, sirolimus, and complete avoidance of glucocorticoids (CSAV) (17). Cyclosporine dosing was reduced from the early post-transplant period, and in consecutive cohorts, was completely discontinued at earlier intervals post-transplant: first at 12 months, and later at 6, and then 4 months post-transplant. The study was also designed to withdraw mycophenolate mofetil at two years, resulting in sirolimus monotherapy as maintenance immunosuppression beyond two years post-transplant. With a mean of three years follow-up (18) patient survival was 97% and death-censored graft survival was 86%, with a one-year acute rejection rate of 14% and a three year acute rejection rate of 21%. 90% of patients remained glucocorticoid-free, 87% remained CNI-free. This study showed that early CSWD and CNI minimization could be achieved simultaneously under potent T cell depleting induction therapy.

Multicenter CSWD Trials

Astellas Multicenter Randomized, Double Blind Trial Comparing Early CSWD with Chronic Glucocorticoid Maintenance Therapy

The Astellas CSWD trial presented the longest blinding period (5 years) of any trial conducted to date in transplantation. In designing the Astellas double blinded trial, several features were retained from the earlier pilot study of early CSWD conducted under tacrolimus/ mycophenolate mofetil based immunosuppression. These features included: 1) initial and early loading of mycophenolate mofetil following transplantation, 2) inclusion of African American transplant recipients; and 3) an acceptance of lower WBC counts to minimize reductions in mycophenolate mofetil dosing (18). In the Astellas trial, each transplant center could decide their induction

antibody therapy (IL-2 receptor antibody or antithymocyte globulin). The study excluded patients with delayed graft function, high PRA, or repeat transplants in order to achieve a substantial degree of homogeneity in the study population. This trial was also designed to have an extensive evaluation of diabetes and other cardiovascular risk factors, including evaluation of new onset diabetes after transplantation (NODAT) by multiple definitions and criteria. The final five year results of this study have been reported (19). The study included adult recipients of deceased and living donor kidney transplants. Patients were randomized to receive prednisone (5 mg/day after 6 months post-transplant) or early CSWD, and blinding was maintained for 5 years. 386 patients were enrolled: CSWD n= 191, chronic glucocorticoids (CCS) n=195. All results are presented as (CSWD; CCS). No differences were observed at 5 years in the primary end point (composite of death, graft loss, or moderate/severe acute rejection) (30/191 (15.7%); 28/195 (14.4%)), patient death (11/191(5.8%);13/195 (6.7%)), death-censored graft loss (11/191 (5.8%); 7/195(3.6%)), biopsy confirmed acute rejection (34/191 (17.8%); 21/195(10.8%), p=0.058), moderate/severe acute rejection (15/191(7.9%); 12/195 (6.2%)).

Increased biopsy confirmed acute rejection episodes in the CSWD group were primarily glucocorticoid-sensitive Banff 1A rejections: the incidence of antibody-treated biopsy confirmed acute rejection was similar between groups (11/191(5.8%); 13/195 (6.7%)). No differences in renal function were observed at 5 years: mean serum creatinine (1.5 ± 0.6; 1.5 ± 0.7 mg/dL), or Cockcroft Gault calculated creatinine clearance (58.6 ± 19.7; 59.8 ± 20.5 mL/min). CSWD was shown to be associated with improved serum triglycerides at all time points (except 5 years). NODAT was similar with respect to proportions who required treatment (23/107 (21.5%), 18/86 (20.9%); however, fewer CSWD patients required insulin for NODAT at 5 years (4/107 (3.7%)); 10/86 (11.6%), *P* = 0.049). Changes in HgA1c values (from baseline) were lower in CSWD patients at all time points except 4 years. In summary, this five year double blind study demonstrated that when compared to chronic glucocorticoid maintenance therapy, early CSWD was associated with improvements in several cardiovascular risk parameters with minimal increased risk in acute rejection (19). Of note in this study was the impact of induction therapy on acute rejection. This study also highlighted the importance of potent T-cell depleting induction therapy, as patients undergoing early CSWD experienced a biopsy confirmed acute rejection of 14.4% compared to a rate of 24.2% in early CSWD patients receiving IL-2 inhibitor induction.

Multicenter Pilot Study of Early (4 day) CSWD under Sirolimus-Based Immunosuppression.

This study was sponsored by Wyeth Ayerst and represented the first prospective trial of early CSWD under a sirolimus-based immunosuppressive regimen. Because this was the first experience with this particular immunosuppressive regimen, patients at high risk for acute rejection were excluded from study entry (African American recipients and patients with a current cytotoxic PRA >25%). The study was a single limb, open label pilot study. A major reason for conducting this study was to determine whether early CSWD would ameliorate two of the primary adverse effects of sirolimus therapy— hyperlipidemia and poor wound healing. Immunosuppression induction therapy included IL-2 receptor antibody (Simulect) and maintenance immunosuppression included tacrolimus and sirolimus with glucocorticoid cessation at four days post-transplant. The final, 12- month study report has previously been published (20). Patient and graft survival were both 100% at twelve months and the biopsy-proven acute rejection rate was 13%. Relatively small changes were observed in cholesterol and triglycerides and new anti-lipid therapy was instituted in only 34% of patients. This rate of new anti-lipid therapy was lower than that reported in the pivotal trials that led to sirolimus approval. These results indicated that CSWD could reduce the observed lipogenic effects of sirolimus.

TRIMS Multicenter Trial

This multicenter trial was designed to determine the effects of potent T cell depleting induction therapy in early CSWD regimens in living donor transplantation (21). In this study, patients were randomized in a 2:1 ratio to receive either CSWD or triple immunosuppression therapy with tacrolimus/mycophenolate mofetil/steroids. No differences occurred in the primary endpoint (CSWD 84.4%, triple therapy 74.4%), patient survival (CSWD 100%, triple therapy 93.8%), graft survival (CSWD 98.1%, triple therapy 93.8%), or biopsy proven acute rejection (CSWD 13.9% vs. triple therapy 19.4%). This study, therefore demonstrated that early CSWD with potent T cell depleting induction therapy could provide results comparable to the most commonly used non-induction regimen with steroid-based immunosuppressive therapy.

INTAC Multicenter Trial

A recent trial (INTAC) compared alemtuzumab induction with IL-2 receptor antibody induction in low risk populations and alemtuzumab with rabbit antithymocyte globulin in populations at high risk for acute rejection. High risk patients were defined as recipients who were African American, or had a current PRA>20%, or were a repeat transplant recipient. Inclusion criteria included being adult recipients of living or deceased donor transplants. Baseline immunosuppression in each group included tacrolimus, mycophenolate mofetil, and early CSWD. At the end of the study, acute rejection rates were lower in alemtuzumab patients compared to those receiving IL-2 receptor antibody induction in the low risk population. Acute rejection rates were similar in the high risk population when comparing alemtuzumab and rabbit antithymocyte globulin (22). Therefore, this trial demonstrated that T-cell depleting induction therapy with either rabbit antithymocyte globulin or alemtuzumab provided superior acute rejection rates compared to non depleting T-cell induction therapy with an IL-2 receptor antibody.

Acute Rejection Risk

This study analyzed and reported multivariate analyses of individual risk factors for acute rejection with early CSWD (23). This analysis revealed that the risk factors for acute rejection under early CSWD were similar to those previously reported under other immunosuppressive regimens. The greatest risks were observed for high PRA and repeat transplant recipients (patients with a current cytotoxic PRA >25%, or a peak cytotoxic PRA >50%) (23). Also, African American and female recipients were at increased risk for acute rejection. These high risk groups are important in designing future trials of CSWD, particularly with respect to inclusion/exclusion criteria and stratification and data analysis. Failures to recognize these higher risk groups have led to problems in previous CSWD including the Canadian multicenter trial (1) and the NIH/Roche United States double blind trial (24).

This multivariate analysis (23) also showed a 40% reduction in acute rejection risk when T-cell-depleting induction therapy was employed.

Belatacept

Renal transplant is the most effective treatment for end-stage renal disease. It provides improved survival and quality of life. Maintenance of a functioning renal transplant mandates lifelong immunosuppressive therapy to prevent immune destruction of the graft. Current immunosuppressive regimens yield 1-year survival rates of 89% for cadaveric and 94% for living-donor grafts. Over time, however, there is progressive loss of both subjects and grafts. Five-year graft survival for cadaveric and living related donor renal transplants is 67% and 80%, respectively. (24)

The most common causes of long-term subject and graft loss in kidney transplant recipients are cardiovascular disease and chronic allograft nephropathy (CAN), respectively. (25, 26) Paradoxically, the principal immunosuppressive therapies for renal transplant, the calcineurin inhibitors (CNIs), cyclosporine (CsA) and tacrolimus, directly contribute to long-term allograft loss and subject death, since they are inherently nephrotoxic and can cause or exacerbate cardiovascular risks including hypertension, hypercholesterolemia, and diabetes mellitus.

There is, therefore, a substantial unmet medical need for new therapies in renal transplant that can provide short-term subject and graft survival comparable to the CNIs without their long-term nephrotoxic, cardiovascular, and metabolic effects. Because belatacept can be administered at the time of engraftment rather than in a delayed fashion, as is frequently necessary with CNIs – especially in those allografts with initial impaired renal function-- it affords immunosuppression in a timely manner. Unlike CNIs, the targeted mechanism of action of belatacept should provide immunosuppression without nephrotoxicity or adverse effects on the cardiovascular/metabolic profile.

Results from analysis of the Phase 3 data confirm that by Year 3: (1) patient and graft survival remained comparable between belatacept and CsA, (2) renal function benefits associated with belatacept were sustained, and (3) blood pressure was consistently lower in belatacept than in the comparator groups, and increases in blood lipids were smaller, in subjects treated with belatacept.

The totality of data in the belatacept renal transplant program, including 36-month results of the ongoing Pivotal Phase 3 trials, continues to support a favorable risk-benefit profile for belatacept.

Summary of Results of Belatacept Investigational Program

A total of 949 subjects have been treated with belatacept (30-minute intravenous [IV] infusion) in 3 core *de novo* renal transplant studies: 2 pivotal Phase 3 studies (IM103008 and IM103027) (27, 33, 28, 35) and one supportive Phase 2 study. (29) in which belatacept dosing regimens (more intensive [MI] and less intensive [LI]) were compared with a cyclosporine A (CsA) regimen. Efficacy results were consistent in the two pivotal Phase 3 studies and demonstrated comparable subject and graft survival at Month 12 between belatacept-treated subjects and CsA-treated subjects, with improved renal function, less new onset diabetes mellitus (NODM), lower blood pressure and a more favorable lipid profile. Extended follow-up over 3 years demonstrated

evidence of ongoing efficacy that did not differ between the 2 belatacept dose regimens (MI and LI). Results of the earlier Phase 2 study were consistent with these findings.

Belatacept is also being evaluated in 3 supportive Phase 2 studies, IM103034, IM103010, and IM103045 in combination with different immunosuppressants or in different populations. Studies IM103010 and IM103034 are being conducted in renal transplant recipients, and IM103045 is a study in liver transplant recipients. These studies have reached their 1-year endpoints. Additional studies include a pharmacokinetic (PK) study in renal transplant recipients (IM103047), studies in healthy subjects, a study in subjects with rheumatoid arthritis, and investigator-sponsored studies.

One of the extensions of a liver transplant study was stopped early due to an excess of deaths in one of the belatacept groups (less intense regimen with MMF). A causal relationship to belatacept could not be clearly established, but it could not be rejected. In consultation with the Independent Data Monitoring Committee, BMS decided to terminate the study and recommended that all belatacept patients be switched to local standard of liver transplant care. Because of differences in patient population and treatment regimens studied, the termination of this Phase 2 belatacept liver study is not considered to impact the benefit/risk assessment in renal transplant. (30)

Pharmacology of Belatacept

Belatacept is in a new class of immunosuppressive therapy for renal transplant. It is a soluble chimeric fusion protein that binds to the B7 molecules on the surface of antigen-presenting cells (APCs), inhibiting requisite co-stimulation for T-cell activation. Belatacept differs from existing immunosuppressants in the restricted distribution of its molecular target and the specificity of its effect. Belatacept was derived from CTLA4Ig (abatacept), a fusion protein consisting of the extracellular domain of human CTLA4 fused to a fragment of the Fc domain of a human immunoglobulin (Ig) G1 antibody. By binding avidly to CD80/86, CTLA4Ig blocks the interaction of the T-cell's CD28 with the antigen-presenting cell's CD80/CD86, thus preventing T-cells from receiving the required second costimulatory signal. In the absence of this second signal, the T-cell becomes anergic (unresponsive) or undergoes apoptosis. The binding affinity for murine CD80 and CD86 is lower with belatacept than with the parent molecule.

Preclinical Toxicology of Belatacept

Data for the parent molecule abatacept is relevant in certain animal species in order to increase the understanding of the pharmacology and toxicology of belatacept. Studies that assessed the effect of abatacept on host responses against infection in mice suggest that CD28 blockade in mice largely preserves innate immunity against most pathogens; however, agents such as belatacept that block CD28 may increase the risk of clinical infection by some pathogens that require an effective D4+ T cell-mediated immune response for eradication or control, and may increase the risk of some virally induced tumors. No drug-related findings were observed in standard evaluations of safety pharmacology parameters of cardiovascular, respiratory, and neurologic function conducted in monkeys as part of the pivotal, repeat-dose toxicity studies for up to 6 months with belatacept or 1 year with abatacept. Belatacept has less activity in rodents than abatacept has. Because of abatacept's similarity to belatacept in structure and mechanism of action and its higher activity in rodents, abatacept was used as a more active homolog for

belatacept in rodents. Therefore, preclinical studies conducted with abatacept have been used to support the safety of belatacept in addition to the studies conducted with belatacept.

Mutagenesis and Carcinogenesis

No mutagenicity or clastogenicity was observed with abatacept in a battery of *in vitro* studies. In a mouse carcinogenicity study, increases in the incidence of malignant lymphomas and mammary tumors (in females) occurred. The increased incidence of lymphomas and mammary tumors observed in mice treated with abatacept was likely associated with decreased control of murine leukemia virus and mouse mammary tumor virus, respectively, in the presence of long-term immunomodulation. However, the relevance of these findings to the clinical use of belatacept is unknown. In a six-month and one-year toxicity study in cynomolgus monkeys with belatacept and abatacept, respectively, no significant toxicity was observed at up to 6 times the exposure associated with the maximum recommended human dose (MRHD). Reversible pharmacological effects consisted of minimal decreases in serum IgG and minimal to severe lymphoid depletion of germinal centers in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphologic changes was observed in either study. This was despite the confirmed presence of lymphocryptovirus in the abatacept study and presumed presence of this virus in the belatacept study. Lymphocryptovirus is known to cause lesions in immunosuppressed monkeys within the time frame of these studies. Thus, long-term treatment of monkeys with pharmacologically active doses of belatacept did not lead to reactivation of an oncogenic virus.

Reproductive and Developmental Toxicity

In rats, belatacept had no undesirable effects on male or female fertility. Belatacept was not teratogenic when administered to pregnant rats and rabbits at doses up to 200 mg/kg and 100 mg/kg daily, respectively, representing approximately 16 and 19 times the exposure associated with the MRHD of 10 mg/kg based on area under the concentration time curve (AUC). Belatacept administered to female rats daily during gestation and throughout the lactation period was associated with infections in a small percentage of dams at all doses (≥ 20 mg/kg, ≥ 3 times the MRHD exposure based on AUC), and produced no adverse effects in offspring at doses up to 200 mg/kg. Belatacept was shown to cross the placenta in rats and rabbits. It is not known whether the non-clinical findings in abatacept and belatacept indicate a risk for development of autoimmune diseases in humans exposed *in utero* to abatacept or belatacept.

Single- and Repeat-Dose Toxicity

In non-human primate studies, IV administration of belatacept as a single dose up to 90 mg/kg or as repeat doses up to 50 mg/kg every other day for 30 days or every week for 6 months was not associated with any significant drug-related toxicity. Reversible pharmacologic effects observed at all doses consisted of minimal decreases in serum immunoglobulin (Ig)G (no effect on IgM or IgA) levels and minimal-to-moderate decreases in the diameter and number of lymphoid germinal centers in the spleen and/or lymph nodes, reflective of decreased germinal center activity. No evidence of infections or hyperplastic, preneoplastic, or neoplastic changes were observed in the peripheral blood cells or lymphoid tissues of any monkey. In the 6-month study, functional activity of the immune system was demonstrated at all doses by a robust antibody response to the

neoantigen KLH following immunization after an 8-week dose-free period. The no-observable-adverse effect level (NOAEL) in the 6-month study was 50 mg/kg/weekly, which resulted in systemic exposures that were 5.8, 13, and 20 times the exposures observed in subjects given belatacept during the first month, fourth month, and maintenance phase of the LI regimen, respectively. An increased susceptibility to opportunistic infections observed in juvenile rats on abatacept is likely associated with the exposure to abatacept prior to development of memory responses. The relevance of these results to humans greater than 6 years of age is unknown, as memory responses in patients older than 6 have more time to develop.

Local Tolerance

In a local tolerance study in rabbits, belatacept was not significantly irritating when administered by IV, paravenous, or intra-arterial injection at the highest concentration intended for use in humans (20 mg/mL). In IV repeat-dose studies in monkeys, no significant injection site irritation occurred at concentrations of 25 mg/mL. Furthermore, no significant injection site irritation occurred following a single SC dose of the IV ready-to-use SC formulation containing Poloxamer 188 at concentrations up to either 100 or 125 mg/mL.

Safety Pharmacology

No adverse cardiovascular, respiratory, or neurological effects have been detected in any of the single- or repeat-dose toxicity studies of belatacept when given to monkeys for up to 6 months. In these studies, electrocardiograms (ECGs) were obtained near Cmax (3 hours after dosing). In addition, no belatacept-related changes were observed in histamine, complement (C3a), TNF-α, or IL-6 levels in the plasma or serum, mediators associated with hemodynamic changes and anaphylactoid responses.

Clinical Pharmacology

Belatacept is a second-generation, higher avidity variant of abatacept (CTLA4-Ig), differing from the parent molecule (abatacept) by 2 amino acids within the region that binds CD80 and CD86 (L104→E and A29→Y). Belatacept shows ~ 2-fold greater binding avidity for human CD80 and ~ 4-fold greater binding avidity for human CD86 than the parent molecule. Belatacept is approximately 5- to 10-fold more potent *in vitro* on a per-dose basis than abatacept at inhibiting human T cell proliferation and T cell cytokine production in response to alloantigen stimulation.

Clinical Pharmacodynamics of Belatacept

Belatacept demonstrated concentration-dependent CD86 receptor binding in a steroid avoidance phase 2 study in renal transplant recipients who received the belatacept MI regimen.

The generation of antibodies directed against the donor human leukocyte antigens (HLA) antigens (donor-specific antibodies [DSA]) is an essential criterion for the diagnosis of antibody-mediated rejection, a type of rejection associated with poor outcomes in renal transplant. The presence of DSA may also preclude development or signal the absence of functional tolerance, leading to chronic rejection. For clinical evaluation of belatacept's effect on the humoral response to the graft, serum samples collected from participants were evaluated for the presence or

absence of donor-specific alloantibodies. In the Phase 3 clinical studies, fewer belatacept-treated subjects had detectable antibodies to donor-specific HLA compared to CsA-treated subjects.

Human Pharmacokinetics of Belatacept

Table 1 summarizes the PK parameters of belatacept in healthy adult subjects after a single 10 mg/kg IV infusion (IM103024), in kidney transplant subjects after multiple 10 mg/kg and 5 mg/kg IV infusions (IM103100 PK Substudy and IM103047), and in liver transplant subjects following Day 84 infusion of belatacept at 10 mg/kg.

Table 1. Pharmacokinetic Parameters of Belatacept (5 to 10 mg/kg) Across Studies

Pharmacokinetic Parameters ± SD (range)	Healthy subjects (After 10 mg/kg Single Dose) N=15	Kidney Transplant Subjects (After 10 mg/kg Multiple Doses) N=10	Kidney Transplant Subjects (After 5 mg/kg Multiple Doses) N=14	Liver Transplant Subjects (after 10 mg/kg Multiple dose)
Peak concentration: Cmax (µg/mL)	300±77 (190-492)	247±68 (161-340)	139±28 (80-176)	209.55±42.57 (130-287) N=11
AUC*(µg•h/mL)	26398±5175 (18964-40684)	22252±7868 (13575-42144)	14090±3860 (7906-20510)	20106.93±4359.40 (14982-27015) N=6
Terminal half-life: T-HALF (days)	9.8±2.8 (6.4-15.6)	9.8±3.2 (6.1-15.1)	8.2±2.4 (3.1-11.9)	8.66±1.3 (7.01-10.95) N=7
Systemic clearance :CLT	0.39±0.07 (0.25-0.53)	0.49±0.13 (0.23-0.70)	0.51±0.14 (0.33-0.75)	0.46±0.10 (0.05-0.14) N=6
Volume of distribution: Vss (L/kg)	0.09±0.02 (0.07-0.15)	0.11±0.03 (0.067-0.17)	0.12±0.03 (0.09-0.17)	0.11±0.03 (0.05-0.14) N=6

Source: IM103024 clinical study report (CSR), IM103047 Interim CSR, IM103100 PK Substudy , IM103045 CSR

*AUC=AUC (INF) after single dose and AUC(TAU) after multiple dose, where TAU=4 weeks. Values represent mean±SD (range)

In healthy subjects, the PK of belatacept was linear, and the exposure to belatacept increased proportionally after a single IV infusion dose of 1 to 20 mg/kg. The PK of belatacept in *de novo* kidney transplant subjects, liver transplant subject and healthy subjects was comparable. Following once every 4 weeks (q4week) IV infusion of 10 mg/kg and 5 mg/kg, there was minimal systemic accumulation of belatacept in kidney transplant subjects at steady-state during the maintenance phase. Following the administration of LI or MI regimen, C_{min} of belatacept gradually decreased from the initial phase to the maintenance phase post-transplant, consistent with the

decrease dose and dosing frequency of LI or MI regimen and the need to provide maximal immunosuppression during the initial period post-transplant as the allograft engrafts. In the LTE phase of the Phase 2 Study and two Phase 3 studies, C_{min} of belatacept were consistently maintained (~4 µg/mL at 4-week schedule) during the maintenance phase up to Month 60 and Month 36 post-transplant, respectively. After SC administration (IM103029 and IM103046) in healthy subjects, the T_{max} of belatacept was reached between 60 and 96 hours, and the exposure increased in a dose proportional manner across the dose range of 50 to 250 mg. The absolute bioavailability of the SC formulation was estimated to be 79%.

Metabolism and Elimination

No studies of the metabolism of belatacept in humans were conducted. Generally, therapeutic proteins are cleared through their interactions with specific receptors, as well as interactions with the FcgR1 receptors. Proteins are also cleared non-specifically through proteolysis in the Kupffer cells in the liver and macrophage activity in the spleen. These non-specific mechanisms of clearance are the presumed primary routes of elimination for belatacept. Renal function does not play a significant role in the overall clearance of belatacept. One subject who experienced PML underwent plasmapheresis for approximately 1.5 hours on two occasions. There was a 79% reduction in serum belatacept concentration after 2 cycles of plasmapheresis. Limited data suggest that plasmapheresis may accelerate removal of belatacept from systemic circulation.

Drug-Drug Interaction

Like most therapeutic proteins, belatacept is not expected to be metabolized by CYP and therefore is not expected to have significant interactions with molecules that are metabolized by CYP.

Use with Mycophenolate Mofetil

In a PK substudy of two Phase 3 studies, the plasma concentrations of mycophenolic acid (MPA) were measured in 41 subjects who received fixed MMF doses of 500 to 1500 mg twice daily with either belatacept 5 mg/kg or CsA. The mean dose-normalized MPA Cmax and AUC0-12 were approximately 20% and 40% higher, respectively, with belatacept co-administration than with cyclosporine coadministration, consistent with the fact that inhibition of MPA enterohepatic recirculation occurs with CsA but not with belatacept. Therefore, there is a potential change of MPA exposure after crossover from cyclosporine to belatacept or from belatacept to CsA in subjects concomitantly receiving MMF.

