Belatacept Conversion in Proteinuric Renal Transplant Recipients and B7-1 Positivity Status on Biopsy: an Interventional Multi-Center Trial

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Short Title: B7-1 Study

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I. Study Synopsis

Background: Proteinuria develops in about 30% of kidney transplant recipients and is a strong predictor of graft loss. The amount of proteinuria has a direct correlation with the risk of graft failure. Novel therapies are urgently needed to reduce proteinuria and prevent graft loss in