Background Immunosuppressive Therapy with Belatacept

A cross-study comparison of PK data suggested a lack of effect of background immunosuppressive therapy (MMF + corticosteroids) on belatacept PK. Pharmacokinetics of belatacept in healthy subjects who received belatacept 5 mg/kg alone were compared with the PK in the renal transplant subjects with background immunosuppressive therapy of MMF, corticosteroids and basiliximab. Pharmacokinetic parameters of belatacept are comparable with respect to C_{max}, AUC (INF), T-HALF, CLT, and Vss.

Population Pharmacokinetic Analysis

Population PK analysis confirmed that the PK of belatacept is linear and time-invariant post-transplant. There was a trend toward higher clearance of belatacept with increasing body weight, supporting a weight-based dose of belatacept. Age, gender, race, renal function (measured by calculated GFR), hepatic function (measured by albumin), diabetes, and concomitant dialysis did not affect clearance of belatacept. Liver transplant subjects with marked abnormalities in liver function test post-transplant (defined as aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥ 5x upper limit of normal [ULN] and bilirubin ≥ 3x ULN) had similar belatacept trough concentrations (Cmin) to those who did not have marked abnormalities in liver function test. Limited data indicated that proteinuria and neutralizing antibody against belatacept did not affect the PK of belatacept in renal transplant subjects.

Plasma Concentration-Effect Relationship

The exposure-response (E-R) analyses suggested that the hazard of acute rejection decreases with time post-transplant and increases with baseline body weight.

In the time-to-event exposure-response analysis of acute rejection, no definitive relationship could be made between belatacept concentration and acute rejection hazard within the concentrations observed in subjects in the 2 belatacept phase 3 studies. Calculated GFR in renal transplant subjects did not differ for the 4 quartiles of average belatacept serum concentration (C_{avg}). These relationships suggested that the more intense regimen with twice the exposure to belatacept during Months 2 to 6 did not confer additional immunosuppressive benefit beyond that of the less intense regimen.

Graphic E-R analysis suggested that renal transplant subjects with CNS events (CNS PTLD and CNS infections, including the 1 renal transplant recipient with PML) tended to have higher C_{avg} during the first 6 months post-transplant compared with subjects who did not have these events. Additionally, there was a suggestion of an exposure-response relationship for serious infections; the risk of infections increased with higher exposure. Although definitive relationships could not be established because of limited data, the exposure-response data, when viewed in totality, showed an association between higher belatacept exposure and increased numbers of serious infections and CNS events. These data are consistent with the finding that less intense regimen is associated with a favorable safety profile compared with the MI regimen.

Clinical Safety with Belatacept

The adverse reaction profile associated with immunosuppressive agents is often difficult to establish because of the clinical events associated with the underlying disease and the concurrent use of multiple medicinal products.

The frequency of AEs was similar across treatment groups up to Month 36 in the core studies. The most common adverse events (≥ 20% on belatacept treatment) are anemia, diarrhea, urinary tract infection, peripheral edema, constipation, hypertension, pyrexia, graft dysfunction, cough, nausea, vomiting, headache, hypokalemia, hyperkalemia, and leukopenia.(31,32,39)

Safety in Healthy Subjects

In all the studies in healthy subjects, belatacept was generally well tolerated following single IV infusion doses of 0.1 to 20 mg/kg or following single subcutaneous doses of 50 mg to 250 mg. There were no deaths or SAEs. No subject discontinued due to AEs during the study. No dose-related trends in AEs were noted. All AEs were mild to moderate in intensity. There were no significant changes in vital signs or ECG parameters.

Overall, the percentage of healthy subjects that developed antibodies to belatacept was high (up to 100%) after receiving single doses of belatacept. However, these findings are not clinically relevant, because the incidence of drug-specific antibody formation in renal transplant recipients is low when belatacept is a component of multi-dose multi-drug immunosuppressive regimens

Safety in Core Renal Transplant Studies

A total of 949 subjects (477 in the MI regimen and 472 in the LI regimen) were treated in the 3 core *de novo* renal transplant studies.

In the pooled analysis, 311 (65%), 328 (70%), and 264 (57%) subjects had at least 36 months of exposure to the study medication in the belatacept MI, LI, and CsA groups, respectively. As expected in a transplant population, nearly all subjects experienced one or more adverse events (AEs). The frequency of serious adverse events (SAEs) was similar across the 3 treatment groups. The proportion of subjects with AEs leading to treatment discontinuation was lower in both belatacept groups than in the CsA group.

The cumulative number of deaths was lower in the belatacept LI regimen than with the belatacept MI regimen or CsA. The frequency of malignancies was lower with the belatacept LI regimen than with the belatacept MI regimen or CsA. The higher frequency in the belatacept MI group was driven by more cases of post-transplant lymphoproliferative disorder (PTLD) and squamous cell carcinoma of the skin.

The frequency of AEs leading to discontinuation was lower in both belatacept groups than in the CsA group (14%, 15%, and 19% in the belatacept MI, LI, and CsA groups, respectively). Most individual AEs leading to discontinuation were reported for no more than 1 subject. AEs leading to discontinuation in > 1% of belatacept subjects in either treatment group were transplant rejection, CMV infection, renal vein thrombosis, transplant rejection, and complications of transplanted kidney.

Clinically important AEs such as infections, malignancies (including PTLD), graft thrombosis, infusional events, proteinuria, and autoimmunity reported in the core studies are described below.

Drug-Related Adverse Events

Adverse events considered by the investigator to be related to the study drug were reported up to Month 36 in the core studies in 65%, 64%, and 78% subjects in the belatacept MI, LI, and CsA groups, respectively. The most common (≥ 2%) drug related AEs in the belatacept-treated subjects were UTI, CMV infection, nasopharyngitis, oral herpes, oral candidiasis, herpes zoster, upper respiratory tract infection, blood creatinine increased, dyslipidemia, hypercholesterolemia,

pyrexia, peripheral edema, diarrhea, proteinuria, hypertension, cough, headache, and transplant rejection. There were higher frequencies of related AEs of dyslipidemia, increased blood creatinine, hypertension, tremor, and hirsutism/hypertrichosis in the CsA group.

Drug-Related Serious Adverse Events

The most serious adverse reactions reported with belatacept were PTLD, predominantly central nervous system PTLD, and other malignancies, as well as serious infections, including JC virus-associated progressive multifocal leukoencephalophathy and polyoma virus nephropathy.

Other Significant Drug-Related Adverse Events

Post transplant Lymphoproliferative Disorder

An important risk observed with belatacept was PTLD, with the central nervous system being the predominant site of presentation. The overall risk of PTLD was higher in belatacept-treated subjects compared with CsA-treated subjects. Most cases of PTLD occurred during the first 18 months post-transplant. Although the highest risk of PTLD with belatacept was observed in Epstein-Barr virus (EBV)-negative subjects, EBV-positive subjects treated with belatacept also appeared to be at somewhat higher risk of PTLD than corresponding subjects treated with CsA.

The risk of PTLD was higher in EBV-seronegative patients compared with EBV-seropositive patients. EBV-seropositive patients are defined as those with evidence of acquired immunity shown by the presence of IgG antibodies to viral capsid antigen (VCA) and EBV nuclear antigen (EBNA). Epstein-Barr virus serology should be ascertained before starting administration of belatacept, and only patients who are EBV-seropositive should receive belatacept. Transplant recipients who are EBV seronegative, or who have unknown serostatus should not receive belatacept. Other known risk factors for PTLD include cytomegalovirus infection and T-cell-depleting therapy. T-cell-depleting therapies to treat acute rejection should be used cautiously.

Prophylaxis for CMV is recommended for at least 3 months after transplant. Patients who are EBV seropositive and CMV seronegative may be at increased risk for PTLD compared with patients who are EBV seropositive and CMV seropositive.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy is an often rapidly progressive and fatal opportunistic infection of the CNS that is caused by the JC virus, a human polyoma virus. In clinical trials with belatacept, two cases of PML were reported in patients who were receiving belatacept at higher cumulative doses and more frequently than the recommended regimen, along with mycophenolate mofetil and corticosteroids; one case occurred in a kidney transplant recipient, and the second case occurred in a liver transplant recipient. As PML has been associated with high levels of overall immunosuppression, the recommended doses and frequency of belatacept and concomitant immunosuppressive agents, including MMF, should not be exceeded. PML is usually diagnosed by brain imaging, cerebrospinal fluid testing for JC viral DNA by polymerase chain reaction, and/or brain biopsy. Consultation with a specialist (e.g., neurologist and/or infectious disease) should be considered for any suspected or confirmed cases of PML. If PML is

diagnosed, consideration should be given to reduction or withdrawal of immunosuppression, taking into account the risk to the allograft.

Infections

Patients receiving immunosuppressants, including belatacept, are at increased risk of developing bacterial, viral (CMV and herpes), fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Prophylaxis for cytomegalovirus is recommended for at least 3 months after transplant. Prophylaxis for *Pneumocystis jiroveci* also is recommended after transplant. Tuberculosis was more frequently observed in patients receiving belatacept than cyclosporine in clinical trials. Patients should be evaluated for tuberculosis and tested for latent infection prior to initiating belatacept. Treatment of latent tuberculosis infection should be initiated prior to belatacept use.

The frequency of infections including cytomegalovirus infection was similar in the belatacept LI, MI, and CsA groups. Serious infections, polyoma virus infection and fungal infections were less frequent in the belatacept LI group than in the belatacept MI and CsA groups. Herpes virus infections were more frequent in the belatacept MI and LI groups compared with the CsA group. Most reports of herpes virus infections were nonserious and did not lead to treatment discontinuation.

Tuberculosis (TB) was more common in both belatacept groups compared with the CsA group. Most cases of TB occurred in subjects who currently or previously resided in endemic areas. Central nervous system infections were reported at similar rates in the belatacept LI and CsA groups, but occurred more frequently in the belatacept MI group.

Polyoma Virus-Associated Nephropathy

Two cases of progressive multifocal leukoencephalopathy (PML) have been reported with belatacept; both occurred in subjects receiving the belatacept MI regimen, 1 in the renal transplant study IM103027 and 1 in the liver transplant study IM103045. Both subjects received the MI regimen as well as concomitant immunosuppressive therapy. The MI regimen in the liver transplant study is a more intensified regimen compared with the MI regimen in the renal transplant studies. In addition, the subject in the liver transplant study was receiving mycophenolate mofetil (MMF) at higher than the recommended dose for approximately 6 months. No cases of PML have been reported in subjects receiving the LI dose.

PVAN is associated with serious outcomes, including deteriorating renal function and kidney graft loss. Patient monitoring may help detect patients at risk for PVAN. Reductions in immunosuppression should be considered for patients who develop evidence of PVAN.

Immunosuppressant Drugs and Skin Cancer

Patients receiving any immunosuppressant, including belatacept, are at increased risk of developing malignancies (including those of the skin). Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Drug-Related Deaths

The table below lists all deaths that occurred in the core studies supporting the kidney transplant indication.

Table 2: Summary of All Deaths Reported Up to Database Lock: Pooled Core Study Population

Death Reason	Belatacept More Intense Regimen N = 477	Belatacept Less Intense Regimen N = 472	Cyclosporine N = 476
TOTAL DEATHS	38 (8.0)	32 (6.8)	40 (8.4)
UNKNOWNa	2 (0.4)	7 (1.5)	0
AES WITH OUTCOME OF DEATHb	36 (7.5)	25 (5.3)	40 (8.4)
TOTAL INFECTIONS AND INFESTATIONS	14 (2.9)	10 (2.1)	16 (3.4)
ACINETOBACTER INFECTION	0	1 (0.2)	0
BRONCHOPNEUMONIA	0 1	1 (0.2)	0
BRONCHOPULMONARY ASPERGILLOSIS	1	(0.2)	
CEREBRAL FUNGAL INFECTION	1 (0.2)	0	0
CRYPTOCOCCOSIS	0	1 (0.2)	0
CYTOMEGALOVIRUS INFECTION	1 (0.2)	0	0
DISSEMINATED TUBERCULOSIS	0	1 (0.2)	0
LOBAR PNEUMONIA	0	0	1 (0.2)
LUNG INFECTION	1 (0.2)	0	0
MENINGITIS CRYPTOCOCCAL	0	1 (0.2)	0
MUCORMYCOSIS	0	0	1 (0.2)
NECROTISING FASCIITIS	0	1 (0.2)	0

Table 2: Summary of All Deaths Reported Up to Database Lock: Pooled Core Study Population

OSTEOMYELITIS	1 (0.2)	0	0
PNEUMONIA	3 (0.6)	0	5 (1.1)
PNEUMONIA KLEBSIELLA	0	0	1 (0.2)
POLYOMAVIRUS-ASSOCIATED NEPHROPATHY	0	2 (0.4)	0
POSTOPERATIVE WOUND INFECTION	0	0	1 (0.2)
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY	1 (0.2)	0	0
PYELONEPHRITIS	0	0	1 (0.2)
SEPSIS	4 (0.8)	4 (0.8)	2 (0.4)
SEPTIC SHOCK	1 (0.2)	1 (0.2)	5 (1.1)
UROSEPSIS	0	0	1 (0.2)
WEST NILE VIRAL INFECTION	1 (0.2)	0	0
CARDIAC DISORDERS	10 (2.1)	5 (1.1)	14 (2.9)
ACUTE CORONARY SYNDROME	0	0	1 (0.2)
ACUTE MYOCARDIAL INFARCTION	1 (0.2)	0	0
AORTIC VALVE DISEASE	1 (0.2)	0	0
ARRHYTHMIA	1 (0.2)	0	0
ARTERIOSCLEROSIS CORONARY ARTERY	1 (0.2)	0	0
ATRIAL FIBRILLATION	0	0	1 (0.2)
CARDIAC ARREST	3 (0.6)	2 (0.4)	5 (1.1)
CARDIAC FAILURE	0	0	2 (0.4)
CARDIAC FAILURE CONGESTIVE	2 (0.4)	0	0

Table 2: Summary of All Deaths Reported Up to Database Lock: Pooled Core Study Population

CARDIO-RESPIRATORY ARREST	2 (0.4)	0	3 (0.6)
INTRACARDIAC THROMBUS	0	0	1 (0.2)
MYOCARDIAL INFARCTION	0	2 (0.4)	2 (0.4)
MYOCARDIAL ISCHAEMIA	0	0	2 (0.4)
PERICARDITIS	0	1 (0.2)	0
VENTRICULAR FIBRILLATION	0	0	1 (0.2
GENERAL DISORDERS AND ADMINISTRATION			
SITE CONDITIONS	7 (1.5)	3 (0.6)	1 (0.2)
CARDIAC DEATH	0	1 (0.2)	0
DEATH	0	1 (0.2)	0
MULTI-ORGAN FAILURE	2 (0.4)	0	1 (0.2)
SUDDEN DEATH	5 (1.0)	1 (0.2)	0
RESPIRATORY, THORACIC AND MEDIASTINAL			
DISORDERS	3 (0.6)	4 (0.8)	7 (1.5)
ACUTE PULMONARY OEDEMA	1 (0.2)	0	0
ACUTE RESPIRATORY FAILURE	0	1 (0.2)	2 (0.4)
DYSPNOEA	0	1 (0.2)	1 (0.2)
HYPOXIA	0	0	1 (0.2)
INTERSTITIAL LUNG DISEASE	0	0	1 (0.2)
PULMONARY EMBOLISM	0	0	2 (0.4)
PULMONARY	1 (0.2)	0	0

Table 2: Summary of All Deaths Reported Up to Database Lock: Pooled Core Study Population

HYPERTENSION			
PULMONARY OEDEMA	0	0	1 (0.2)
RESPIRATORY ARREST	1 (0.2)	1 (0.2)	0
RESPIRATORY FAILURE	0	1 (0.2)	0
GASTROINTESTINAL DISORDERS	3 (0.6)	2 (0.4)	3 (0.6)
ABDOMINAL PAIN	0	0	1 (0.2)
GASTRITIS EROSIVE	0	0	1 (0.2)
GASTROINTESTINAL HAEMORRHAGE	1 (0.2)	0	0
INGUINAL HERNIA OBSTRUCTIVE	1 (0.2)	0	0
INTESTINAL ISCHAEMIA	1 (0.2)	0	0
INTESTINAL OBSTRUCTION	0	0	1 (0.2)
LARGE INTESTINE PERFORATION	0	1 (0.2)	0
MESENTERIC OCCLUSION	0	1 (0.2)	0
THROMBOSIS MESENTERIC VESSEL	1 (0.2)	0	0
NEOPLASMS BENIGN MALIGNANT AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS)	2 (0.4)	5 (1.1)	4 (0.8)
B-CELL LYMPHOMA	1 (0.2)	0	0
CENTRAL NERVOUS SYSTEM LYMPHOMA	0	1 (0.2)	0
EPSTEIN-BARR VIRUS-ASSOCIATED LYMPHOPROLIFERA	0	1 (0.2)	1 (0.2)

Table 2: Summary of All Deaths Reported Up to Database Lock: Pooled Core Study Population

TIVE DISORDER			
KAPOSI'S SARCOMA	0	0	1 (0.2)
LUNG ADENOCARCINOMA	0	1 (0.2)	0
LUNG CANCER METASTATIC	0	0	1 (0.2)
LUNG NEOPLASM MALIGNANT	1 (0.2)	0	0
METASTASES TO LIVER	0	1 (0.2)	0
NON-SMALL CELL LUNG CANCER	0	1 (0.2)	0
SARCOMA	1 (0.2)	0	0
TRANSITIONAL CELL CARCINOMA	0	1 (0.2)	1 (0.2)
NERVOUS SYSTEM DISORDERS	2 (0.4)	2 (0.4)	2 (0.4)
CEREBELLAR SYNDROME	0	1 (0.2)	0
CEREBROVASCULAR ACCIDENT	2 (0.4)	0	2 (0.4)
COGNITIVE DISORDER	0	1 (0.2)	0

a Unknown death reason provided for subjects with death reported only on follow-up page

b Death reason was provided by adverse events with outcome of death for other subjects

Table includes all randomized and transplanted subjects from Studies -008 and -027.

All randomized, transplanted and treated subjects from Study -100.

Adverse events counting from randomization date for studies -008 and -027 and from transplant date and time for study -100.

56-day counting rule not applied for adverse events with outcome of death.

MedDRA Version: 13.0

Clinical Efficacy of Belatacept

Clinical efficacy is summarized in Table 3, which presents outcomes up to Year 3 in studies IM103008 and IM103027.

Table 3: Key Efficacy Outcomes Up to Year 3 in IM103008 and IM3027

	IM103008 (SCD Population)			IM103027 (ECD Population)		
	Belatacept MI N = 219	**Belatacept LI N = 226**	**CsA N = 221**	**Belatacept MI N = 184**	**Belatacept LI N = 175**	**Cyclosporine N = 184**
Subject and Graft Survival (n, %)						
Month 12	**209 (95.4)**	**218 (96.5)**	**206 (93.2)**	**159 (86.4)**	**155 (88.6)**	**157 (85.3)**
Difference from CsA (97.3% CI)	2.2 (-2.9, 7.5)	3.2 (-1.5, 8.4)	---	1.1 (-7.1, 9.3)	3.2 (-4.8, 11.3)	---
Graft Loss (n, %)	4 (1.8)	5 (2.2)	8 (3.6)	17 (9.2)	16 (9.1)	20 (10.9)
Death (n, %)	6 (2.7)	4 (1.8)	7 (3.2)	8 (4.3)	5 (2.9)	8 (4.3)
Imputed as Graft Loss or Death (%)	0	0	1 (0.5)	2 (1.1)	0	2 (1.1)
Month 36	**202 (92.2)**	**208 (92.0)**	**196 (88.7)**	**148 (80.4)**	**144 (82.3)**	**147 (79.9)**
Difference from CsA (97.3% CI)	3.5 (-2.8, 10.0)	3.3 (-2.9, 9.8)	---	0.5 (-8.7, 9.8)	2.4 (-6.9, 11.6)	---
Graft Loss (n, %)	10 (4.6)	9 (4.0)	10 (4.5)	18 (9.8)	21 (12.0)	23 (12.5)
Death (n, %)	9 (4.1)	10 (4.4)	15 (6.8)	22 (12.0)	15 (8.6)	17 (9.2)
Imputed as Graft Loss or Death (%)	0 (0.0)	0 (0.0)	1 (0.5)	0	0	1 (0.5)
Mean (SD) measured GFR with Imputation[a] (mL/min/1.73 m^2)						
Month 12	**65.0 (30.0)**	**63.4 (27.7)**	**50.4 (18.7)**	**52.1 (21.9)**	**49.5 (25.8)**	**45.2 (21.1)**
Estimated diff. from CsA (97.3% CI)	14.6 (8.9, 20.4)	13.0 (7.3, 18.7)	---	6.9 (1.1, 12.7)	4.3 (-1.5, 10.1)	---
P-Value	< 0.0001	< 0.0001	---	0.0089	0.0995	---
Month 24	**65.0 (27.2)**	**67.9 (29.9)**	**50.5 (20.5)**	**51.5 (22.2)**	**49.7 (23.7)**	**45.0 (27.2)**
Estimated diff. from CsA (97.3% CI)	14.5 (8.5, 20.5)	17.4 (11.5, 23.4)	---	6.6 (0, 13.1)	4.7 (-1.8, 11.3)	---
P-Value	<0.0001	<0.0001	---	0.0276	0.1080	---

	IM103008 (SCD Population)			IM103027 (ECD Population)		
	Belatacept MI N = 219	**Belatacept LI N = 226**	**CsA N = 221**	**Belatacept MI N = 184**	**Belatacept LI N = 175**	**Cyclosporine N = 184**
Month 36 (not performed per protocol)	---	---	---	---	---	---
Mean (SD) cGFR with Imputation[b] (mL/min/1.73 m^2)						
Month 12	**65.2 (23.5)**	**65.4 (22.9)**	**50.1 (21.0)**	**44.4 (22.8)**	**44.5 (21.8)**	**36.5 (21.1)**
Difference from CsA (97.3% CI)	15.1 (10.1, 20.1)	15.3 (10.3, 20.3)	---	7.8 (2.4, 13.2)	8.0 (2.5, 13.4)	---
Month 36	**65.2 (23.6)**	**65.8 (27.0)**	**44.4 (26.3)**	**42.7 (27.6)**	**42.2 (25.2)**	**31.5 (22.1)**
Difference from CsA (97.3% CI)	20.8 (14.8, 26.9)	21.4 (15.4, 27.4)	---	11.2 (4.7, 17.7)	10.7 (4.3, 17.2)	---
Acute Rejection (n, %)[c]						
Month 12	**49 (22.4)**	**39 (17.3)**	**16 (7.2)**	**32 (17.4)**	**31 (17.7)**	**26 (14.1)**
Difference from CsA (97.3% CI)	15.1 (7.9, 22.7)[d]	10.0 (3.3, 17.1)	---	3.5 (-5.2, 11.8)	3.4 (-5.0, 12.3)	---
Month 36	**53 (24.2)**	**39 (17.3)**	**21 (9.5)**	**33 (17.9)**	**33 (18.9)**	**29 (15.8)**
Difference from CsA (97.3% CI)	14.7 (7.0, 22.6)	7.8 (0.6, 15.0)	---	2.2 (-6.6, 10.9)	3.1 (-5.8, 12.1)	---

a Imputation Method: No imputation for subjects with graft loss or death, however, if a value was available, it was used in the analysis. For other missing data, measured GFR at other time-points or cGFR at the same time point was used to impute the missing values at Month 12 or 24.

b For missing data due to graft loss or death, cGFR after graft loss or death was imputed as 0 (primary analysis) by Month 36.

c Acute rejection is defined as central biopsy proven rejection that was either (1) clinically suspected by protocol defined reasons or (2) clinically suspected by other reasons and treated.

d The 20 % non-inferiority margin was not met in the belatacept MI group.

Table 4 summarizes key efficacy findings up to Month 12 in study IM103100.

Table 4: Efficacy Findings Up to Month 12 in Study IMI03100

Key Efficacy Findings up to Month 12	Belatacept MI N = 74	Belatacept LI N = 71	CsA N = 73
Acute Rejection at Month 6 (n, %)[a]	5 (6.8)	4 (5.6)	6 (8.2)
Difference from CsA (95% CI)	-1.5 (-10.0, 7.0)	-2.6 (-10.9, 5.7)	---
Acute Rejection at Month 12 (n, %)	5 (6.8)	4 (5.6)	6 (8.2)
Difference from CsA (95% CI)	-1.5 (-10.0, 7.0)	-2.6 (-10.9, 5.7)	---
BPAR at Month 6	11 (14.9)	17 (23.9)	13 (17.8)
Difference from CsA (95% CI)	-2.9 (-14.9, 9.0)	6.1 (-7.1, 19.4)	---
BPAR at Month 12	14 (18.9)	21 (29.6)	13 (17.8)
Difference from CsA (95% CI)	1.1 (-11.4, 13.6)	11.8 (-2.0, 25.5)	---
Death or Graft Loss (n, %)	4 (5.4)	1 (1.4)	6 (8.2)
Difference from CsA (95% CI)	-2.8 (-11.0, 5.3)	-6.8 (-13.7, 0.1)	---
Graft Loss (n, %)	3 (4.1)	1 (1.4)	3 (4.1)
Death (n, %)	1 (1.4)	0	4 (5.5)
Mean (SD) measured GFR mL/min/1.73 m^2	66.3 (20.7)	62.1 (15.9)	53.5 (16.4)
Mean (SD) calculated GFR mL/min/1.73 m^2	72.4 (22.5)	73.2 (22.5)	68.0 (28.1)
Prevalence of CAN (n, %) up to Month 12	15 (28.8)	11 (20.4)	20 (44.4)
Difference from CsA (95% CI)	-15.6 (-34.6, 3.4)	-24.1 (-42.1, 6.0)	---

OVERALL RISK/BENEFIT ASSESSMENT

Belatacept represents a potential new treatment option for renal transplant recipients, which addresses the current unmet need for an immunosuppressive treatment that provides short-term outcomes comparable to calcineurin inhibitors (CNIs) with the potential to avoid their renal, cardiovascular, and metabolic toxicities. In the Phase 3 studies in renal transplant recipients of kidneys from standard or extended criteria donors, belatacept was comparable to cyclosporine (CsA) on the proportion of patients who survive with a functioning allograft, and on overall mortality. In addition, belatacept resulted in clinically meaningful reductions in the proportions of patients with advanced renal dysfunction, defined as CKD stage 4 or 5. While rates of acute rejection (AR) were higher with belatacept than CsA, the rates of rejection that led to severe renal dysfunction or graft loss were low.

The principal risks associated with belatacept are PTLD with CNS involvement and serious infections, including PML. The impact of these concerns on the patient and the graft were captured in the primary survival endpoint, indicating that, while important, they did not outweigh the overall benefits of belatacept to the patient or the allograft.

Due to differences in patient populations and treatment regimens studied, the termination of the Phase 2 belatacept liver study is not considered to impact the benefit/risk assessment in renal transplantation.

Based upon the totality of available evidence, the current study offers a favorable benefit/risk profile to study subjects, and the potential to continue to provide important data for the development of new immunosuppressive regimens that address important unmet needs.

Initial Experience with Belatacept and Early CSWD/CNI Free Immunosuppression

A major reason to pursue early CSWD and also CNI free immunosuppression is to reduce CV risk in renal transplant recipients. It is well known that renal transplant recipients (and dialysis patients also) are at significantly increased risk for cardiovascular disease, and that the primary modifiable risk factors are renal function (GFR)- which is modifiable primarily by renal transplantation, obesity (modifiable by medical or surgical weight loss), and immunosuppressant-associated exacerbation of CV risk factors.

As noted above, substantial prior studies with early CSWD under modern immunosuppression have shown that CV risk can be substantially reduced with an acceptably low risk of acute rejection. However, renal transplant recipients remain at increased CV risk because of the exacerbation of CV risk factors by calcineurin inhibitors - hypertension, diabetes, and hyperlipidemia are all worsened by calcineurin inhibitors.

Therefore, the next step in optimizing CV-risk profiles of immunosuppressive regimens is to minimize calcineurin inhibitor exposure in a steroid free setting. As noted above, such an approach is reasonable, because glucocorticoids and CNIs exert similar effects on cardiovascular risk parameters, and it appears likely that their effects may be additive based on results from previous CSWD trials. Of particular relevance to the proposed multicenter randomized CSWD trial with belatacept, is a pilot study of belatacept-based CNI free/CSWD phase 2, 1 year, randomized, open label, multi-center trial in which recipients of living donor or standard criteria deceased donor kidney transplants were randomized 1:1:1 to receive one of three immunosuppressive regimens under early CSWD with thymoglobulin induction (26). The control group received tacrolimus/ mycophenolate mofetil, and the two belatacept groups both were CNI free: in one, patients received mycophenolate mofetil and in the other, patients received sirolimus. All subjects received thymoglobulin (1.5 mg/kg IV on Days 1, 2, 3, and 4) and glucocorticoids (for four days following transplantation). Belatacept dose regimen was the more intense (MI) regimen (24, 25). The primary endpoint was acute rejection at 6 months post-transplantation. Results are presented in the Table below:

Outcome at 12 months # pts (% of pts)	Belatacept + MMF	Belatacept + Sirolimus	Tacrolimus + MMF
# patients	33	26	30
Acute rejection	4 (12)	1 (4)	1 (3)
Acute rejection at month 6	5 (15)	1 (4)	1 (3)
Patient and graft survival	30 (91)	24 (92)	30 (100)
Death	1 (3)	0	0
Graft Loss	2 (6)	2 (8)	0
Mean cGFR ml/min/m_2	64 (27)	62 (31)	54 (15)
CNI and steroid free patients	24 (73)	18 (69)	1 (3)
Steroid free patients	24 (73)	20 (77)	28 (93)
Mouth ulceration	2 (6)	6 (23)	0
Wound dehiscence	0	0	3 (10)
Tremors	1 (3)	0	7 (23)

The single patient death occurred due to pneumonia. Cardiovascular risk data including hypertension, serum lipids, new-onset diabetes after transplant (NODAT) were collected, but data are not yet available.
In conclusion, this pilot study demonstrated acceptable patient survival, graft survival, and acute rejection rates with excellent renal function and cardiovascular outcomes.

Upon review of clinicaltrials.gov, two ongoing trials were identified that incorporated the combination of alemtuzumab induction and belatacept maintenance therapy. The trials are entitled, “Belatacept Post Depletional Repopulation to Facilitate Tolerance” (NCT00565773) and “Optimization of Belatacept Usage as a Means of Avoiding CNI and Steroids in Renal Transplantation” (NCT01436305). The current results of first trial initiated in 2007 were recently summarized in abstract form at the American Transplant Congress, June 2012. This abstract entitled, “Kidney Transplantation Using Alemtuzumab Induction and Belatacept/Sirolimus Maintenance Therapy” reported results of 20 patients enrolled with a mean follow-up of >700 days. The current patient and graft survival rate is 100% with a mean serum creatinine at 24 months of 1.2mg/dL with no graft thrombosis. Personal communications with the investigative team confirmed there have been no graft thrombosis in these patients. In addition, the timing of alemtuzumab and belatacept administration was clarified. Their protocol states that alemtuzumab is administered intraoperatively and the belatacept is given within the first 24hrs post transplant. Their communications stated that this typically translates to the administration of belatacept at approximately 18hrs post alemtuzumab infusions. They have identified no unexpected SAEs during this trial.

The second trial, “Optimization of Belatacept Usage as a Means of Avoiding CNI and Steroids in Renal Transplantation” (NCT01436305) was initiated in September 2011. This trial compares three treatment arms consisting of the following. Arm 1: Alemtuzumab induction, MMF and tacrolimus maintenance, Arm 2: Alemtuzumab induction, MMF and belatacept maintenance, and Arm 3: Basiliximab induction, tacrolimus for 3 months, MMF and belatacept maintenance. To date 19 patients have been consented to the trial. Six out of the 19 were randomized to Arm 2 with Alemtuzumab induction, MMF, and belatacept maintenance however; there have been two graft thromboses that occurred in this arm. The first thrombosis occurred on December 27, 2011, and the second on March 28, 2012. Only one case resulted in graft loss. In the first case, alemtuzumab was administered over 1.5hrs in the OR followed immediately by a belatacept infusion in a living donor kidney transplant recipient. The following day, the renal ultrasound confirmed reversal of flow in the renal artery with no visualization of the renal vein. The patient was returned to the OR for re exploration. The kidney was noted to have a renal vein thrombosis, which was treated by explantation, surgical thrombectomy, and re-implantation. Minimal flow was noted following reimplantation. The patient was also noted to have laboratory evidence of disseminated intravascular coagulation at this time. The investigator identified the renal vein thrombosis and allograft loss as possibly related to alemtuzumab or belatacept.

In the second case a deceased donor kidney transplant recipient received an alemtuzumab infusion over 2 hours during the transplant procedure, which was followed by a 30 minute belatacept infusion. The patient developed reduced urine output despite biphasic renal flow on repeated ultrasounds. Upon reexploration, a non-occlusive platelet plug was found lining the arterial anastomosis and was removed with renal blood flow re established. The subject currently has a functioning graft and the event has resolved without sequelae. The investigator considered the arterial thrombosis to be possibly related to alemtuzumab and belatacept.

DAIT NIAID, the study sponsor, the manufacturer and ourselves have evaluated these cases and do not believe they represent an unanticipated problem that places enrolled subjects at greater risk than previously known or recognized. However, protocol adjustments have been made to mitigate any risk that may be associated with thrombosis secondary to co administration of these agents. Actions that have been taken include the following

1. Proper timing of methylprednisolone administration 30-60 minutes prior to alemtuzumab administration with the induction of anesthesia to minimize any first dose reactions associated with the cytokine release syndrome that may occur following alemtuzumab administration.
2. Administer the first dose of belatacept within 12-24 hours post reperfusion. The timing will allow for adequate separation of administration to identify any potential adverse events associated with either agent while not exposing the subjects to additional risks.

The proposed Phase 4 study is designed to determine whether belatacept, in combination with other immunosuppressive agents (rabbit antithymocyte globulin, mycophenolate mofetil/EC mycophenolate sodium), may provide acceptable efficacy and safety in de novo kidney transplant recipients, in a regimen that provides simultaneous CNI freedom and early CSWD.

2. Purpose and Study Hypothesis

Purpose:

The study purpose is to determine the safety and efficacy of a belatacept-based immunosuppressive regimen (calcineurin inhibitor free) with alemtuzumab or rabbit antithymocyte globulin induction and early glucocorticoid withdrawal (CSWD) compared to a tacrolimus-based regimen with rabbit antithymocyte globulin induction and early glucocorticoid withdrawal in renal transplant recipients.

Study Hypotheses:

Belatacept-based immunosuppressive regimen with alemtuzumab induction, MMF/MPA, and early glucocorticoid withdrawal (Group A) in renal transplant recipients will lead to less risk of graft loss, patient death, or reduced renal function at 12 months as compared to a tacrolimus-based immunosuppressive regimen with rabbit antithymocyte globulin, MMF/MPA, and early glucocorticoid withdrawal in renal transplant recipients (Group C).

OR

Belatacept-based immunosuppressive regimen with rabbit antithymocyte globulin induction, MMF/MPA and early glucocorticoid withdrawal (Group B) in renal transplant recipients will lead to less risk of graft loss, patient death, or reduced renal function at 12 months as compared to a tacrolimus-based immunosuppressive regimen with rabbit antithymocyte globulin, MMP/MPA, and early glucocorticoid withdrawal in renal transplant recipients (Group C).

3. Objectives/Endpoints:

3.1 Primary Endpoint:

Primary Endpoint:

The primary endpoint is to ascertain the combinatorial endpoint rate at 12 months as defined as

- Patient Death or Graft Loss or estimated GFR (eGFR) (MDRD) < 45 mL/min

3.2 Secondary and Tertiary Endpoints:

Key Secondary Endpoints:

Key secondary endpoints will extensively assess efficacy associated with each regimen at 6, 12, and 24 months to further quantitate these outcomes.

- Composite endpoint at 6 and 24 months (12 months was selected as the time for evaluating the composite endpoint as the primary endpoint, as above)
- Incidence by Banff 2007 criteria of biopsy proven acute rejection (BPAR) stratified by type (ACR, AMR, or Mixed rejection)
- Death-Censored Graft Survival
- Proportion of patients with eGFR (MDRD) < 30 mL/min
- Proportion of patients developing anti-HLA antibodies against the donor (donor specific antibodies) (DSA) after transplantation

Tertiary Endpoints:

Tertiary endpoints will extensively assess additional safety, efficacy and salient endpoints associated with each regimen at 6, 12, and 24 months to further quantitate these outcomes.

- Severity of rejection by Banff 2007 criteria, treatment, and outcome of BPAR stratified by type (ACR, AMR, or Mixed rejection)
- Proportion of patients requiring anti-lymphocyte therapy for BPAR

- Causes of patient and graft loss
- Incidence, severity and treatment of metabolic and cardiovascular comorbidity (new onset diabetes after transplantation [NODAT], exacerbation of preexisting diabetes, hyperlipidemias [total serum cholesterol, HDL, LDL, triglycerides], hypertension, number of anti-hypertensive medications)
- Patient weight change and BMI from pre-transplant
- Change in Framingham Heart Study Coronary Score Heart Disease Risk Point Total
- Cardiovascular events (myocardial infarction, angina, cerebral vascular accident, transient ischemic attack, cardiovascular intervention/procedure or sudden death)
- Incidence of infections and posttransplant malignancies (including PTLD)
- Incidence of leukopenia (White Blood Cell Count < 2000 cells/uL)
- Incidence of anemia (Hg < 7 g/dL)
- Incidence of proteinuria (elevated protein/creatinine ratio >0.8 grams protein per gram creatinine)
- Cumulative total thymoglobulin dosing for induction (mg)
- Renal function assessment by calculated GFR and urine protein creatinine ratio
- Proportion of subjects that remain glucocorticoid-free
- Proportion of subjects on glucocorticoids and mean glucocorticoid dose (mg)
- Patient quality of life (QoL)/Side Effect Assessment
- Incidence of discontinuation of study treatment
- Comparison of immunosuppression-related adverse effects by treatment group
- To determine the earliest reliable time-point that can be used for prediction of future onset of acute rejection and NODAT

4. Study Design

4.1 Patient Population:

4.1.1 Inclusion criteria:

1. Male and female patients ≥ 18 years of age.
2. Patient who is receiving a renal transplant from a living or deceased donor.
3. Female patients of child bearing potential must have a negative urine or serum pregnancy test within the past 48 hours prior to study inclusion.
4. The patient has given written informed consent to participate in the study.

4.1.2 Exclusion criteria:

Patients meeting any of the following criteria at baseline will be excluded from study participation.

1. Patient has previously received an organ transplant other than a kidney.
2. Patient is receiving an HLA identical living donor transplant.
3. Patient who is a recipient of a multiple organ transplant.
4. Patient has a most recent cytotoxic PRA of >25% or calculated PRA >50% where multiple moderate level HLA antibodies exist and in the opinion of the PI represents substantial HLA sensitization.
5. Patient with a positive T or B cell crossmatch that is primarily due to HLA antibodies.
6. Patient with a donor specific antibody (DSA) as deemed by the local PI to be associated with significant risk of rejection.
7. Patient has received an ABO incompatible donor kidney.
8. The deceased donor and/or deceased donor kidney meet any of the following extended criteria for organ donation (ECD):

a. Donor age ≥ 60 years
OR
b. Donor age 50-59 years and 1 of the following:
    i. Cerebrovascular accident (CVA) + hypertension + SCr > 1.5 mg/dL **OR**
    ii. CVA + hypertension **OR**
    iii. CVA + SCr > 1.5 mg/dL **OR**
    iv. Hypertension + SCr > 1.5 mg/dL
OR
c. CIT ≥ 24 hours, donor age > 10 years
OR
d. Donation after cardiac death (DCD)

9. Recipients will be receiving a dual or en bloc kidney transplant.
10. Donor anticipated cold ischemia is >30hours.
11. Recipient that is seropositive for hepatitis C virus (HCV) with detectable Hepatitis C viral load are excluded. HCV seropositive patients with a negative HCV viral load testing may be included.
12. Recipients who are Hepatitis B core antibody seropositive are eligible if their hepatitis B viral loads are negative. After transplant, their hepatitis B viral loads will be monitored every three months for the first year after transplant. If hepatitis B viral loads become positive, patients will be treated per institutional standard of care.
13. Patients who are Hepatitis B surface antibody seropositive and who receive a kidney from a Hepatitis B core surface antibody positive donor may be included.
14. Recipient or donor is known to be seropositive for human immunodeficiency virus (HIV).
15. Recipient who is seronegative for Epstein Barr virus (EBV).
16. Patient has uncontrolled concomitant infection or any other unstable medical condition that could interfere with the study objectives.
17. Patients with thrombocytopenia (PLT <75,000/mm_3), and/or leucopoenia (WBC < 2,000/mm_3), or anemia (hemoglobin < 6 g/dL) prior to study inclusion.
18. Patient is taking or has been taking an investigational drug in the 30 days prior to transplant.
19. Patient who has undergone desensitization therapy within 6 months prior to transplant.
20. Patient has a known hypersensitivity to belatacept, tacrolimus, mycophenolate mofetil, alemtuzumab, rabbit anti-thymocyte globulin, or glucocorticoids.
21. Patient is receiving chronic steroid therapy at the time of transplant.
22. Patients with a history of cancer (other than non-melanoma skin cell cancers cured by local resection) within the last 5 years, unless they have an expected disease free survival of ≥95%.
23. Patient is pregnant, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by positive human Chorionic Gonadotropin (hCG) laboratory test.
24. Women of childbearing potential must use reliable contraception simultaneously, unless they are status post bilateral tubal ligation, bilateral oophorectomy, or hysterectomy.
25. Patient has any form of substance abuse, psychiatric disorder or a condition that, in the opinion of the investigator, may invalidate communication with the investigator.
26. Inability to cooperate or communicate with the investigator.

4.2 Number of Centers and Patients

A total of 315 patients will be consecutively enrolled at eight centers. Patients receiving a renal transplant and meeting enrollment criteria will be randomized 1:1:1 into three groups, with 105 patients in each group. Group C is considered the control group and Groups A and B are considered the test groups.

4) **Group A (n = 105):** Alemtuzumab + belatacept + mycophenolate mofetil /Enteric coated mycophenolate sodium + early cessation of steroids

5) **Group B (n = 105):** Rabbit antithymocyte globulin + belatacept + mycophenolate mofetil /Enteric coated (EC) mycophenolate sodium + early cessation of steroids

6) **Group C (n = 105):** Rabbit antithymocyte globulin + tacrolimus + mycophenolate mofetil /Enteric coated (EC) mycophenolate sodium + early cessation of steroids

4.3 Randomization Procedures

Once the subject has consented and has met all entry criteria (inclusion and exclusion), the subject may be randomized. The randomization will be stratified by center, African American vs. non-African American race, and living vs deceased donor. Adverse Event reporting for all subjects will begin at the time of transplantation, not randomization. Each subject who is qualified for treatment will be assigned a unique randomization number. Allocation of the randomization will be concealed to all study staff prior to randomization. There is no blinding in this study.

4.4 Study duration

The active study duration will be approximately 42 months total with an 18 month enrollment period and 24 months of follow-up. The enrollment period will begin with study drug availability.

A 3-6 month period before open enrollment will be required for study activation with an additional 3-6 month period post last follow-up for data analysis.

5. Study Treatments

The overall immunosuppressive plan is outlined below in text and table.

Agent/Class	Group A	Group B	Group C
Induction Agent	Alemtuzumab	Antithymocyte globulin	Antithymocyte globulin
Belatacept/Tacrolimus	Belatacept	Belatacept	Tacrolimus
Antiproliferative	MMF/Myfortic	MMF/Myfortic	MMF/Myfortic
Corticosteroids	CSWD	CSWD	CSWD

INDUCTION IMMUNOSUPPRESSION

Group A:

Alemtuzumab will be dosed on day of transplant (Study Day 1) at dose of 30 mg given intravenously (IV) over a period of 2 hours after induction of anesthesia. Methylprednisolone IV will be administered 30-60 minutes prior to the administration of alemtuzumab.

Groups B and C:

All patients will receive rabbit antithymocyte globulin.

Rabbit antithymocyte globulin will be dosed post-operatively at a total cumulative dose of 4.0-6.0mg/kg given by days 5-10 post-transplant. It will be administered by local standards of care with the following recommendations. The initial intravenous intra-operative dose will be administered approximately one hour after the methylprednisolone dose. The first dose will be administered so that approximately 25% of the dose is infused prior to revascularization of the graft. Subsequent doses will be administered over a minimum of 4 hours. Premedication with acetaminophen 650mg p.o. and diphenhydramine 25mg p.o. prior to rabbit antithymocyte globulin dose will be given to reduce the incidence of infusion reactions.

MAINTENANCE IMMUNOSUPPRESSION

Groups A and B will receive belatacept in combination with mycophenolate mofetil/EC mycophenolate sodium/early glucocorticoid withdrawal

Belatacept will be administered via intravenous (IV) infusion according to the FDA approved dosage recommendations. Subjects randomized to belatacept arms will receive the first dose of IV belatacept (10 mg/kg) within 12-24 hours post reperfusion. The second dose will be given between post-transplant days 4 -6 (Study Days 5-7), and then study days 14, 28, 56, and 84 (12 weeks) and then subjects will receive belatacept at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial at 24 months (104 weeks). Study Day 1 is defined as the day of transplant.

Group C will receive tacrolimus in combination with mycophenolate mofetil/EC mycophenolate sodium/early glucocorticoid withdrawal

Tacrolimus will be administered orally twice daily (BID). The recommended total initial dose of tacrolimus is 0.1 mg/kg/day in two divided doses orally. Tacrolimus should be started post-transplant within 48 hours or when serum

creatinine drops lower than 4mg/dL, whichever comes first. The initial targeted trough level of tacrolimus will be 8 - 12 ng/mL for Days 1 through 30, with dose reduction to achieve a 12-hour trough target of 5 - 10 ng/mL thereafter.

Groups A, **B and C** will receive mycophenolate mofetil/EC mycophenolate sodium and early glucocorticoid withdrawal.

The first dose of mycophenolate mofetil/EC mycophenolate sodium will be administered pre-operatively. Patients receiving mycophenolate mofetil will be dosed 1000 mg twice daily (2000mg/day). Patients receiving EC mycophenolate sodium will be dosed 720 mg twice daily (1440 mg/day). Dose may be increased for African American transplant recipients to mycophenolate mofetil 1500 mg twice daily (3000mg/day) or EC mycophenolate sodium 1080 mg twice daily (2160 mg/day).

These doses of mycophenolate mofetil and EC mycophenolate sodium have shown efficacy, pharmacokinetic and pharmacodynamic equivalence.

Subsequent dosage adjustments based on physician discretion are permitted due to toxicity only.

Glucocorticoid therapy will be administered as described. Methylprednisolone will be administered on Days 1 through 3. Additional tapering doses of glucocorticoids will continue to be given until Day 5 as below:
Day 1 (day of transplant): 500mg IV prior to alemtuzumab (Group A) or rabbit antithymocyte globulin (Groups B and C)
Day 2: 250mg IV
Day 3: 125mg IV
Day 4: 80mg p.o.
Day 5: 60mg p.o.
No further steroids

5.1. **Study Immunosuppressant Treatment Table**

	Belatacept (Groups A&B)		**Tacrolimus (Group C)**	**Induction (Group A)**	**Induction (Groups B&C)**	**Steroids (All Groups)**	**Mycophenolate mofetil/EC Mycophenolate Sodium (All Groups)**
	10 mg/kg	**5 mg/kg**	**0.1mg/kg/day p.o. divided twice daily**	**Alemtuzumab 30mg IV**	**Rabbit antithymocyte globulin 1.5mg/kg IV**		
Day of Transplant (D1)	X1		Start tacrolimus when Scr < 4 mg/dL or within 48 hours of transplant Goal tacrolimus trough 8-12 ng/mL until day 30	X	X	Methylpred 500mg IV	Introduce Mycophenolate mofetil/EC Mycophenolate Sodium on D1 pre-op. Mycophenolate mofetil 1g p.o. BID (EC Mycophenolate Sodium 720mg p.o. BID). African American recipients may receive Mycophenolate mofetil 1.5 g p.o. BID (EC Mycophenolate Sodium 1080mg p.o. BID). Dose adjustments can be made based on MD discretion
D2					Subsequent thymo doses should be given so that total cumulative dose of 4-6 mg/kg is given by days 5-10	Methylpred 250mg IV	
D3						Methylpred 125mg IV	
D4						Prednisone 80mg p.o.	
D5	X2					Prednisone 60mg p.o.	
D6						No further steroids	
D7							
D8							
D9							
D 10							
W2 (D14)	X						
D15-D 20							
D 21-D27							
W4 (D 28)	X						
W8 (D 56)	X		Goal tacrolimus trough 5-10 ng/mL thereafter				
W12 (M 3)	X						
W16		X					
W20		X					
W24 (M 6)		X					
W28		X					
W32		X					
W36 (M 9)		X					
W40		X					
W44		X					
W48		X					
W52 (M12)		X					
W56		X					
W60		X					
W64 (M 15)		X					
W68		X					
W72		X					
W76		X					
W80 (M18)		X					
W84		X					
W88		X					
W92 (M21)		X					
W96		X					
W100		X					
W104 (M24)		X					

1. **Initial Belatacept dose will be <u>administered</u>** <u>within 12-24 hours post reperfusion</u>
2. **Belatacept dose is to be given once between Study days 5 – 7, with intention of administering as an outpatient.**

5.2 Individual Immunosuppressive Agent Administration and Monitoring

5.2.1 Alemtuzumab Administration

Alemtuzumab will be dosed on day of transplant (Day 1) at dose of 30 mg given intravenously (IV) over a period of 2 hours. Methylprednisolone IV will be administered 30-60 minutes prior to the administration of alemtuzumab. Infusion of the alemtuzumab should not begin until after the surgeon has made an initial preoperative assessment, and has concluded that the subject remains a transplant candidate.

5.2.2 Rabbit antithymocyte globulin Administration and Monitoring

Rabbit antithymocyte globulin will be dosed post-operatively at a total cumulative dose of 4.0-6.0mg/kg given by days 5-10 post-transplant. It will be administered by local standards of care with the following recommendations. The initial intravenous intra-operative dose will be administered approximately one hour after the methylprednisolone dose. Infusion of the rabbit antithymocyte globulin should not begin until after the surgeon has made an initial preoperative assessment, and has concluded that the subject remains a transplant candidate. The first dose will be administered so that approximately 25% of the dose is infused prior to revascularization of the graft. Subsequent doses will be administered over a minimum of 4 hours. Premedication with acetaminophen 650mg p.o. and diphenhydramine 25mg p.o. prior to rabbit antithymocyte globulin dose will be given to reduce the incidence of infusion reactions.

Rabbit antithymocyte globulin recommended dosage adjustments are as follows.

WBC (cells/μL) and Platelets (cells/μL)	**Reduction in current rabbit antithymocyte globulin dose**
WBC > 3000 cells/μL, PLT >100,000 cells/μL	None
WBC <3000 and >2000 cells/μL, PLT 50,000 – 100,000 cells/μL	Reduce dose by 50%
WBC <2000 cells/μL and PLT <50,000 cells/μL	Hold until WBC > 2000 cells/μL or PLT > 50,000 cells/μL

5.2.3 Glucocorticoid Administration

Group A, B, and C:
Glucocorticoid therapy will be administered as described. Methylprednisolone will be administered on Days 1 through 3. Additional tapering doses of glucocorticoids will continue to be given until Day 5 as below:
Day 1 (day of transplant): 500mg IV prior to alemtuzumab (Group A) or rabbit antithymocyte globulin (Groups B and C)
Day 2: 250mg IV
Day 3: 125mg IV
Day 4: 80mg p.o.
Day 5: 60mg p.o.
No further steroids

5.2.4 Belatacept Administration and Monitoring

Subjects randomized to either group A or B will receive belatacept via intravenous (IV) infusion according to the FDA approved dosage recommendations. Subjects randomized to belatacept arms will receive the first dose of IV belatacept (10 mg/kg) within 12-24 hours post reperfusion. The second dose will be given between post-transplant days 4 -6 (Study Days 5-7), and then study days 14, 28, 56, and 84 (12 weeks) and then subjects will receive belatacept at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial at 24 months (104 weeks). Study Day 1 is defined as the day of transplant.

Infusion of the initial Study Day 1/Study Day 2 belatacept dose must be given within 12-24 hours post reperfusion. It cannot be administered prior to or concurrently with either induction immunosuppressive agent. Infusion doses will be based on the subject's actual body weight at study Day 1 (day of transplant), and will not be modified during the course of the study, unless there is a change of body weight greater than ± 10%. Study drug should be administered to the subject at a relatively constant rate over 30 minutes. No additional monitoring will be required during the infusion.

A negative urine or serum pregnancy test is required prior to transplant and every 3 months prior to belatacept administration. Patients are required to report any known pregnancy to the investigator immediately. See Section 7.5.

Commercial belatacept will be provided by the manufacturer for administration during the study period and will be considered study drug.

Infusion center services may be offered at belatacept infusion only visits based on each institutions preference and where it is feasible.

Belatacept Infusion Visit Table

	D 1-2	D 5-7	W 2	W 4	W 8	W12 M3	W 16	W 20	W24 M6	W 28	W 32	W36 M9	W 40	W 44	W 48	W52 M12
Belatacept Infusion	X_1	X_3	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X_2					X			X			X				X

1. **Initial Belatacept dose will be administered** within 12-24 hours post reperfusion**.**
2. **Pregnancy test should be done at baseline within 7 days prior to transplant and before patient receives a dose of belatacept**
3. **Belatacept dose is to be given once between Study days 5 – 7, with intention of administering as an outpatient**

	W 56	W 60	W 64 M15	W 68	W 72	W 76	W 80 M18	W 84	W88	W92 M21	W 96	W 100	W 104 M24
Belatacept Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test			X				X			X			X

5.2.5 Tacrolimus Administration

Patients in Group C will receive tacrolimus. Tacrolimus will be administered orally twice daily (BID). The recommended total initial dose of tacrolimus is 0.1 mg/kg/day in two divided doses orally. Tacrolimus should be started post-transplant within 48 hours or when serum creatinine drops lower than 4mg/dL, whichever comes first. The initial targeted trough level of tacrolimus will be 8 - 12 ng/mL for Days 1 through 30, with dose reduction to achieve a 12-hour trough target of 5 - 10 ng/mL thereafter. Tacrolimus trough levels will be monitored at each study visit time point after tacrolimus is initiated.

5.2.6 Mycophenolate mofetil/EC mycophenolate sodium Administration

All patients (Groups A, B, and C) will receive Mycophenolate mofetil/EC mycophenolate sodium first dose will be administered pre-operatively. Patients receiving mycophenolate mofetil will be dosed 1000 mg twice daily (2000mg/day). Patients receiving EC mycophenolate sodium will be dosed 720 mg twice daily (1440 mg/day). These doses of mycophenolate mofetil/EC mycophenolate sodium have shown efficacy, pharmacokinetic and pharmacodynamic equivalence. Dose may be increased for African American transplant recipients to mycophenolate mofetil 1500 mg twice daily (3000mg/day) or EC mycophenolate sodium 1080 mg twice daily (2160 mg/day).

Subsequent dosage adjustments based on physician discretion are permitted due to toxicity only.

5.2.7 Recommended Dosage Adjustment of Mycophenolate mofetil/EC mycophenolate sodium

Mycophenolate mofetil/EC mycophenolate sodium dosage adjustments are strongly discouraged within the first month post-transplant; however, may be permitted by the study investigator. Dosage adjustments for leucopenia are permitted as described in the table below.

WBC cells/µL	**Reduction in current IS dose**
>3000 cells/µL	None
<3000 and >2000 cells/µL	Decrease current dose by 25%
<2000 with ANC >1000 cells/µL	Decrease current dose by 50%
ANC<1000 cells/µL	Hold until ANC > 1000 cells/µL, GCSF may be administered per physician discretion

MPA AUCs may be performed in patients with rejection, infection, or leucopenia.

Attempts will be made to avoid drug interactions with any of the immunosuppressants studied. However, when at the physician discretion, the clinical situation necessitates the administration of an interacting drug, increased therapeutic drug monitoring will be conducted. If interacting drugs are co-administered, the same targeted levels of immunosuppressant will be the treatment goal.

All options will be exercised to maintain the patient on the randomized immunosuppressive regimen. However, some patients may experience dose limiting toxicity requiring adjustments. The physician will use discretion as to how long to continue a patient on the randomized immunosuppressive regimen. While dose adjustments are allowed as described below, deviations from the randomized immunosuppressive regimen must be discussed with the principal investigator. These deviations from the randomized immunosuppressive regimen would be considered major protocol deviations.

5.2.8 Anti-infective Prophylaxis Recommendations

Anti-infectives will be administered per institution standard of care. Below is a recommended protocol.

Anti-Infective prophylaxis

Antiviral	CMV D+/R-	Valganciclovir[1]	450-900mg po QD	365 days
	CMV D+/R+ CMV D-/R+ CMV D-/R-	Valganciclovir [1]	225mg po QD or 450mg PO QOD	90 days
Antifungal	All	Nystatin	5ml TID swish & swallow	90 days
PCP	All	Bactrim SS[2]	1 po MWF	365 days
	Sulfa allergic	Pentamidine	300mg neb Q 4 weeks	
	Sulfa allergic	Mepron	1500mg po QD or 750mg BID (t*rue sulfa allergy and Pentamidine intolerant)*	
	Other	Dapsone	50-100mg po MWF	

1 = Valganciclovir renal dose adjustment (Starting Dose = 450mg QD)
CrCl 40-59ml/min = 450mg qd
CrCl 25-39ml/min = 450mg every other day or 225mg qd
CrCl 10-24ml/min = 450mg 2 times a week
Valganciclovir renal dose adjustment (Starting Dose = 900mg QD)
CrCl 40-59ml/min = 900mg qd
CrCl 25-39ml/min = 450mg daily
CrCl 10-24ml/min = 450mg every other day or 225mg qd
2 = If unable to start Bactrim by POD 7, administer alternative PCP prophylaxis

5.2.9 Reasons for permanent study drug discontinuation

Study drug must be discontinued if the investigator determines that continuing it would result in a significant safety risk for that patient. Reasons for study drug discontinuation are or can be:

- AE(s) (including infections), abnormal laboratory value(s), abnormal test procedure result(s) including ECG abnormalities, unsatisfactory therapeutic effect (i.e. demonstrated by acute rejection), graft loss, death, significant protocol deviation, withdrawal of consent, or lost to follow-up.

The following circumstances require study drug discontinuation:

1. Malignancy (except non-melanoma skin cancer)
2. Pregnancy

In addition to these requirements for study drug discontinuation, the investigator should discontinue study drug for a given patient if, in his/her professional judgment, it is felt that continuation would be detrimental to the patient's well-being.

Patients may withdraw from the study for any reason at any time.

5.2.10 Discontinuation of study treatment and premature patient withdrawal

Patients may voluntarily withdraw from the study treatment or from the study for any reason at any time. They may be considered withdrawn from the study if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study.

The investigator should discontinue study treatment for a given patient or withdraw the patient from study if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Patients who discontinue study treatment should NOT be considered withdrawn from the study and should continue to be followed until the end of the study, unless consent is withdrawn.

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

5.2.11 Study completion and post-study treatment

Patients who attend the Month 24 study visit and undergo all study-related procedures and evaluations will be deemed to have completed the study. The only reasons for premature discontinuation from the study are death, lost-to-follow-up, or withdrawal of consent (to the study).

Patients who elect to discontinue participation in the study or those for whom, in the opinion of the investigator, continued participation is ill-advised must undergo all End-of-Study/End-of-Treatment procedures and evaluations. Early termination/End of Study visit will be the same as the Month 24 visit requirements.

Patients may permanently discontinue from the study regimen for any reason at any time. They may be considered permanently discontinued from a study regimen (but not the study) if e.g. they state an intention to withdraw consent, or fail to return for visits etc. This may also happen on the initiative of the investigator if necessary for the patients' wellbeing.

Except for discontinuations due to death, loss to follow-up, and withdrawal of consent (to the study), patients who discontinue the study regimen should remain in the study (off study regimen) and attend scheduled follow-up visits as per schedule of assessments to obtain follow-up information and assessments.

All patients who permanently discontinue the study regimen will attend the End of Treatment (EOT) visit.

Every attempt should be made to obtain key endpoint information at the Month 12 and 24 time points.

All patients who discontinue the study regimen prior to the study completion at Month 24 will be converted to immunosuppression treatment as per standard local practice. No further study drugs will be provided.

5.2.12 Early study termination

The study can be terminated at any time for any reason by the Principle Investigator or Bristol-Myers Squibb. Should this be necessary, the patient should be seen as soon as possible and treated as described in a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6. Laboratory and Clinical Assessments

6.1. Laboratory and Clinical Assessment Flowchart

	Baseline Pretxp (within 10 days of txp, unless indicated otherwise)	Day of Transplant	Study Visits Time post Transplant [Day (D), Week (W), Month (M)]											
		D 1	D 7	W 2	W 4	W 8	W 12 M3	W24 M6	W 36 M9	W 52 M 12	W 64 M 15	W 80 M 18	W 92 M21	W 104 M24
Study windows			± 1	± 2	±2	±3	±3	±7	±7	±7	±7	±14	±14	±14
Consent	X													
Randomize[1]	X													
Crossmatch, Tissue Typing, PRA[2]	X													
Inclusion/Exclusion Criteria	X													
Medical History[2]	X													
Physical Exam[2]	X													
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X		X
Serologies[4]	X													
Serum Chemistries[5]	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology[6]	X	X	X	X	X	X	X	X	X	X	X	X		X
Tacrolimus Trough			X	X	X	X	X	X	X	X	X	X		X
Fasting Lipids[7]	X							X		X				X
Spot Urine Protein/Creatnine[8]	X							X		X				X
HgA1c[9]	X							X		X				X
Pregnancy Test[10]	X						X	X	X	X	X	X	X	X
DSA and ELISA assessment[11]	X						X	X		X				X
QPCR assessment[12]	X						X	X		X				X
Renal Biopsy[13]		X												
FRS Score	X							X		X				X
QoL/Side Effect Assessments	X									X				X
Clinical Assessments[14]		X	X	X	X	X	X	X	X	X	X	X		X

1. Randomization will occur within 72 hours of transplant.
2. Screening tests/procedures can be completed within 30 days of transplant. PRA just needs to be the most recent PRA, not necessarily within 30 days.
3. Vital signs include BP, weight, and height (including BMI) at baseline visit. BP and weight only at subsequent visits.
4. Serologies for CMV, Epstein-Barr, hepatitis B & C and HIV for donor and recipient done at any previous evaluation within one year will be accepted for eligibility criteria as long as it is documented.
5. Serum chemistries must include serum creatinine (Scr), albumin (Alb), blood urea nitrogen (BUN), and fasting blood glucose (FBG) with an eGFR (MDRD) assessment.
6. Hematology includes WBC, Hgb, and platelet count (PLT).
7. Subjects must be fasting. Lipid testing include total cholesterol, LDL, HDL, triglycerides.
8. Urinalysis for spot urine protein creatinine ratio.
9. HgAIc is needed in ALL patients. This will be used to help assess NODAT and exacerbation of diabetes.
10. Urine or serum pregnancy tests in women of child bearing potential will be required prior to belatacept infusions at visits on months 3, 6, 9, 12, 15, 18, 21, and 24.
11. Anti-donor HLA antibodies (DSA) and ELISA assessment (10ml red top) - additional blood samples are to be obtained at the time of any suspected rejection episode(s).
12. QPCR assessment of acute rejection signature (2.5ml Paxgene tube) – additional blood samples are to be obtained at the time of any suspected rejection episode(s)
13. There are no protocol biopsies. Implant biopsy will be performed as standard of care.
14. Includes assessments of sitting blood pressure (BP), # BP meds and type, weight changes, BMI, smoking, adverse events, CV events, study drug doses, allograft rejection, infection or malignancy, insulin or oral anti-diabetic agents, anti-lipid agents, aspirin, need for dialysis, hospitalization, re-transplant status, and other immunosuppressant medications.

6.2 Laboratory Assessments by Study Visit and Test

Laboratory evaluations will be performed at certified local laboratories according to the study schedule. The only laboratory evaluation that will be performed at the central laboratory is the DSA assessments. Required tests are specified in the Laboratory and Clinical Assessment Flowchart.

6.2.1 Baseline/Pretransplant (Study window within 10 days of transplant, unless indicated otherwise)

Logistic issues surrounding achievement of the following procedures for living donor versus deceased donor transplant recipients will vary. Screening procedures may occur as soon as a potential transplant recipient is identified with a viable donor.

- All inclusion/exclusion criteria will be evaluated and supporting documentation for all provided.
- HLA data such as crossmatch, tissue typing (including A, B, C, DR, and DQ loci if available), PRA testing for the donor and recipient will be evaluated based on the most recent PRA available, not necessarily within 30 days of transplant.
- An abbreviated medical history (hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, and smoking history and treatments for these conditions) and physical exam including vital signs will be provided within 30 days of transplant.
-Medications of special interest (oral and insulin agents, total # units of insulin, anti-lipid agents, and anti-hypertensive agents, and aspirin.
- Vital signs will include sitting blood pressure (systolic and diastolic), height, weight (kg) and body mass index (BMI) (kg/m_2).
- Quality of Life/Side Effect Assessment studies performed including MTSOSDS and the Memphis Survey
- Framingham Risk Score Assessment
- Baseline laboratory assessments will include the following:
    - Serum chemistries must include serum creatinine (Scr), albumin (Alb), blood urea nitrogen (BUN), and fasting blood glucose (FBG) with an eGFR (MDRD) assessment.
    - Fasting lipid profile (total cholesterol, LDL, HDL, triglycerides)
    - HgA1c in ALL patients
    - Hematology including a white blood cell count (WBC), hemoglobin (Hg), and platelet count (PLT)
    - Serologies for CMV, Epstein-Barr, hepatitis B & C and HIV for donor and recipient done at any previous evaluation within one year will be accepted.
    - Urine or Serum Pregnancy test in women of child bearing potential
    - Urinalysis for spot urine protein and creatinine ratio
    - Donor Specific Antibody (DSA) and ELISA assessment for NODAT testing (10ml red top tube)
    - QPCR assessment of acute rejection (2.5ml PAXgene tube)

Consent will be obtained prior to transplantation and any study related procedure.
Randomization will occur within 72hr of transplantation.

6.2.2 Day 1 (Day of Transplant)

- Chemistries must include serum creatinine (Scr), albumin (Alb), blood urea nitrogen (BUN), and fasting blood glucose (FBG) with an eGFR (MDRD) assessment
- Hematology including a WBC, Hgb, and PLT
- Routine renal transplant biopsy sample
- Clinical Assessment includes sitting blood pressure, weight changes (kg), BMI (kg/m_2), smoking, adverse events, CV events, study drug doses, allograft rejection, infection or malignancy, insulin or oral anti-diabetic agents, # units of insulin, anti-lipid agents, aspirin therapy, need for dialysis, hospitalization, re-transplant status, and other immunosuppressant medications.

6.2.3 Day 7 (± 1 day), Weeks 2 and 4 (± 2 days), and Week 8 (± 3 days)

- Chemistries must include serum creatinine (Scr), albumin (Alb), blood urea nitrogen (BUN), and fasting blood glucose (FBG) with an eGFR (MDRD) assessment
- Hematology including a WBC, Hgb, and PLT
- Tacrolimus trough level

- Clinical Assessment includes sitting blood pressure, weight changes (kg), BMI (kg/m2), smoking, adverse events, CV events, study drug doses, allograft rejection, infection or malignancy, insulin or oral anti-diabetic agents, # units of insulin, anti-lipid agents, aspirin therapy, need for dialysis, hospitalization, re-transplant status, and other immunosuppressant medications.

6.2.4 Month 3 (± 3 days)

- Chemistries must include serum creatinine (Scr), albumin (Alb), blood urea nitrogen (BUN), and fasting blood glucose (FBG) with an eGFR (MDRD) assessment
- Hematology including a WBC, Hgb, and PLT
- Urine or Serum Pregnancy test in women of child bearing potential
- Tacrolimus trough level
- Donor Specific Antibody (DSA) and ELISA assessment for NODAT testing (10ml red top tube)
- QPCR assessment of acute rejection (2.5ml PAXgene tube)
- Clinical Assessment includes sitting blood pressure, weight changes (kg), BMI (kg/m2), smoking, adverse events, CV events, study drug doses, allograft rejection, infection or malignancy, insulin or oral anti-diabetic agents, # units of insulin, anti-lipid agents, aspirin therapy, need for dialysis, hospitalization, re-transplant status, and other immunosuppressant medications.

6.2.5 Month 9 (± 7 days), Month 15 (± 7 days), and Month 18 (± 14 days)

- Chemistries must include serum creatinine (Scr), albumin (Alb), blood urea nitrogen (BUN), and fasting blood glucose (FBG) with an eGFR (MDRD) assessment
- Hematology including a WBC, Hgb, and PLT
- Urine or Serum Pregnancy test in women of child bearing potential
- Tacrolimus trough level
- Clinical Assessment includes sitting blood pressure, weight changes (kg), BMI (kg/m2), smoking, adverse events, CV events, study drug doses, allograft rejection, infection or malignancy, insulin or oral anti-diabetic agents, # units of insulin, anti-lipid agents, aspirin therapy, need for dialysis, hospitalization, re-transplant status, and other immunosuppressant medications.

6.2.6 Month 21 (± 14 days)

- Urine or Serum Pregnancy test in women of child bearing potential

6.2.7 Months 6 and 12 (± 7 days), and Month 24 (± 14 days)

- Chemistries must include serum creatinine (Scr), albumin (Alb), blood urea nitrogen (BUN), and fasting blood glucose (FBG) with an eGFR (MDRD) assessment
- Hematology including a WBC, Hgb, and PLT
- Fasting lipid profile (total cholesterol, LDL, HDL, triglycerides)
- Tacrolimus trough level
- Urine or Serum Pregnancy test in women of child bearing potential
- HgA1c
- Urinalysis for protein creatinine ratio
- Donor Specific Antibody (DSA) and ELISA assessment for NODAT testing (10ml red top tube)
- QPCR assessment of acute rejection (2.5ml PAXgene tube)
- Framingham Risk Score Assessment
- Quality of Life/Side Effect Assessment studies performed including MTSOSDS and the Memphis Survey (Months 12 and 24 only, not required at 6 months)
- Clinical Assessment includes sitting blood pressure, weight changes (kg), BMI (kg/m2), smoking, adverse events, CV events, study drug doses, allograft rejection, infection or malignancy, insulin or oral anti-diabetic agents, # units of insulin, anti-lipid agents, aspirin therapy, need for dialysis, hospitalization, re-transplant status, and other immunosuppressant medications.

6.3 Clinical Assessments at Each Study Visit

6.3.1 General Clinical Assessment

All patients will undergo clinical evaluation by the investigator or the investigator's designee at the times specified in the Laboratory and Clinical Assessment Flowchart.

Clinical Assessment includes sitting blood pressure, weight changes (kg), BMI (kg/m_2), smoking, adverse events, CV events, study drug doses, allograft rejection, infection or malignancy, insulin or oral anti-diabetic agents, anti-lipid agents, aspirin therapy, need for dialysis, hospitalization, re-transplant status, and other immunosuppressant medications.

Smoking at the time of transplant is defined as currently smokes, or a significant h/o >20yrs, or quit within last year prior to transplant. Smoking at all post-transplant time points is defined as patient who is currently smoking.

6.3.2 Graft Function Assessment

Graft function will be assessed as described below. Serum creatinine will be assessed immediately post-operatively to establish initial renal function. Baseline serum creatinine after the initial post-transplant period of 3 to 7 days is defined as the median of 5 consecutive serum creatinine measurements immediately preceding the renal allograft biopsy.

6.3.2.1 Initial renal function:

Classified post transplant in the following categories:
1. DGF(delayed graft function)=Dialysis with in the first 7 days post transplant
2. OA (oliguric ATN) =<500cc/d UOP and <10% drop SCr by Day 7
3. NOA (non-oliguric ATN) = >500cc/d and <10% drop SCr by Day 7
4. DCI (Delayed clearance) = >500cc/d and 10-50% drop SCr by Day 7
5. Good initial graft function = >50% drop in SCr from baseline by Day 7

6.3.2.2 Acute renal dysfunction

Renal dysfunction will be monitored by serial measurements of serum creatinine. All episodes of renal dysfunction, defined as an incremental increase in serum creatinine concentration 20% above baseline or $\geq$ 0.3 mg/dl will be evaluated for rejection by renal biopsy and ultrasound, after exclusion of causes other than rejection. In cases where renal biopsy is delayed, empiric treatment of rejection with up to methylprednisolone 1000mg within 48 hours of biopsy is acceptable.

In addition, a biopsy may be performed in cases that do not meet the above acute renal dysfunction criteria but that there is clinical suspicion of rejection determined by the local investigator.

An additional DSA sample should be collected at each biopsy for suspected rejection.

6.3.2.3 Rejection

Biopsy proven Acute Cellular Rejection (BPACR) is defined as: Elevation of serum creatinine of 20% above baseline or an absolute increase of > 0.3 mg/dl with renal allograft biopsy showing IA or greater grade of rejection by Banff 2007 criteria.

Biopsy proven Antibody Mediated Rejection (BPAMR) is defined as: Elevation of serum creatinine of 20% above baseline or an absolute increase of > 0.3 mg/dl with renal allograft biopsy meeting Banff 2007 criteria for AMR.

Biopsy Proven Mixed Acute Rejection (BPMAR) is defined as: Elevation of serum creatinine of 20% above baseline or an absolute increase of > 0.3 mg/dl with renal allograft biopsy showing IA or greater grade of rejection by Banff 2007 criteria with the presence of either donor specific anti-HLA antibody (DSA) or C4d positivity on biopsy.

Renal biopsy should be performed in all cases of renal dysfunction (after exclusion of causes other than rejection), to confirm a rejection episode. All patients must have biopsy confirmation of rejection episodes either before or within 24 hours of onset of treatment for rejection.

Guidelines for Defining Response to Rejection Therapy:

Baseline Serum Creatinine is the median of the 5 consecutive serum creatinine measurements immediately preceding the renal allograft biopsy.

Peak Serum creatinine is the highest value observed within 2 weeks of initiation of anti-rejection treatment.

Rejection Reversal is a return of serum creatinine to within 115% of the baseline value, or histologic reversal occurring within 14 days of initiation of treatment.

Recurrent Rejection is histologic evidence of rejection noted on a biopsy specimen obtained up to 3 months after documented rejection reversal.

Refractory Rejection is a rejection that does not obtain histologic rejection reversal or a serum creatinine decrease to within 115% of the baseline value within 14 days of initiation of treatment.

Clinically Evident Rejection is a biopsy proven rejection with renal dysfunction defined as increase in serum creatinine concentration 20% above baseline or ≥ 0.3 mg/dl above baseline.

Clinically Silent Rejection is a biopsy proven rejection without renal dysfunction.

Progressive deterioration is defined as a refractory rejection causing a progressive decrease in renal function leading to graft loss despite treatment.

Glucocorticoid-resistant acute rejection is defined as a biopsy-confirmed acute rejection episode and no decrease in serum creatinine after three days of methylprednisolone treatment, OR continued rejection documented by renal biopsy within 2 weeks of initiation of methylprednisolone/prednisone treatment (i.e., when an initial favorable response to methylprednisolone/prednisone treatment is not sustained, and a second biopsy is required to confirm the presence of continued rejection).

Chronic Rejection will be defined as a serum creatinine increase of 30% above baseline or proteinuria > 2 gm/24hrs with a biopsy demonstrating histologic features of chronic rejection.

All episodes of kidney dysfunction will be evaluated for possible rejection after exclusion of other causes. The diagnosis of biopsy proven acute rejection will be based on clinical signs and symptoms and will be confirmed histologically using 2007 Banff criteria by the local pathologist. The biopsy must be obtained within 24 hours of starting treatment for the rejection episode.

Residual renal biopsy tissue samples will be stored for analysis as determined scientifically beneficial for research related to solid organ transplantation. Patient samples will be identified by study subject number and no other identifiable subject information only for purposes of linking the sample to data previously described as collected during the study.

Anti-infective prophylaxis should be administered (as detailed at the time of transplantation) for all patients being treated for acute rejection.

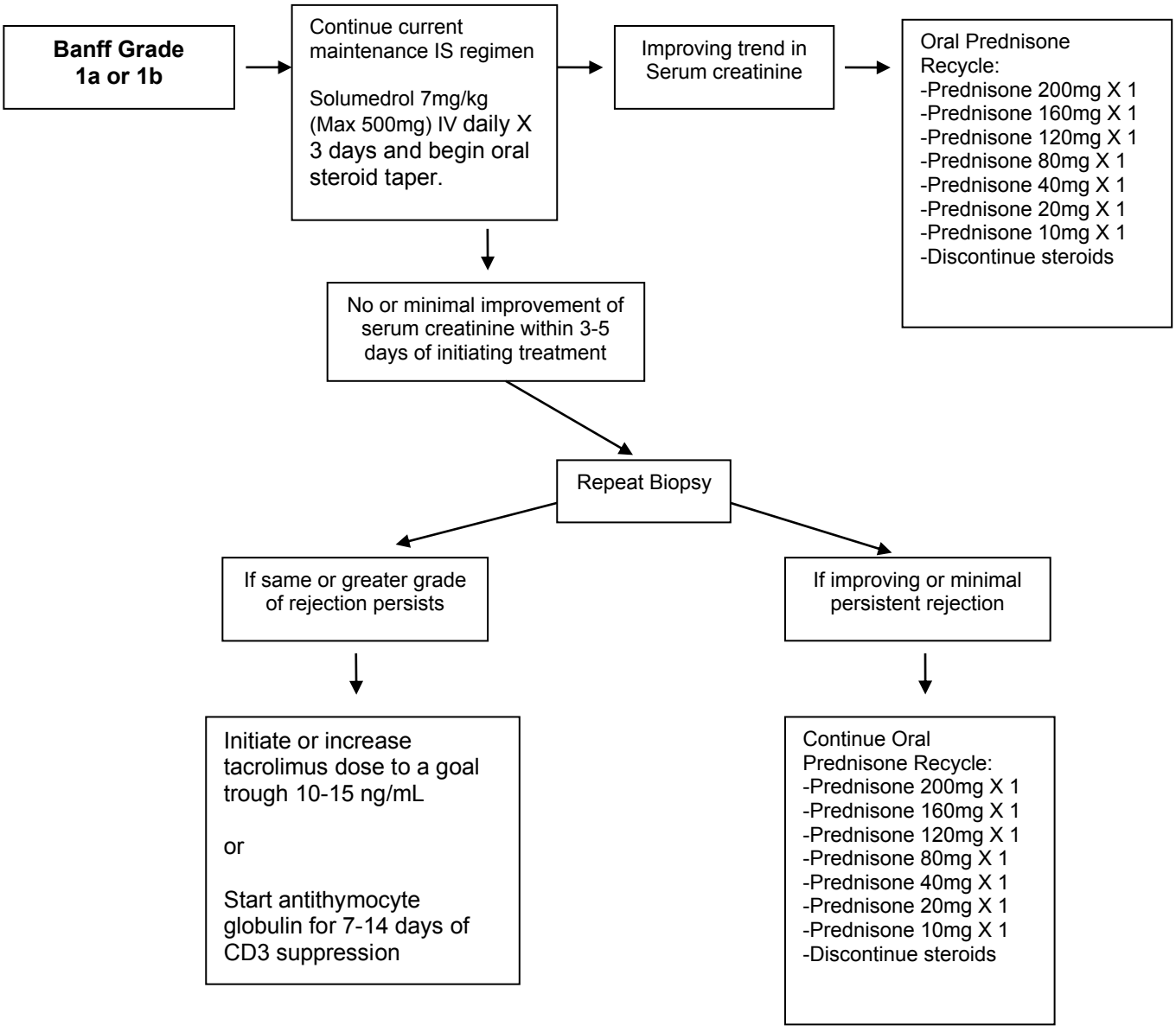
If unable to assess response to therapy based on the above guidelines, defer to PI for determining rejection response.

The guidelines for treatment of acute rejection are presented in the following sections.

6.3.2.3.1 BPACR Banff Grade 1a-1bTreatment

Continue current regimen of belatacept or tacrolimus, Solumedrol 7mg/kg (Max 500mg) IV daily X 3 days. If improving trend in Scr, then initiate oral Prednisone recycle (Prednisone 200mg X 1, Prednisone 160mg X 1, Prednisone 120mg X 1, Prednisone 80mg X 1, Prednisone 40mg X 1, Prednisone 20mg X 1, Prednisone 10mg X 1, then discontinue steroids). If no improving trend in Scr after 3-5 days of treatment initiation, then repeat biopsy. If Banff grade is the same or worse, then initiate or increase tacrolimus to a goal trough of 10-15 ng/mL or initiate rabbit antithymocyte globulin for 7-14 days of CD3 suppression. If Banff grade is improving or minimal persistent rejection, continue oral prednisone recycle.

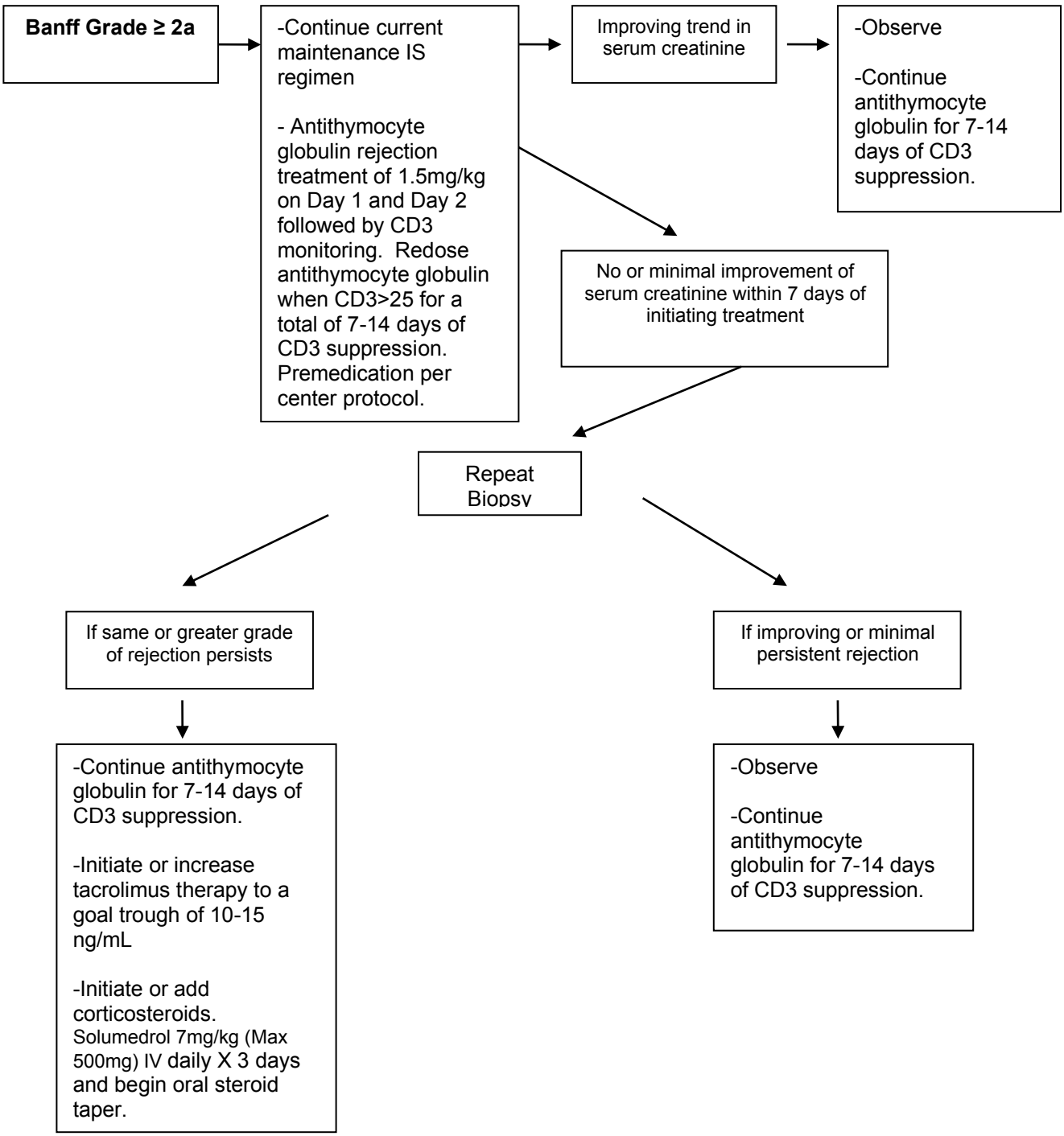
The following schematic is a guideline for the treatment of Banff 2007 Grade 1a or 1b acute rejections



6.3.2.3.2 Recommended BPACR Banff Grade ≥2a Treatment

Continue current regimen of belatacept or tacrolimus, initiate antithymocyte globulin for 7-14 days of CD3 suppression. If no improving trend in Scr after 7 days of treatment initiation, then repeat biopsy. If Banff grade is the same or worse, continue antithymocyte globulin, initiate or increase tacrolimus therapy to a goal trough of 10-15 ng/mL and initiate or add corticosteroid therapy. If Banff grade is improving or minimal persistent rejection, continue antithymocyte globulin.

The following schematic is a guideline for the treatment of Banff 2007 2a, 2b or 3 acute cellular rejections



6.3.2.3.3 Recommended BPAMR or BPMAR Treatment

May treat BPAMR or BPMAR with a bortezomib-based or IVIG-based protocol.

The following schematic is a guideline for the treatment of antibody mediated rejection and mixed rejection with bortezomib-based treatment with rituximab:

Treatment Day	PRE	1	4	7	10
PLASMAPHERESIS 1.5 PV		X	X	X	X
Methylprednisolone 100 mg IVP or PO		X	X		
Methylprednisolone 50 mg IVP or PO				X	X
BORTEZOMIB 1.3 mg/m_2 IVP or SC		X	X	X	X
RITUXIMAB 375 mg/m_2 IV		X			

6.3.3 Safety assessments - Clinical

6.3.3.1 Physical examination and Medical History

A thorough medical history and physical exam will be performed within 30 days prior to transplant.

6.3.3.2 Vital signs

Height should be recorded on baseline visit or day of transplant (Day 1). Blood pressure in mmHg and weight in kg will be recorded at each clinical assessment time point as indicated in schedule of assessments. BMI should be calculated at baseline, month 6, month 12, and month 24.

6.3.3.3 Laboratory evaluations

There is no central laboratory for this study, except for the DSA samples. All laboratory evaluations will be sent locally during the study. Laboratory assessments needed for patient safety during the study will also be performed at the local laboratory. Laboratory samples should be drawn prior to administration of the morning dose of study medications. All samples will be drawn, preferably with the patient in fasting state (recommended more than eight hours after the last meal). Non-fasting blood samples should be clearly identified. For screening evaluation (hematology and blood chemistry) blood samples should be drawn prior to transplantation within 10 days.

Hematology
A white blood cell count, platelet count, and hemoglobin, will be obtained at every visit indicated in schedule of assessments (Baseline, Day 1 and 7, Weeks 2, 4, 8, 12, 24, 36, 52, 68, 80, and 104).

Serum Chemistry
This includes collection of a Serum creatinine (Scr), albumin (Alb), blood urea nitrogen (BUN), and fasting blood glucose (FBG) and an assessment of renal function by estimated glomerular filtration rate (eGFR) using MDRD as described below under renal function. This will be obtained at every visit indicated in schedule of assessments (Baseline, Day 1 and 7, Weeks 2, 4, 8, 12, 24, 36, 52, 68, 80, and 104).

Fasting Lipids
This includes total cholesterol, high density lipoprotein, low density lipoprotein, and triglycerides. This will be collected at baseline, 6 months, 12 months, and 24 months.

Urinalysis
A mid-stream spot urine for quantitative protein/creatinine ratio will be performed at baseline, 6 months, 12 months, and 24 months.

Renal function
Renal function will be assessed at each visit by measuring serum creatinine and using this to calculate eGFR using the MDRD equation.

MDRD should be calculated using the following equation:

eGFR (MDRD) (mL/min/1.73m$_2$) = 170 x (SCr)$_{-0.999}$ * (Age)$_{-0.176}$ * (BUN)$_{-0.170}$ * (Alb)$_{0.318}$ * 0.762 (if female gender) * 1.180 (if African American race)

Levey AS, Bosh JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A New Prediction Equation. *Ann Intern Med* 1999; 130: 461-470.

Hemoglobin A1c
New Onset diabetes and exacerbation of preexisting diabetes will be assessed at each visit by evaluating oral and insulin agents, total # units of insulin, as well as looking at FBG and HgA1c at baseline, 6, 12, and 24 months.

Liver Function Tests
Liver function monitoring will be performed per each institutions standard of care and is not protocol defined.

Donor specific antibodies (DSA), ELISA for NODAT, and QPCR assessment for acute rejection

Serum samples (10ml red top tube and 2.5ml Paxgene tube) will be collected as indicated in schedule of assessments (Baseline, 3 months, 6 months, 12 months, and 24 months and at times of suspected rejection).

Blood samples (10 mL) will be collected in a 'red top clotting tube' and let the specimen stand at room temperature for 30 min until the clot forms. The sample will be centrifuged at 2000 X g for 5 minutes using a swinging bucket rotor. The serum will be transferred to TWO cryotubes and will be stored at -80 °C until shipment. One cryotube will be utilized for DSA testing and one crytotube will be utilized for ELISA NODAT testing.

Blood samples (2.5ml) will be collected in a Paxgene tube and frozen at -80C. This sample will be utilized for QPCR assessment for acute rejection

Patient samples will be identified by study site and subject number and no other identifiable subject information only for purposes of linking the sample to data previously described as collected during the study. ALL frozen patient samples will be batched shipped to the University of Cincinnati monthly, overnight delivery is not required. The tubes should be labeled as per the shipping manual. Shipping boxes must conform to the delivery company's biologics requirements. The shipping address for ALL samples is:

Stefanie Young/Liz Cole
UC Health
University of Cincinnati Physicians
231 Albert Sabin Way
MSB Room 1555
Phone: 513-584-1642
Fax: 513-584-2149
Email: uchtransplant@uc.edu or youngs8@uc.edu or colee@uc.edu

The University of Cincinnati will receive all samples, log, and route to the proper laboratories for analysis.

6.3.3.4 Pregnancy and Assessments of Fertility

A urine or serum pregnancy test will be performed at the baseline visit within 10 days of transplant and every 3 months prior to belatacept infusion in women of child bearing potential. Patients must report any known possible pregnancy to the investigator immediately. See Section 7.5.

6.3.3.5 Tolerability and Acceptability

Tolerability of the regimen as measured by percentage of patients requiring dose reduction or discontinuation of study group will be assessed.

6.3.3.6 Appropriateness of Safety Measurements

The adverse events of special interest selected are expected for this indication/patient population and may be related to immunosuppression and/or comorbid conditions. Expected events related to immunosuppression are those included in the labeling of each immunosuppressive agent utilized. The following safety measurements will be systematically assessed in all patients at each study visit. Events meeting the definition of serious will be reported as a serious adverse event.

6.3.3.7 Adverse Events of Special Interest

6.3.3.7.1 New Onset Diabetes Mellitus After Transplantation (NODAT):

In patients who do not have diabetes mellitus prior to transplantation, new onset diabetes mellitus is defined by:

1) New requirement for therapy with insulin for ≥ 30 days OR
2) New use of oral hypoglycemic agents for ≥ 30 days OR
3) Any treatment (oral or insulin or other) for ≥ 30 days OR
4) FBG > 126 mg/dL x 2 consecutive values OR
5) HgAIC ≥ 6.5% at any time point

Periodic assessments of blood glucose control, total # units of insulin, and specific treatment will be performed at each study visit. FBG and HbA1c levels at 6 months, 12 months, and 24 months will be analyzed to assess for development of NODAT.

6.3.3.7.2 **Exacerbation of Preexisting Diabetes:**

In patients with preexisting diabetes mellitus at the time of transplantation, the exacerbation of the diabetes will be evaluated by analyzing change from baseline at 6, 12, and 24 months in total # units of insulin, oral and insulin agents, and FBG, and HgA1c. Exacerbation will be defined as an increase in the total # units of insulin, increase in number of insulin or oral agents, or a worsening of control as determined by an increase in HgA1c.

6.3.3.7.3 Hyperlipidemia

Clinical practice guidelines for the management of dyslipidemias in renal transplant subjects are available from the National Cholesterol Education Panel, Adult Treatment Panel III (see Appendix V, 36). Treatment will be initiated based upon those guidelines. Periodic assessments of treatment will be performed at each study visit. Fasting lipids and treatment will be collected at 6, 12, and 24 months post-transplant to assess for changes in lipid levels.

6.3.3.7.4 Hypertension

Hypertension will be defined and treated according to Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (see Appendix VI, 37). Seated blood pressure should be taken at a resting state. Treatment will be initiated based upon these guidelines. Blood pressure (systolic and diastolic) and treatment will be collected at each required time point in the study and will be specifically analyzed at 6, 12, and 24 months.

6.3.3.7.5 Framingham Heart Study Coronary Heart Disease Risk Point Total

A coronary heart disease risk factor assessment will be performed in each patient pre-transplant and at 6, 12 and 24 months post-transplant calculated from score sheets in Appendix VII (38). Periodic assessments of cardiac events will be performed at each study visit.

6.3.3.7.6 Infection

Periodic assessments of infections will be performed at each study visit.
Infection is defined as any of the following:

1) Treatment with antimicrobial agent for a specific clinical syndrome (not prophylaxis)
2) Positive cultures, pathologic identification of microbial agents, or significant serologic changes related to clinical symptoms
3) Typical clinical presentation documented by investigator or appropriate consultant.

CMV *infection* is defined as isolation or identification of CMV from blood or sterile site (CMV serum DNA PCR) or positive antigenemia (presence of CMV immunoglobulin IgM or fourfold increase in CMV IgG titers) in the absence of clinical symptoms.

CMV *disease* is defined as invasive or symptomatic CMV infection with histological evidence of viral cytopathic effect or a positive CMV culture from a deep tissue specimen in the setting of suggestive clinical manifestations. Specimens used for diagnosis of CMV disease include liver or lung biopsy, endoscopic mucosal biopsy or brushing, bronchoscopic mucosal biopsy or brushing, bronchoalveolar lavage, and cerebrospinal fluid. The presence of positive serum DNA PCR or seroconversion in the setting of symptomatic infection is also considered sufficient to establish the diagnosis of CMV disease.

BK Virus is defined as one of the following:
BK viremia -BK viral load is present in the blood by DNA PCR
BK Nephropathy -BK viral load is present in the blood AND BK in situ hybridization is positive on allograft biopsy

6.3.3.7.7 Malignancy

Periodic assessments of malignancy will be performed at each study visit.
Development of any post-transplant malignancies will be evaluated at 6 months 12 months, and 24 months.

6.3.3.7.8 Other

Other safety assessments potentially related to immunosuppression that are expected will be captured at each study visit. These include the following toxicities: gastrointestinal, hematologic, nephrotoxicity, neurotoxicity, electrolyte imbalance, wound healing, bone related, or other as assessed by the PI as related to immunosuppression. Events meeting the definition of serious will be reported as a serious adverse event.

Other safety assessments potentially related to immunosuppression that are unexpected will be captured at each study visit as assessed by the PI. Events meeting the definition of serious will be reported as a serious adverse event.

6.3.4 Quality of Life/Side Effect Assessments

Information captured in these assessments will be analyzed retrospectively and information not included in the safety assessment of the protocol.

6.3.4.1 The Memphis Survey

Quality of Life (QoL)/Side Effects will be assessed by the Memphis Survey from the University of Tennessee which assesses side effects of transplant medications and will be administered prior to transplant and at 12 and 24 months (Appendix IV).

6.3.4.2 *Modified Transplant Symptom Occurrence and Symptom*

Distress Scale Questionnaire

Quality of Life (QoL)/Side Effects will also be assessed by the Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSDS) questionnaire that will be administered prior to transplant and at 12 and 24 months (Appendix IV).

7 Adverse Event Management

Any serious adverse event will be reported to the sponsor, and BMS as soon as possible, but no later than 15 working days. Unexpected fatal or life-threatening suspected adverse reactions must be reported not later than 7 calendar days after initial receipt of the information.

7.1. Definitions

7.1.1. Adverse Events Related to Immunosuppression

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject administered immunosuppression. Adverse events are determined by the PI as expected and related to immunosuppression if the adverse event is included in the product labeling. Adverse events as determined by the PI as related to immunosuppression and unexpected may also occur. Adverse event reporting will focus on adverse events of special interest. The adverse events of special interest have been detailed within the protocol.

7.1.2. Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- 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
- is 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 (eg, 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 (eg, 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 7.5 for reporting pregnancies).

Any serious adverse event will be reported to the sponsor, and BMS as soon as possible, but no later than 15 working days via guidelines outlined in the adverse event management section.

Unexpected fatal or life-threatening suspected adverse reactions must be reported not later than 7 calendar days after initial receipt of the information.

7.1.3. Nonserious Adverse Events

Nonserious adverse events are all adverse events related to immunosuppression that are not classified as SAEs. Non serious adverse event reporting will be focused on adverse events of special interest as detailed in the protocol.

7.2. 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.

7.2.1. 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 of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure.

The investigator should report any SAE.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082728.pdf

All SAEs should be reported locally as per local IRB standards, and simultaneously faxed or e-mailed to the sponsor and BMS at:

Rita Alloway, PharmD
University of Cincinnati
Fax Number: 513.558.4944
Email: (rita.alloway@uc.edu)

and

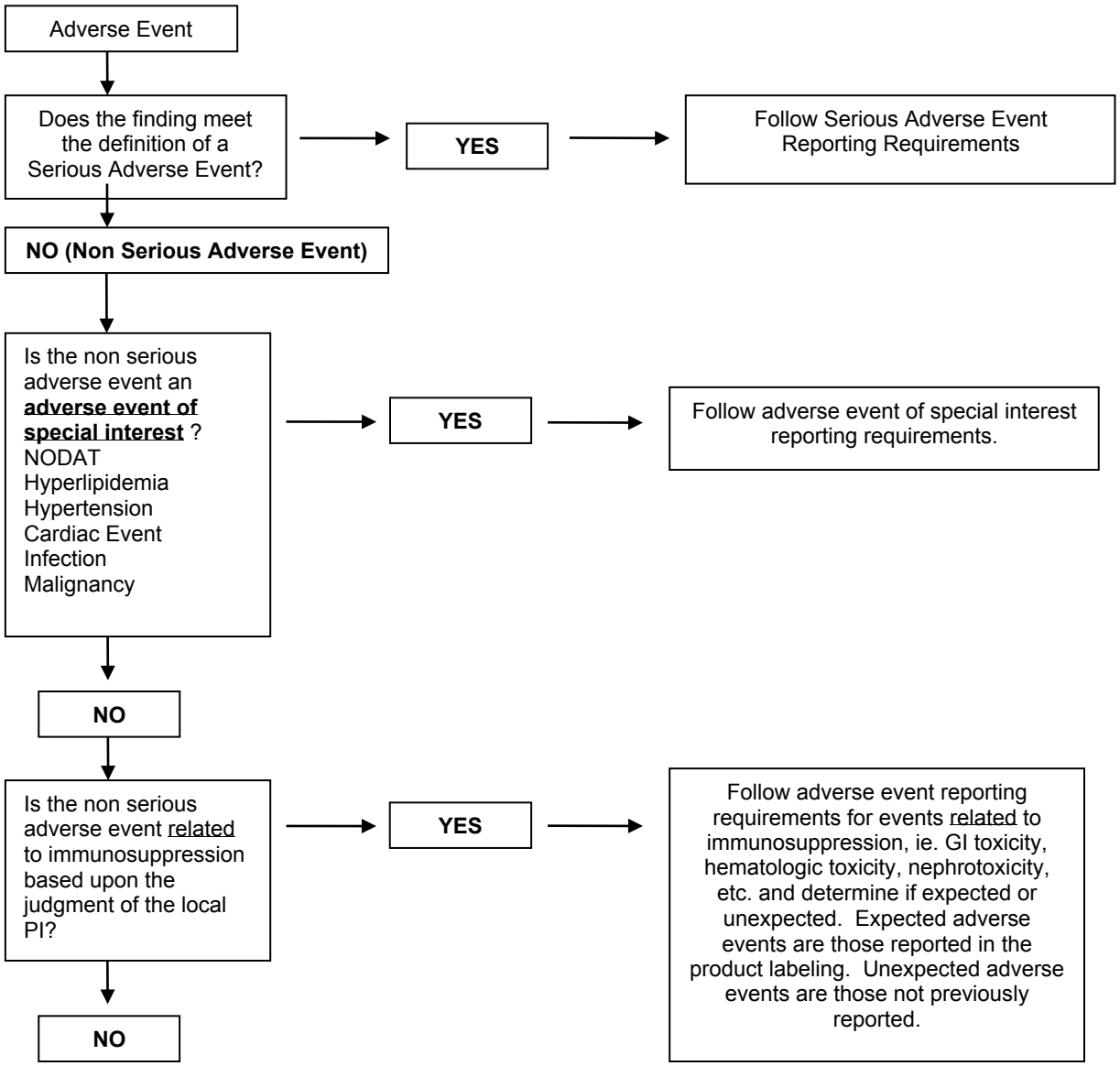
Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

Additional reporting to the FDA will be the responsibility of the sponsor based upon IND status.

7.2.2. Non-Serious Adverse Events (NSAEs) Collecting and Reporting

The collection of non-serious adverse event (NSAE) information related to immunosuppression should begin at initiation of study drug. Non serious adverse event reporting will be focused on adverse events of special interest as detailed in the protocol.

7.2.3 Adverse Event Flowchart



7.3. Laboratory Test Abnormalities

Laboratory abnormalities are not considered adverse events unless serious or otherwise specified.

7.4. 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.

Although overdose is not always serious by regulatory definition, these events must be handled as SAEs (See section 7.1.2).

7.5. Pregnancy

7.5.1. Precautions

Pregnancy tests may be performed on blood or urine via local laboratory or via investigator provided pregnancy kits. The investigator should ensure that pregnancy kits used for testing are not expired. WOCBP should be advised against becoming pregnant or breastfeeding from the beginning of the study until 8 weeks or 5 half lives (whichever is greater) after administration of the last dose.

Female subjects of reproductive potential taking CellCept/Mycophenolate Mofetil/Myfortic will receive contraceptive counseling and must agree to use acceptable contraception for the entire 2-year study and for eight weeks following study drug discontinuation. The investigator and/or study staff will discuss appropriate birth control/contraception options using the chart below as a guide.

<table>
<tr><th colspan="4">Acceptable Contraception Methods</th></tr>
<tr><td>Option 1
Methods to Use Alone</td><td colspan="3">■ Intrauterine devices (IUDs)
■ Tubal sterilization
■ Patient's partner had a vasectomy</td></tr>
<tr><td colspan="4">OR</td></tr>
<tr><td rowspan="2">Option 2
Choose One Hormone Method AND One Barrier Method</td><td>Hormone Methods
choose 1</td><td></td><td>Barrier Methods
choose 1</td></tr>
<tr><td>Estrogen and Progesterone
■ Oral contraceptive pill
■ Transdermal patch
■ Vaginal ring
Progesterone-only
■ Injection
■ Implant</td><td>AND</td><td>■ Diaphragm with spermicide
■ Cervical cap with spermicide
■ Contraceptive sponge
■ Male condom
■ Female condom</td></tr>
<tr><td colspan="4">OR</td></tr>
<tr><td rowspan="2">Option 3
Choose One Barrier Method from each column (must choose two methods)</td><td>Barrier Methods
choose 1</td><td></td><td>Barrier Methods
choose 1</td></tr>
<tr><td>■ Diaphragm with spermicide
■ Cervical cap with spermicide
■ Contraceptive sponge</td><td>AND</td><td>■ Male condom
■ Female condom</td></tr>
</table>

Subjects will be instructed that the use of CellCept/Mycophenolate Mofetil/Myfortic during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations and that

CellCept/Mycophenolate Mofetil/Myfortic reduces blood levels of the hormones in the oral contraceptive pill and could reduce its effectiveness.

Subjects will be instructed to contact the Investigator immediately if pregnancy is suspected (e.g., missed or late menstrual period) while participating in the study or within 8 weeks after stopping participation in this study. The investigator will report the pregnancy to the Mycophenolate Pregnancy Reference Registry (1-800-617-8191) and the subject will be strongly encouraged to enroll in the pregnancy registry by calling the number above. In the event of a positive pregnancy test the subject will be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus, and will no longer be able to participate in the study. The investigator should change the subject's treatment to a different combination of immunosuppressive drugs, and the study medication will be stopped. The subject will still be required to return for periodic follow-up visits and blood work.

Male subjects will be advised to avoid unprotected sex and sperm donation throughout the study and until sperm produced during the period of drug exposure has been cleared. Drug-exposed sperm may be present in the semen for 12 weeks following the passage of 5 half lives of the study drug. Male subjects will be asked to inform the investigator immediately if their female partner becomes or suspects she is pregnant while they are enrolled in this clinical trial or within 12 weeks following the study drug completion. The subject and his partner will be asked to provide information about the pregnancy outcome. The Sponsor has neither set aside any funds for nor does it plan to pay for any aspects of obstetrical, child or related care.

Subjects should be advised to notify the Investigator of any change in birth control method during exposure to Study Drug or if they need to take any prescription drug or other medication not prescribed by the Investigator. The Investigator should be aware of changes in birth control method so that the use of a study-prohibited contraceptive method is identified.

7.5.2. Testing Methods and Timing

7.5.2.1. Methods for Pregnancy Testing

Blood or urine testing is acceptable. Urine pregnancy tests must have a minimum test sensitivity of at least 25 IU/L. Kits measuring either total human chorionic gonadotropin (hCG) or the beta (β) fraction.

7.5.2.2. Timing of Pregnancy Testing

WOCBP receiving belatacept should be tested at screening and every 3 months while receiving belatacept infusions.

7.5.3. Pregnancy Reporting

In the event that a WOCBP becomes pregnant during a clinical trial, the implications (on the health of the mother and fetus) of treatment suspension must be reviewed and considered. If it is determined that continued treatment is desirable, the investigator must immediately notify BMS and the Sponsor of this event in accordance with SAE reporting procedures described in Section 7.2.1.

7.6 Data Safety Monitoring Board (DSMB)

An independent DSMB will be constituted prior to study initiation and will be comprised of 2 clinicians experienced in kidney transplantation and an independent statistician. The DSMB will monitor ongoing efficacy and safety data during the study until the time of its conclusion. The DSMB charter will outline DSMB constitution, scope, operation, and function per relevant FDA Guidance Documents.

Stopping Criteria:

Proposed stopping criteria for the DSMB will include CNS PTLD. The DSMB will be requested to monitor CNS PTLD rates for each study limb during the study. During the study, if 2 more cases of CNS PTLD are noted in either Group A or Group B as compared to Group C, the DSMB will review the individual cases and consider halting enrollment in the study Group in question. If enrollment is permanently halted in Group A or B, accrual will continue in the remaining belatacept-based study group, and the overall number of subjects treated with belatacept would remain the same by adjusting the enrollment ratio to 2:1 with 2 patients in the remaining belatacept arm for every one patient in the control arm.

8. Statistical Analysis Plan

8.1 Population for Analysis

Intent-to-Treat (ITT) Analysis - This study will be analyzed as an intent-to-treat analysis at 12 and 24 months. All patients who were randomized and transplanted (defined as having renal allograft reperfusion) will be included in the intent to treat population for analysis.

Following the ITT principle, patients will be analyzed according to the assigned treatment at randomization.

Per protocol (PP) analysis: PP analysis set will consist of all randomized patients without major protocol deviations (PDs) as defined below and who completed study. Identification of these protocol deviations are for analysis purposes only. Deviations to the protocol made by the PI are made based upon physician discretion related to the optimal individual immunosuppressive management of the study subject reflective of standard of care immunosuppressive management and do not represent reportable regulatory protocol deviations since they are intended to lower the risk for the individual subject.

All analyses will be performed on the ITT population and the PP population.

All datasets will remain blinded and there will be no summary of the study by the individual treatment arms with the exception of an independent DSMB assessment in the course of an interim/futility analysis. Data management and clean up will be done on blinded data sets.

8.1.1 Major Protocol Deviations:

1. Thymoglobulin Major Protocol Deviation (Groups B and C): Any patient who receives less than 4mg/kg total cumulative thymoglobulin dose for induction.

2. Alemtuzumab Major Protocol Deviation (Group A): Any patient who receives less than 1 dose of alemtuzumab for induction.

3. Belatacept Major Protocol Deviation (Groups A and B): Any patient who receives less than 16 doses of belatacept at 52 weeks (Month12) or received less than 29 doses of belatacept at End of study Week 104 (Month 24).

4. Tacrolimus Major Protocol Deviation (Group C): Any patient who has tacrolimus discontinued for > 7 consecutive days.

5. Mycophenolate Mofetil/Mycophenolate Sodium EC Major Protocol Deviation (All Groups): Any patient who has mycophenolate discontinued for greater than 2 consecutive weeks for reasons other than neutropenia, and 4 consecutive weeks for any reason.

6. Glucocorticoids Major Protocol Deviation (All Groups): Any patient who remains on glucocorticoid therapy for > 6 consecutive weeks.

8. Other Maintenance Immunosuppression (All Groups): Any patient who has the addition of any other maintenance immunosuppressive agent not defined in the protocol for > 4 weeks.

8.2 Patient Demographics, Baseline Characteristics, and Patient Disposition

Demographic and baseline characteristics of recipients will be summarized by means and standard deviations for continuous variables, and by the number and percent of patients for categorical variables. Summaries will be performed based on all subjects.

The total number of patients screened and the number of patients who were not randomized will be tabulated by reason.

The following descriptive statistics will be calculated by assigned treatment arm and total. Summary statistics (n, mean, median, standard deviation (SD), minimum, maximum) will be provided for continuous variables and the number and percent of patients for categorical variables.

- Patient disposition analysis will include the following for each of the three treatment groups: # Enrolled, # Randomized, # Transplanted, # Evaluable, # Not meeting eligibility criteria, # Not receiving study drug (belatacept or tacrolimus), # Lost to follow-up, # Withdrawing consent, # Discontinuing study and by reason for discontinuation, and # Completing study.
- Protocol Deviations (minor and major)
- Transplant background information:
    - Recipient demographics: age, gender, predominant race (African American, Asian, Caucasian, Native American, Pacific Islander, other), screening height and weight, and BMI.
    - Donor source (living related, living unrelated, deceased).
    - Recipient background information: end stage disease leading to transplantation, current dialysis, PRA (most recent evaluation, peak evaluation), primary or repeat transplant, PRA evaluation category (0-10%, 10-25%, 25-50%, 50-75%, >75%), number of HLA mismatches at loci A, B, DR, and DQ, cold ischemia time (CIT) (deceased donors only).
    - Recipient and donor viral serology for: EBV, CMV, HCV, HBsAg, and HIV (negative, positive, not done, missing).
    - Medical histories

8.3. Treatments

The following variables will be analyzed by treatment arm at 12 and 24 months. For continuous variables an Analysis of Variance (ANOVA) will be performed with terms for treatment and investigative site. For time-to-event variables, the Kaplan Meier (KM) curves will be estimated and the Log-Rank test performed with site as a stratification variable will be performed. For categorical variables, a Cochran-Mantel_Haenzel (CMH) test will be performed with site as the stratification variable. If the cell sizes are sparse, a Fisher's Exact test will be used. The Hochberg (for KM, CMH) or Tukey-HSD (for ANOVA) adjustment will be used for each endpoint to control the alpha level at 5% for comparing the three treatment groups.

- duration (days) of exposure to PP study regimen
- % of patients with dose adjustments of MMF/EC MPA
- Reasons for dose adjustments of MMF/EC MPA will be summarized
- % of patients with discontinuation of belatacept in Groups A and B
- % of patients with discontinuation of tacrolimus in Group C
- % of patients with discontinuation of MMF/EC MPA
- % of patients on chronic glucocorticoids
- Mean MMF/EC MPA dose
- Mean tacrolimus dose
- Mean tacrolimus level
- % of patients on belatacept
- % of patients on tacrolimus

- Mean daily body weight-adjusted maintenance prednisone equivalent dosages [mg/kg/d]: steroids taken p.o. or administered IV or i.m. for the prophylaxis of rejections will be included. Steroids administered after the discontinuation of randomized study medication or administered for *treatment* of rejection will not be included. Inhaled, intra-nasal, and topically administered corticosteroids will not be included.

Prior medications will be defined as drugs taken prior to first dose of study regimen. Any medication given at least once during the period on study regimen is a concomitant medication, including those which start prior to first dose of study regimen and continued into the treatment period. Any medication started after the discontinuation of study regimen is not considered a concomitant medication.

8.4 Primary Endpoint Analysis

The primary efficacy endpoint is the 12 month incidence of patient death or graft loss or eGFR < 45 mL/min (MDRD).

8.4.1 Statistical model, hypothesis, and method of analysis

Time to event analyses will be performed using the Kaplan-Meier estimates and the Log Rank test with site as a stratification variable. To control the overall alpha level at 5% for the two primary comparisons, the Hochberg adjustment will be used. To evaluate the consistency of results for each of the subgroups listed below, a Cox-Proportional-Hazards model will be performed for each subgroup variable separately.

The primary endpoint will also be assessed for each study group with the following subgroups:

- African Americans versus Non-African Americans
- Living donors versus Deceased donors
- Male versus female
- Primary transplant versus repeat transplant
- Delayed graft function versus no delayed graft function
- HLA DR mismatch = 0 versus HLA DR mismatch > 0
- HLA DQ mismatch = 0 versus HLA DQ mismatch > 0

The following analysis plan will be performed for the secondary and tertiary endpoints. For continuous variables an Analysis of Variance (ANOVA) will be performed with terms for treatment and investigative site. For continuous variables that are analyzed across all time points, a repeated measures ANOVA will be performed with terms for treatment, month, site, treatment by month interaction. If the interaction term is not significant at the 5% level, it will be removed from the model. For time-to-event variables, the Kaplan Meier (KM) estimates and the Log Rank test with site as a stratification variable will be performed. For categorical variables, a Cochran-Mantel_Haenzel (CMH) test will be performed with site as the stratification variable. If the cell sizes are sparse, a Fisher's Exact test will be used. The Hochberg (for KM, CMH) or Tukey-HSD (for ANOVA) adjustment will be used for each endpoint to control the alpha level at 5% for comparing the three treatment groups.

In the event that one active treatment arm is discontinued, a blocking factor will be added to all statistical models indicating the patients who were enrolled when all treatment arms were enrolling versus when only two treatment arms were being enrolled. To evaluate the consistency of the treatment effect across the blocking factor, the treatment by block interaction will be tested for all statistical models.

8.4.2 Handling of missing values/censoring/discontinuations

The 'all events analysis' using a Kaplan-Meier method considers a patient censored if the patient has no event and does not provide information up to the analysis time point *x* (e.g. *x*=Day 365 for the Month 12 analysis). The censoring day will be equal to the day of last study contact. Day of last study contact will be the last visit date in the

x-month database, whichever is earlier. The number of patients at risk at analysis time point *x* will include all patients who completed the study visit associated with time point *x* (e.g. Month 12) no earlier than *x* - 2 weeks.

For eGFR, missing values or censoring for death or graft loss will be imputed. Patients with missing eGFR values due to death or graft loss will have their eGFR values imputed as 0, and a last observation carried forward imputation will be utilized for other missing values, except if the last eGFR measurement was before an acute rejection episode.

Sensitivity analyses will be performed to examine the robustness of the results to the missing data. The primary efficacy endpoint is the 12 month incidence of patient death or graft loss or eGFR < 45 mL/min. Kaplan-Meier estimates and the Log-Rank test will be used to test for differences between groups for the primary endpoint. For patients who are lost to follow-up prior to the 12 month time point, their time-to-event will be censored at the last date for which patient status can be determined. As a sensitivity analysis, the status of the patient will be set to "failure" at the date of the last contact with the patient. Another sensitivity analysis will use multiple imputation techniques as discussed in Rubin (Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987) and Schafer(Schafer JL. Analysis of Incomplete Multivariate Data. New York: Chapman and Hall; 1997.) if the patient's eGFR value is the only unknown component of the primary endpoint.

8.5 Secondary Endpoint Analyses

The primary efficacy variable will be analyzed as described in the primary objective at Month 24 as a secondary endpoint.

The following actual rates for each secondary efficacy variable will be analyzed at Months 6, 12, and 24 as described above: Banff 2007 BPAR (stratified by type: BPAMR, BPACR, and BPMAR)

- Composite endpoint at 6 and 24 months
- Incidence by Banff 2007 criteria of biopsy proven acute rejection (BPAR) stratified by type (ACR, AMR, or Mixed rejection)
- Death Censored Graft Survival
- Proportion of patients with eGFR (MDRD) < 30 mL/min
- Proportion of patients developing DSA after transplantation

8.6 Tertiary Endpoint Analyses

The following efficacy parameters (tertiary endpoints) for each treatment group will be analyzed as described above:

- BPAR 2a or greater
- Steroid-resistant BPACR
- BPAMR or BPMAR
- Biopsy-proven chronic rejection
- Treatment of all acute rejection episodes (Proportion of patients in each assigned treatment group receiving treatment with the following: A) Steroids alone, B) Anti-lymphocyte agents (rabbit antithymocyte globulin, horse antilymphocyte globulin, or alemtuzumab), and C) IVIG and/or plasmapheresis and/or bortezomib and /or rituximab
- Mean individual component Banff scores at time of BPAR
- Mean composite Banff scores at time of BPAR
- Causes of patient death will be summarized
- Causes of graft loss will be summarized
- Severity of acute rejection episodes using the Banff 2007 grading
- Incidence of leucopenia (WBC < 2000/mm^3)
- Incidence of anemia (Hg < 7 g/dL)
- Incidence of proteinuria (elevated protein/creatinine ratio >0.8 grams protein per gram creatinine)

- Incidence of infections
- Incidence of post-transplant lymphoproliferative disorder (PTLD)
- Incidence of non-PTLD malignancy
- Proportion of patients in each group remaining glucocorticoid-free
- Patient quality of life changes from baseline will be summarized
- Metabolic and Cardiovascular comorbidities will be analyzed as follows:
  - Freedom from Cardiovascular events (myocardial infarction, angina, CVA, TIA, cardiovascular intervention/procedure, or sudden death) analyzed.
  - NODAT (defined as any one of the following: 1) New requirement for therapy with insulin for ≥ 30 days OR 2) New use of oral hypoglycemic agents for ≥ 30 days OR 3) Any treatment (oral or insulin or other) for ≥ 30 days OR 4) FBG > 126 mg/dL x 2 consecutive values OR 5) HgAIC ≥ 6.5%)

    NODAT will be analyzed multiple ways. Each definition will be analyzed for incidence and prevalence. Kaplan Meier survival analysis will be used to determine overall NODAT-free per treatment group. NODAT will be analyzed for each treatment group and will be summarized descriptively by frequency distribution for categorical variables (Y/N). Change in HgA1c and FBG from baseline will also be compared between each study group. We will also describe the following per treatment group: 1)% patients on treatment at each study visit, 2)% of patients with NODAT at any time point, % patients on treatment at 6, 12, and 24 months

    Exacerbation of Preexisting Diabetes will be analyzed by evaluating changes from baseline in oral and insulin agents, changes in total # units of insulin, and change from baseline in FBG, and HgA1c at 6, 12 and 24 months.

  - Treatment of hyperlipidemia (Changes in number and type of agents)
  - Treatment of hypertension (Change in number of agents)
- Determine the earliest reliable time-point that can be used for prediction of future onset of acute rejection and NODAT

  In addition, the following metabolic and cardiovascular endpoints will be analyzed using the repeated measures ANOVA as described above:
  - Change in SBP from baseline
  - Change in DBP from baseline
  - Change in total cholesterol from baseline
  - Change in LDL from baseline
  - Change in HDL from baseline
  - Change in Non-LDL from baseline
  - Change in Triglycerides from baseline
  - Change in weight from baseline
  - Change in BMI from baseline
  - Change in Framingham Risk Score from baseline

8.7 Outcome analysis

To evaluate the association between each of the following endpoints and the factors listed below, a logistic regression analysis will be performed.

1. Any BPAR
2. Early BPAR (within 6 months)
3. Late BPAR (> 6 months)
4. eGFR < 45 mL/min
5. Death-Censored Graft Loss
6. NODAT
7. Denovo DSA

The factors that may be included, but are not limited to are: age, race (African American versus non-African American), gender (male versus female), donor type (living donor versus deceased donor), treatment assignment (Group A versus Group B versus Group C), DGF, DSA, cPRA, PRA, DR mismatch >0, DQ mismatch > 0 and repeat transplant.

8.8 Safety Analysis

All Safety analyses will be performed at 6, 12, and 24 months.

All protocol defined AEs and SAEs will be summarized by treatment group. Select laboratory marked abnormalities of interest will also be descriptively summarized.

The safety analysis set will consist of all patients who received at least one dose of belatacept in Groups A and B and at least one dose of tacrolimus in Group C. Patients will be analyzed according to the treatment they have received.

Renal function

The following variables will be analyzed by Fisher's Exact test.:

- eGFR by MDRD Equation by each study group at 6, 12, and 24 months.
- In patients with and without BPAR (BPAR yes or no) in each of the following groups:
  - % of patients with eGFR < 15 mL/min
  - % of patients with eGFR 16-29 mL/min
  - % of patients with eGFR 30-59 mL/min
  - % of patients with eGFR ≥ 60 mL/min

Adverse events/infections

The incidence of the following endpoints will be summarized:

- AEs related and expected to immunosuppression by treatment group
- AEs related and unexpected to immunosuppression by treatment group
- SAEs by treatment group
- SAEs rated to have relationship to study drug by treatment group
- Deaths by treatment group
- AEs leading to discontinuation of a study drug by treatment group
- AEs leading to dose adjustment or interruptions of a study drug by treatment group
- Infections by type of infection (viral, bacterial, fungal, and others)
- Serious infections resulting in hospitalization by type of infection
- DGF, OA, NOA, or DCC

BK-polyoma viremia and nephropathy

The following variables will be analyzed by Fisher's Exact test:

- occurrence of BK-polyoma viremia any time post-transplantation
- occurrence of BK-polyoma virus nephropathy any time post-transplantation

EBV or CMV Viremia or Disease

The following variables will be analyzed by Fisher's Exact test:

- occurrence of CMV or EBV viremia any time post-transplantation
- occurrence of CMV or EBV disease any time post-transplantation

PLTD or Malignancies

The following variables will be analyzed by Fisher's Exact test:

- occurrence of PTLD
- occurrence of CNS PTLD
- occurrence of non-PTLD malignancy

8.9 Sample Size Calculation

Based on the efficacy failure rates seen in belatacept published literature (33, 35), the rate of efficacy failure of the control regimen is assumed to be 50% at month 12 in the control arm Group C, we predict an improvement of 21% or more between that group and the test groups (Groups A and B).

The primary endpoint for this trial is the percentage of patients in each treatment group that meet the composite endpoint at 12 months as defined as patient death or graft loss or estimated GFR < 45 mL/min. It is assumed that the percentage of patients in the Control Group (i.e. Thymo/FK/MMF/CSWD) meeting the primary endpoint is 50%. Each of the test groups will be tested against the control group using Kaplan Meier estimates and the Log Rank test. To control the overall experiment-wise error rate at 5%, the Hochberg method for multiple comparisons will be used. In this procedure, the p-values for the two comparisons will be ordered from largest to smallest. If the largest p-value is less than $\alpha=0.05$, then both comparisons can be tested at $\alpha=0.05$. If the largest p-value is greater than $\alpha=0.05$, then we cannot reject the null hypothesis for that comparison. We then compare the second largest p-value to $\alpha=0.025$ and reject the null hypothesis if the p-value is less than $\alpha=0.025$. A sample size of 105 completed patients per group will provide at least 80% power to detect an absolute difference of 21% between two groups at the two-sided $\alpha=0.025$ if the percentage of patients meeting the primary endpoint in the control group is assumed to be 50%.

9. ADMINISTRATIVE REQUIREMENTS

9.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure/package insert. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

9.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (Appendix VIII). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure/package insert, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator.

9.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

9.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s), auditors, and regulatory authorities access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9.5 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authorities. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC.
Any departures from the protocol must be fully documented in the source documents.

9.6 Drug Accountability

Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return or disposal of the drug (if applicable) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing belatacept will be treated and disposed of as hazardous waste in accordance with governing regulations.

9.7 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data

Should the study be closed prematurely, all study materials must be returned.

9.8 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

9.8 Internal Monitoring Plan

The monitoring plan for investigator initiated studies is dictated by the investigator/sponsor. All monitoring responsibility lies with the PI. An internal monitor will be identified by the Transplant Clinical Research group at the University of Cincinnati. The internal monitor will comply with the Transplant Clinical Research Groups standard operating procedures for selection and training of sites, pre qualification monitoring visit, site initiation visit, ongoing site visits at least every quarter, and close out monitoring visit. Monitoring reports generated at each monitor's visit will be reviewed by the PI and presented at the faculty meeting for review by all investigators and other clinical research team members at the University of Cincinnati.

10. Study progress and result dissemination proposal

The following is the proposed abstract and publication strategy which reflects current targets, but may vary based upon FDA IND approval. Study enrollment will begin with the availability of belatacept study drug on site pending all regulatory and contractual obligations have been met. This calendar may be altered based upon study enrollment. The final study report will be consistent with the publication of the two year data.

October 2012	Enrolling Patients, FPFV
March 2015	LPFV
October 2014	FPLV
March 2017	LPLV
July 2017	Database lock
October 2017	Final data analysis
December 2017	Two year data analysis abstract for AST and publication submission
May 2018	Two year data AST presentation
Dec 2018 (annually to 5 year)	Annual long-term data analysis for AST and International Abstract

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IV. Appendixes

Appendix I: Laboratory and Clinical Assessment Flowchart

	Baseline Pretxp (within 10 days of txp, unless indicated otherwise)	Day of Transplant	Study Visits Time post Transplant [Day (D), Week (W), Month (M)]											
		D 1	D 7	W 2	W 4	W 8	W 12 M3	W24 M6	W 36 M9	W 52 M 12	W 64 M 15	W 80 M 18	W 92 M21	W 104 M24
Study windows			± 1	± 2	±2	±3	±3	±7	±7	±7	±7	±14	±14	±14
Consent	X													
Randomize[1]	X													
Crossmatch, Tissue Typing, PRA[2]	X													
Inclusion/Exclusion Criteria	X													
Medical History[2]	X													
Physical Exam[2]	X													
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X		X
Serologies[4]	X													
Serum Chemistries[5]	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology[6]	X	X	X	X	X	X	X	X	X	X	X	X		X
Tacrolimus Trough			X	X	X	X	X	X	X	X	X	X		X
Fasting Lipids[7]	X							X		X				X
Spot Urine Protein/Creatnine[8]	X							X		X				X
HgA1c[9]	X							X		X				X
Pregnancy Test[10]	X						X	X	X	X	X	X	X	X
DSA and ELISA assessment[11]	X						X	X		X				X
QPCR assessment[12]	X						X	X		X				X
Renal Biopsy[13]		X												
FRS Score	X							X		X				X
QoL/Side Effect Assessments	X									X				X
Clinical Assessments[14]		X	X	X	X	X	X	X	X	X	X	X		X

1. Randomization will occur within 72 hours of transplant.
2. Screening tests/procedures can be completed within 30 days of transplant. PRA just needs to be the most recent PRA, not necessarily within 30 days.
3. Vital signs include BP, weight, and height (including BMI) at baseline visit. BP and weight only at subsequent visits.
4. Serologies for CMV, Epstein-Barr, hepatitis B & C and HIV for donor and recipient done at any previous evaluation within one year will be accepted for eligibility criteria as long as it is documented.
5. Serum chemistries must include serum creatinine (Scr), albumin (Alb), blood urea nitrogen (BUN), and fasting blood glucose (FBG) with an eGFR (MDRD) assessment.
6. Hematology includes WBC, Hgb, and platelet count (PLT).
7. Subjects must be fasting. Lipid testing include total cholesterol, LDL, HDL, triglycerides.
8. Urinalysis for spot urine protein creatinine ratio.
9. HgAIc is needed in ALL patients. This will be used to help assess NODAT and exacerbation of diabetes.
10. Urine or serum pregnancy tests in women of child bearing potential will be required prior to belatacept infusions at visits on months 3, 6, 9, 12, 15, 18, 21, and 24.
11. Anti-donor HLA antibodies (DSA) and ELISA assessment (10ml red top) - additional blood samples are to be obtained at the time of any suspected rejection episode(s).
12. QPCR assessment of acute rejection signature (2.5ml Paxgene tube) – additional blood samples are to be obtained at the time of any suspected rejection episode(s)
13. There are no protocol biopsies. Implant biopsy will be performed as standard of care.
14. Includes assessments of sitting blood pressure (BP), # BP meds and type, weight changes, BMI, smoking, adverse events, CV events, study drug doses, allograft rejection, infection or malignancy, insulin or oral anti-diabetic agents, anti-lipid agents, aspirin, need for dialysis, hospitalization, re-transplant status, and other immunosuppressant medications.

Appendix II: Study Immunosuppressant Treatment Table

	Belatacept (Groups A&B)		Tacrolimus (Group C)	Induction (Group A)	Induction (Groups B&C)	Steroids (All Groups)	Mycophenolate mofetil/EC Mycophenolate Sodium (All Groups)
	10 mg/kg	**5 mg/kg**	**0.1mg/kg/day p.o. divided twice daily**	**Alemtuzumab 30mg IV**	**Rabbit antithymocyte globulin 1.5mg/kg IV**		
Day of Transplant (D1)	X1		Start tacrolimus when Scr < 4 mg/dL or within 48 hours of transplant Goal tacrolimus trough 8-12 ng/mL until day 30	X	X	Methylpred 500mg IV	Introduce Mycophenolate mofetil/EC Mycophenolate Sodium on D1 pre-op. Mycophenolate mofetil 1g p.o. BID (EC Mycophenolate Sodium 720mg p.o. BID). African American recipients may receive Mycophenolate mofetil 1.5 g p.o. BID (EC Mycophenolate Sodium 1080mg p.o. BID). Dose adjustments can be made based on MD discretion
D2					Subsequent thymo doses should be given so that total cumulative dose of 4-6 mg/kg is given by days 5-10	Methylpred 250mg IV	
D3						Methylpred 125mg IV	
D4						Prednisone 80mg p.o.	
D5	X2					Prednisone 60mg p.o.	
D6						No further steroids	
D7							
D8							
D9							
D 10							
W2 (D14)	X						
D15-D 20							
D 21-D27							
W4 (D 28)	X						
W8 (D 56)	X		Goal tacrolimus trough 5-10 ng/mL thereafter				
W12 (M 3)	X						
W16		X					
W20		X					
W24 (M 6)		X					
W28		X					
W32		X					
W36 (M 9)		X					
W40		X					
W44		X					
W48		X					
W52 (M12)		X					
W56		X					
W60		X					
W64 (M 15)		X					
W68		X					
W72		X					
W76		X					
W80 (M18)		X					
W84		X					
W88		X					
W92 (M21)		X					
W96		X					
W100		X					
W104 (M24)		X					

1. **Initial Belatacept dose will be administered** within 12-24 hours post reperfusion**.**

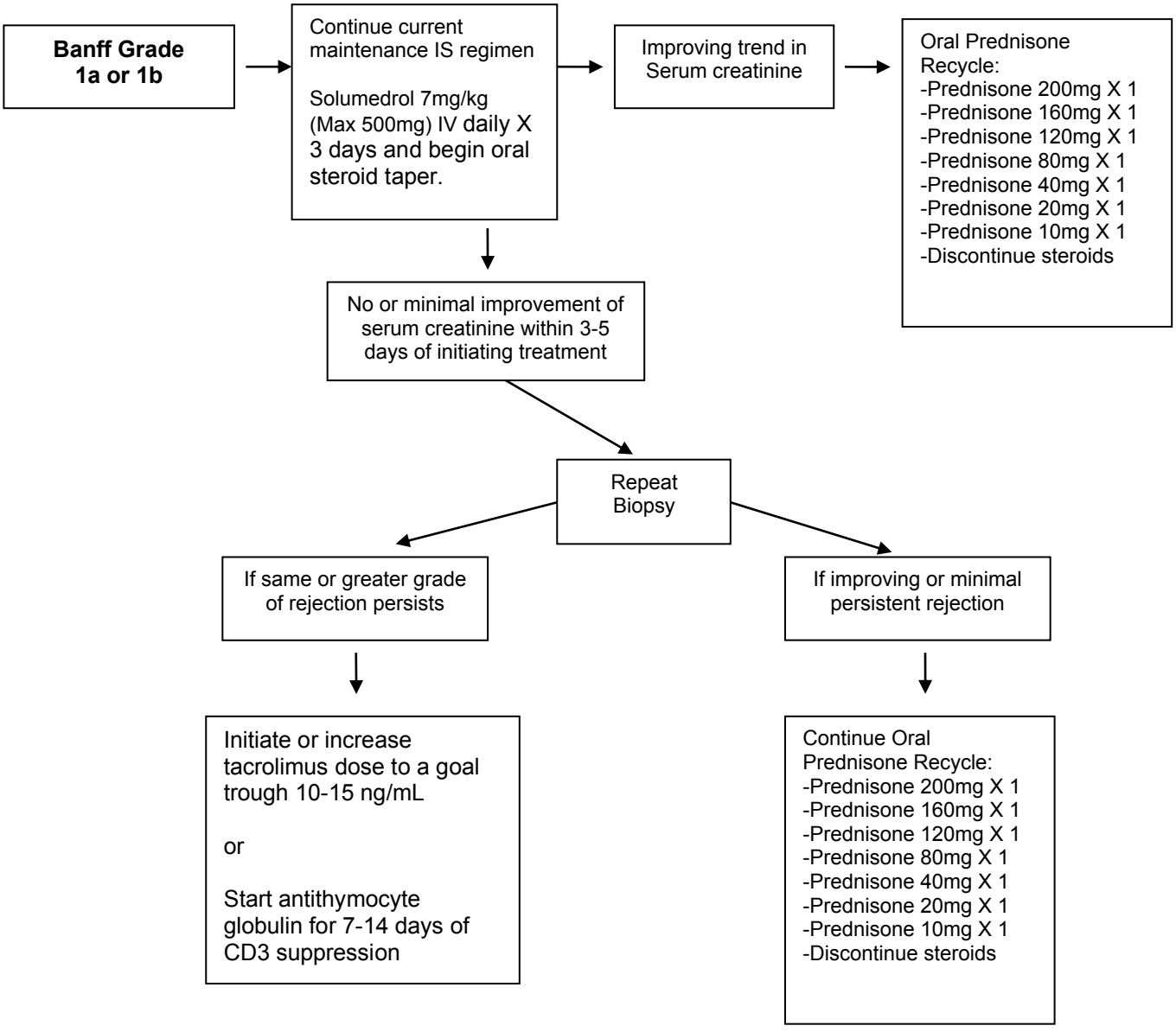
2. **Belatacept dose is to be given once between Study days 5 – 7, with intention of administering as an outpatient.**

Appendix III: Recommended Treatment of Rejection

BPACR Banff Grade 1a-1bTreatment

Continue current regimen of belatacept or tacrolimus, Solumedrol 7mg/kg (Max 500mg) IV daily X 3 days. If improving trend in Scr, then initiate oral Prednisone recycle (Prednisone 200mg X 1, Prednisone 160mg X 1, Prednisone 120mg X 1, Prednisone 80mg X 1, Prednisone 40mg X 1, Prednisone 20mg X 1, Prednisone 10mg X 1, then discontinue steroids). If no improving trend in Scr after 3-5 days of treatment initiation, then repeat biopsy. If Banff grade is the same or worse, then initiate or increase tacrolimus to a goal trough of 10-15 ng/mL or initiate rabbit antithymocyte globulin for 7-14 days of CD3 suppression. If Banff grade is improving or minimal persistent rejection, continue oral prednisone recycle.

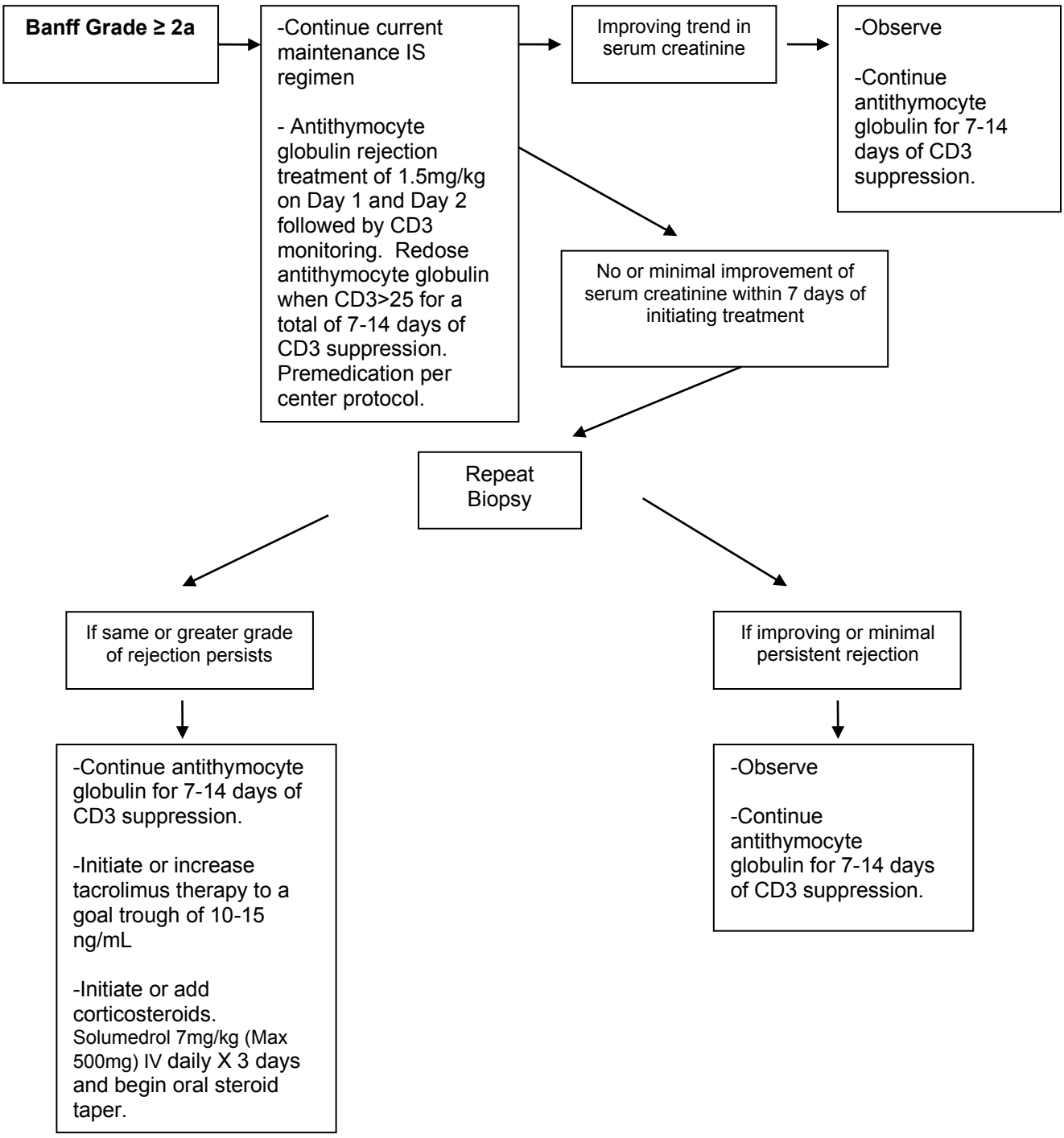
The following schematic is a guideline for the treatment of Banff 2007 Grade 1a or 1b acute rejections



6.3.2.3.2 Recommended BPACR Banff Grade ≥2a Treatment

Continue current regimen of belatacept or tacrolimus, initiate antithymocyte globulin for 7-14 days of CD3 suppression. If no improving trend in Scr after 7 days of treatment initiation, then repeat biopsy. If Banff grade is the same or worse, continue antithymocyte globulin, initiate or increase tacrolimus therapy to a goal trough of 10-15 ng/mL and initiate or add corticosteroid therapy. If Banff grade is improving or minimal persistent rejection, continue antithymocyte globulin.

The following schematic is a guideline for the treatment of Banff 2007 2a, 2b or 3 acute cellular rejections



6.3.2.3.3 Recommended BPAMR or BPMAR Treatment

May treat BPAMR or BPMAR with a bortezomib-based or IVIG-based protocol.

The following schematic is a guideline for the treatment of antibody mediated rejection and mixed rejection with bortezomib-based treatment with rituximab:

Treatment Day	PRE	1	4	7	10
PLASMAPHERESIS 1.5 PV		X	X	X	X
Methylprednisolone 100 mg IVP or PO		X	X		
Methylprednisolone 50 mg IVP or PO				X	X
BORTEZOMIB 1.3 mg/m_2 IVP or SC		X	X	X	X
RITUXIMAB 375 mg/m_2 IV		X			

Appendix IV : Quality of Life/Side Effect Assessments

The Memphis Survey
SIDE EFFECTS BECAUSE OF TRANSPLANT MEDICINES

The following questions describe problems you might be having because of the transplant or the medicine you are taking. For each problem, you will be asked how frequently you experience it (the first row) and how troubling it is (the second row). Please answer every question.

	Not at all	Very little	Sometimes or Moderately troubling	Often or Very troubling	All the time or Extremely troubling
Enlarged gums					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Increased hunger					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Staying asleep					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Weight gain					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Increased hair growth					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Infections					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Trembling hands					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
High blood pressure					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Easy bruising					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Loss of interest in sex					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Sexual performance					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Diabetes					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□

	Not at all	Very little	Sometimes or Moderately troubling	Often or Very troubling	All the time or Extremely troubling
Hair Loss					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Stomach pain					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Nausea					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Diarrhea					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Vomiting					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Stomach gas					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Indigestion					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Mood Changes					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Depression					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Nervousness or anxiety					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Irritability					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Anger					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Keeping a positive attitude					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□

	Not at all	Very little	Sometimes or Moderately troubling	Often or Very troubling	All the time or Extremely troubling
Feelings of uselessness					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Being worried					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Worthlessness					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Hopelessness					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Ability to concentrate					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Completing daily errands					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Participating in social activities					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Doing housework					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Doing yardwork					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Performing my job					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Participating in physical activities					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Participating in leisure pastimes					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□
Driving					
Do you have this problem?	□	□	□	□	□
How troubling is it?	□	□	□	□	□

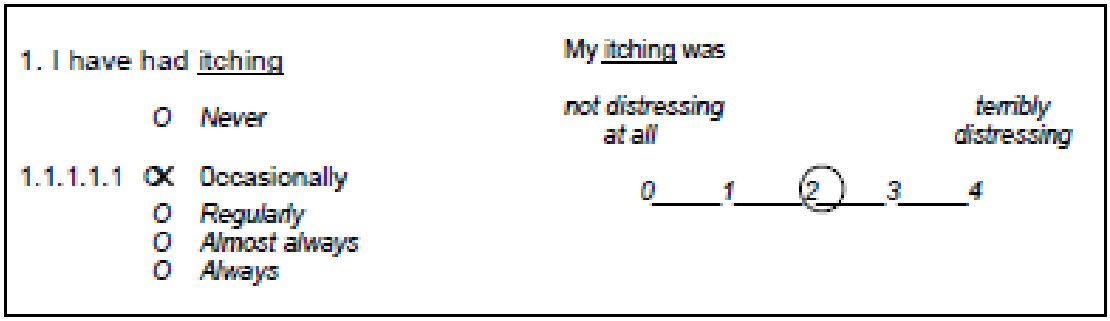
	Not at all	Very little	Sometimes or Moderately troubling	Often or Very troubling	All the time or Extremely troubling
Being independent					
Do you have this problem?	☐	☐	☐	☐	☐
How troubling is it?	☐	☐	☐	☐	☐
Ability to travel on vacations					
Do you have this problem?	☐	☐	☐	☐	☐
How troubling is it?	☐	☐	☐	☐	☐
Reading					
Do you have this problem?	☐	☐	☐	☐	☐
How troubling is it?	☐	☐	☐	☐	☐
Decreased muscle strength					
Do you have this problem?	☐	☐	☐	☐	☐
How troubling is it?	☐	☐	☐	☐	☐
Climbing stairs					
Do you have this problem?	☐	☐	☐	☐	☐
How troubling is it?	☐	☐	☐	☐	☐
Walking					
Do you have this problem?	☐	☐	☐	☐	☐
How troubling is it?	☐	☐	☐	☐	☐
Bone pain					
Do you have this problem?	☐	☐	☐	☐	☐
How troubling is it?	☐	☐	☐	☐	☐
Stiff joints					
Do you have this problem?	☐	☐	☐	☐	☐
How troubling is it?	☐	☐	☐	☐	☐
Foot pain					
Do you have this problem?	☐	☐	☐	☐	☐
How troubling is it?	☐	☐	☐	☐	☐
Hip pain					
Do you have this problem?	☐	☐	☐	☐	☐
How troubling is it?	☐	☐	☐	☐	☐

THE MTSOSDS QUESTIONNAIRE

MODIFIED TRANSPLANT SYMPTOM OCCURRENCE AND SYMPTOM DISTRESS SCALE

Instructions
Taking medication after transplantation is associated with certain side effects, which may or may not be distressing to you. In this questionnaire, each question is divided into two columns, as shown in the example below.

Example:



The ***left*** column asks about the ***occurrence*** of the **side effects**. Please indicate how frequently or how severely you have experienced a given symptom **during the past 4 weeks** by checking off the appropriate answer.

In the ***right*** column you will find questions asking you whether these symptoms are **distressing** to you. Please circle the number that corresponds with how distressing this symptom is to you.

If a symptom **does not occur**, answer **"never"** or **"not"** in the left column and go directly to the **next question**.

At the end of the questionnaire, you can add additional side effects that you may have experienced during the **past 4 weeks**. Please check if you have completed all items and all pages. Please also be sure that you have completed both the right and left column of the questionnaire.

Developed to assess occurrence and distress experienced by the side effects of Cyclosporine, Tacrolimus, Mycophenolate Mofetil, Azathioprine, Prednisolone, Sirolimus, LEA29Y.
Partly based on the Transplant Symptom Frequency and Symptom Distress Scale: Lough ME, Lindsey AM, Shinn JA, Stotts NA. Life satisfaction following heart transplantation. J Heart Transplantation 1985; 4: 446-449 & Lough ME, Lindsey AM, Shinn JA, Stotts NA. Impact of symptom frequency and symptom distress on self-reported quality of life in heart transplant recipients. Heart Lung 1987; 16: 193-200.

During the past 4 weeks (including today):

1. I have had itching O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My itching was *not distressing at all* ... *terribly distressing* *0 1 2 3 4*
2. I have had chest pain O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My chest pain was *not distressing at all* ... *terribly distressing* *0 1 2 3 4*
3. I have had wind O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My wind was *not distressing at all* ... *terribly distressing* *0 1 2 3 4*
4. I have had increased thirst O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My increased thirst was *not distressing at all* ... *terribly distressing* *0 1 2 3 4*
5. I have felt restless or nervous O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My restlessness or nervousness was *not distressing at all* ... *terribly distressing* *0 1 2 3 4*

During the past 4 weeks (including today):

6. I have had hearing loss

- O *Not*
- O *A little*
- O *Moderately*
- O *Greatly*
- O *Very greatly*

My hearing loss was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

7. I have had an abnormal skin color

- O *Not*
- O *A little*
- O *Moderately*
- O *Greatly*
- O *Very greatly*

My abnormal skin color was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

8. I have had increased sweating

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My increased sweating was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

9. My face and neck have been red

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

The redness in my face and neck was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

10. I have had brittle fingernails

- O *Not*
- O *A little*
- O *Moderately*
- O *Greatly*
- O *Very greatly*

My brittle fingernails were

not distressing at all — *terribly distressing*

0 1 2 3 4

During the past 4 weeks (including today):

11. My breasts have been larger

- O *Not*
- O *A little*
- O *Moderately*
- O *Greatly*
- O *Very greatly*

My breast enlargement was

not distressing at all — *terribly distressing*

0 1 2 3 4

12. I have had sores on my lips and/or in my mouth

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My sores on lips and/or in mouth were

not distressing at all — *terribly distressing*

0 1 2 3 4

13. I have had an altered voice

- O *Not*
- O *A little*
- O *Moderately*
- O *Greatly*
- O *Very greatly*

My altered voice was

not distressing at all — *terribly distressing*

0 1 2 3 4

14. I have had oily skin

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My oily skin was

not distressing at all — *terribly distressing*

0 1 2 3 4

During the past 4 weeks (including today):

15. I have felt dizzy

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My dizziness was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

16. My hands have trembled

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My trembling hands were

not distressing at all — *terribly distressing*

0 1 2 3 4

---

17. I have had an increased urge to urinate

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My increased urge to urinate was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

18. I have had a feeling of warmth in my hands and feet

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

The feeling of warmth in my hands and feet was

not distressing at all — *terribly distressing*

0 1 2 3 4

During the past 4 weeks (including today):

19. I have had bruises more easily

O *Never*
O *Occasionally*
O *Regularly*
O *Almost always*
O *Always*

My bruises were

not distressing at all — *terribly distressing*

0 1 2 3 4

---

20. I have had sores or warts around my genitals

O *Never*
O *Occasionally*
O *Regularly*
O *Almost always*
O *Always*

My sores or warts around genitals were

not distressing at all — *terribly distressing*

0 1 2 3 4

---

21. I have had spots on my face and/or my back

O *Never*
O *Occasionally*
O *Regularly*
O *Almost always*
O *Always*

My spots on my face and/or back were

not distressing at all — *terribly distressing*

0 1 2 3 4

---

22. I have had an excessive appetite

O *Never*
O *Occasionally*
O *Regularly*
O *Almost always*
O *Always*

My excessive appetite was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

23. I have felt depressed

O *Never*
O *Occasionally*
O *Regularly*
O *Almost always*
O *Always*

My feelings of depression were

not distressing at all — *terribly distressing*

0 1 2 3 4

During the past 4 weeks (including today):

24. My gums have swollen O *Not* O *A little* O *Moderately* O *Greatly* O *Very greatly*	My swollen gums were *not distressing at all* ... *terribly distressing* *0 1 2 3 4*
25. I have had swollen glands in my neck, armpit or groin O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My swollen glands were *not distressing at all* ... *terribly distressing* *0 1 2 3 4*
26. I have had thinning of hair or hair loss O *Not* O *A little* O *Moderately* O *Greatly* O *Very greatly*	My hair thinning or hair loss was *not distressing at all* ... *terribly distressing* *0 1 2 3 4*
27 A. I have had menstrual problems *(for females only)* O *Not* O *A little* O *Moderately* O *Greatly* O *Very greatly*	My menstrual problems were *not distressing at all* ... *terribly distressing* *0 1 2 3 4*

During the past 4 weeks (including today):

27 B. I have had <u>erectile problems</u> *(for males only)* O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My <u>erectile problems</u> were *not distressing at all* — *terribly distressing* *0 1 2 3 4*
28. I have had a <u>puffy face (moon face)</u> O *Not* O *A little* O *Moderately* O *Greatly* O *Very greatly*	My <u>puffy face</u> was *not distressing at all* — *terribly distressing* *0 1 2 3 4*
29. I have had <u>swollen ankles or feet</u> O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My <u>swollen ankles or feet</u> were *not distressing at all* — *terribly distressing* *0 1 2 3 4*
30. I have had <u>diarrhea</u> O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My <u>diarrhea</u> was *not distressing at all* — *terribly distressing* *0 1 2 3 4*

During the past 4 weeks (including today):

31. I have had tingling or numbness in my hands or feet

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My tingling or numbness in my hands or feet was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

32. I have had back pain

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My back pain was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

33. I have had a brittle skin

- O *Not*
- O *A little*
- O *Moderately*
- O *Greatly*
- O *Very greatly*

My brittle skin was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

34. I have felt anxious

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My feelings of anxiety were

not distressing at all — *terribly distressing*

0 1 2 3 4

During the past 4 weeks (including today):

35. I have been experiencing mood swings

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My mood swings were

not distressing at all — *terribly distressing*

0 1 2 3 4

---

36. I have had headaches

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My headaches were

not distressing at all — *terribly distressing*

0 1 2 3 4

---

37. My facial features have changed

- O *Not*
- O *A little*
- O *Moderately*
- O *Greatly*
- O *Very greatly*

My changed facial features were

not distressing at all — *terribly distressing*

0 1 2 3 4

---

38. I have had fat deposits on my neck and back ("buffalo hump")

- O *Not*
- O *A little*
- O *Moderately*
- O *Greatly*
- O *Very greatly*

My fat deposits on neck and back were

not distressing at all — *terribly distressing*

0 1 2 3 4

During the past 4 weeks (including today):

39. I have had difficulty concentrating and/or memory problems O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My concentration difficulties and/or memory problems were *not distressing at all* — *terribly distressing* *0 1 2 3 4*
40. I have had warts on hands and feet O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My warts on hands and feet were *not distressing at all* — *terribly distressing* *0 1 2 3 4*
41. I have had increased hair growth on face and body O *Not* O *A little* O *Moderately* O *Greatly* O *Very greatly*	My increased hair growth on face and body were *not distressing at all* — *terribly distressing* *0 1 2 3 4*
42. I have had sleep difficulties O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My sleep difficulties were *not distressing at all* — *terribly distressing* *0 1 2 3 4*

During the past 4 weeks (including today):

43. I have had muscle weakness

- O *Not*
- O *A little*
- O *Moderately*
- O *Greatly*
- O *Very greatly*

My muscle weakness was

not distressing at all ... *terribly distressing*

0 1 2 3 4

---

44. My sense of taste has changed

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

The change in my sense of taste was

not distressing at all ... *terribly distressing*

0 1 2 3 4

---

45. I have had a poor appetite

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My poor appetite was

not distressing at all ... *terribly distressing*

0 1 2 3 4

---

46. I have felt tired

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My tiredness was

not distressing at all ... *terribly distressing*

0 1 2 3 4

---

47. I have had lack of energy

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My lack of energy was

not distressing at all ... *terribly distressing*

0 1 2 3 4

During the past 4 weeks (including today):

48. I have had stomach complaints, I have felt nauseous and/or I had to vomit

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My stomach complaints, nausea or vomiting were

not distressing at all — *terribly distressing*

0 1 2 3 4

---

49. I have had pain in my joints

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My joint pain was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

50. I have had a rash on my skin

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My skin rash was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

51. I have had muscle cramps

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My muscle cramps were

not distressing at all — *terribly distressing*

0 1 2 3 4

During the past 4 weeks (including today):

52. I have had nightmares O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My nightmares were *not distressing at all* — *terribly distressing* *0 1 2 3 4*
53. I have been short of breath O *Not* O *A little* O *Moderately* O *Greatly* O *Very greatly*	My shortness of breath was *not distressing at all* — *terribly distressing* *0 1 2 3 4*
54. I have had a dry skin O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My dry skin was *not distressing at all* — *terribly distressing* *0 1 2 3 4*
55. I have had palpitations O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My palpitations were *not distressing at all* — *terribly distressing* *0 1 2 3 4*
56. I have had constipation O *Never* O *Occasionally* O *Regularly* O *Almost always* O *Always*	My constipation was *not distressing at all* — *terribly distressing* *0 1 2 3 4*

During the past 4 weeks (including today):

---

57. I have had difficulty seeing well

- O *Not*
- O *A little*
- O *Moderately*
- O *Greatly*
- O *Very greatly*

My seeing difficulties were

not distressing at all — *terribly distressing*

0 1 2 3 4

---

58. I have had a reduced interest in sex

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My reduced interest in sex was

not distressing at all — *terribly distressing*

0 1 2 3 4

---

59. My eyes have been sensitive to light

- O *Never*
- O *Occasionally*
- O *Regularly*
- O *Almost always*
- O *Always*

My sensitivity to light was

not distressing at all — *terribly distressing*

0 1 2 3 4

Please check if you have completed all items and all pages.
Please also be sure that you have completed both the right and left column of the questionnaire.

THANK YOU VERY MUCH FOR YOUR COOPERATION

Appendix V : National Cholesterol Education Panel, Adult Treatment Panel III[36]

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

- Cigarette smoking
- Hypertension (BP ≥ 140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)†
- Family history of premature CHD
    - CHD in male first degree relative <55 years
    - CHD in female first degree relative <65 years
- Age (men 45 years; women 55 years)

† HDL cholesterol 60 mg/dL counts as "negative" risk factor; its presence removes one risk factor from the total count.

Three Categories of Risk that Modify LDL-Cholesterol

Goals Risk Category	LDL Goal (mg/dL)
CHD and CHD risk equivalents	<100
Multiple (2+) risk factors	<130
Zero to one risk factor	<160

ATP III Lipid and Lipoprotein Classification

LDL Cholesterol (mg/dL)

- <100 Optimal
- 100-129 Near optimal/above optimal
- 130-159 Borderline high
- 160-189 High
- 190 Very high

HDL Cholesterol (mg/dL)

- <40 Low
- >60 High

Total Cholesterol (mg/dL)

- <200 Desirable
- 200-239 Borderline high
- >240 High Primary

LDL Cholesterol Goals and Cut points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC) (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD Risk Equivalents (10-year risk >20%)	<100	100	130 (100–129: drug optional)
2+ Risk Factors (10-year risk ≤20%)	<130	130	10-year risk 10–20%: 130 10-year risk <10%: 160
0–1 Risk Factor	<160	160	190 (160–189: LDL-lowering drug optional)

LDL Cholesterol Goal and Cut points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Patients with CHD and CHD Risk Equivalents (10-Year Risk >20%)

LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
<100 mg/dL	100 mg/dL	130 mg/dL (100–129 mg/dL: drug optional)

LDL Cholesterol Goals and Cut points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC) (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD Risk Equivalents (10-year risk >20%)	<100	100	130 (100–129: drug optional)
2+ Risk Factors (10-year risk ≤20%)	<130	130	10-year risk 10–20%: 130 10-year risk <10%: 160
0–1 Risk Factor	<160	160	190 (160–189: LDL-lowering drug optional)

Appendix VI : JNC VII Guide to Prevention and treatment of Hypertension Recommendations[37]

CVD Risk Factors

- Hypertension*
- Cigarette smoking
- Obesity* (BMI ≥ 30 kg/m2)
- Physical inactivity
- Dyslipidemia*
- Diabetes mellitus*
- Microalbuminuria or estimated GFR <60 ml/min
- Age (older than 55 for men, 65 for women)
- Family history of premature CVD (men under age 55 or women under age 65)

*Components of the metabolic syndrome.

Blood Pressure Classification

BP Classification	SBP mmHg		DBP mmHg
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 Hypertension	140–159	or	90–99
Stage 2 Hypertension	≥ 160	or	≥ 100

Algorithm for Treatment of Hypertension

				Initial drug therapy	
BP classification	SBP* mmHg	DBP* mHg	Lifestyle modification	Without compelling indication	With compelling indications
Normal	<120	and <80	Encourage		
Prehypertension	120–139	or 80–89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications.***
Stage 1 Hypertension	140–159	or 90–99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.*** Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 2 Hypertension	≥ 160	or ≥ 100	Yes	Two-drug combination for most** (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	Drug(s) for the compelling indications.*** Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

*Treatment determined by highest BP category.
**Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.
***Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mmHg.

Appendix VII : Framingham Heart Study Coronary Heart Disease Risk Score[38]

Score Sheet for Males :

Step 1

Age		
Years	LDL Pts	Chol Pts
30-34	-1	[-1]
35-39	0	[0]
40-44	1	[1]
45-49	2	[2]
50-54	3	[3]
55-59	4	[4]
60-64	5	[5]
65-69	6	[6]
70-74	7	[7]

Step 2

LDL - C		
(mg/dl)	(mmol/L)	LDL Pts
<100	<2.59	-3
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-190	4.15-4.92	1
≥190	≥4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
<160	<4.14	[-3]
160-199	4.15-5.17	[0]
200-239	5.18-6.21	[1]
240-279	6.22-7.24	[2]
≥280	≥7.25	[3]

Step 3

HDL - C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
<35	<0.90	2	[2]
35-44	0.91-1.16	1	[1]
45-49	1.17-1.29	0	[0]
50-59	1.30-1.55	0	[0]
≥60	≥1.56	-1	[-2]

Step 4

Blood Pressure				
Systolic (mm Hg)	Diastolic (mm Hg) <80	80-84	85-89	90-99	≥100
<120	0 [0] pts				
120-129		0 [0] pts			
130-139			1 [1] pts		
140-159				2 [2] pts	
≥160					3 [3] pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

(sum from steps 1-6)

Step 7

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL - C	
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point total	_____

(determine CHD risk from point total)

Step 8

CHD Risk			
LDL Pts Total	10 Yr CHD Risk	Chol Pts Total	10 Yr CHD Risk
<-3	1%		
-2	2%		
-1	2%	[<-1]	[2%]
0	3%	[0]	[3%]
1	4%	[1]	[3%]
2	4%	[2]	[4%]
3	6%	[3]	[5%]
4	7%	[4]	[7%]
5	9%	[5]	[8%]
6	11%	[6]	[10%]
7	14%	[7]	[13%]
8	18%	[8]	[16%]
9	22%	[9]	[20%]
10	27%	[10]	[25%]
11	33%	[11]	[31%]
12	40%	[12]	[37%]
13	47%	[13]	[45%]
≥14	≥56%	[≥14]	[≥53%]

(compare to average person your age)

Step 9

Comparative Risk			
Age (years)	Average 10 Yr CHD Risk	Average 10 Yr Hard* CHD Risk	Low** 10 Yr CHD Risk
30-34	3%	1%	2%
35-39	5%	4%	3%
40-44	7%	4%	4%
45-49	11%	8%	4%
50-54	14%	10%	6%
55-59	16%	13%	7%
60-64	21%	20%	9%
65-69	25%	22%	11%
70-74	30%	25%	14%

Key	
Color	Relative Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

* Hard CHD events exclude angina pectoris

** Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dL or cholesterol 160-199 mg/dl, HDL-C 45 mg/dL for men or 55 mg/dL for women, non-smoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

Score Sheet for Females :

Step 1

Age		
Years	LDL Pts	Chol Pts
30-34	-9	[-9]
35-39	-4	[-4]
40-44	0	[0]
45-49	3	[3]
50-54	6	[6]
55-59	7	[7]
60-64	8	[8]
65-69	8	[8]
70-74	8	[8]

Step 2

LDL - C		
(mg/dl)	(mmol/L)	LDL Pts
<100	<2.59	-2
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-190	4.15-4.92	2
≥190	≥4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
<160	<4.14	[-2]
160-199	4.15-5.17	[0]
200-239	5.18-6.21	[1]
240-279	6.22-7.24	[1]
≥280	≥7.25	[3]

Step 3

HDL - C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
<35	<0.90	5	[5]
35-44	0.91-1.16	2	[2]
45-49	1.17-1.29	1	[1]
50-59	1.30-1.55	0	[0]
≥60	≥1.56	-2	[-3]

Step 4

Blood Pressure					
Systolic (mm Hg)	Diastolic (mm Hg) <80	80-84	85-89	90-99	≥100
<120	-3 [-3] pts				
120-129		0 [0] pts			
130-139			0 [0] pts		
140-159				2 [2] pts	
≥160					3 [3] pts

+ Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	4	[4]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

(sum from steps 1-6)

Step 7

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL - C	
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point total	_____

(determine CHD risk from point total)

Step 8

CHD Risk			
LDL Pts Total	10 Yr CHD Risk	Chol Pts Total	10 Yr CHD Risk
≤-2	1%	[≤-2]	[1%]
-1	2%	[-1]	[2%]
0	2%	[0]	[2%]
1	2%	[1]	[2%]
2	3%	[2]	[3%]
3	3%	[3]	[3%]
4	4%	[4]	[4%]
5	5%	[5]	[4%]
6	6%	[6]	[5%]
7	7%	[7]	[6%]
8	8%	[8]	[7%]
9	9%	[9]	[8%]
10	11%	[10]	[10%]
11	13%	[11]	[11%]
12	15%	[12]	[13%]
13	17%	[13]	[15%]
14	20%	[14]	[18%]
15	24%	[15]	[20%]
16	27%	[16]	[24%]
≥17	≥32%	[≥17]	[≥27%]

(compare to average person your age)

Step 9

Comparative Risk			
Age (years)	Average 10 Yr CHD Risk	Average 10 Yr Hard* CHD Risk	Low** 10 Yr CHD Risk
30-34	<1%	<1%	<1%
35-39	<1%	<1%	1%
40-44	2%	1%	2%
45-49	5%	2%	3%
50-54	8%	3%	5%
55-59	12%	7%	7%
60-64	12%	8%	8%
65-69	13%	8%	8%
70-74	14%	11%	8%

Key	
Color	Relative Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

* Hard CHD events exclude angina pectoris

** Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dL or cholesterol 160-199 mg/dl, HDL-C 45 mg/dL for men or 55 mg/dL for women, non-smoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

Appendix VIII : World Medical Association Declaration of Helsinki:

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue

influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving

research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.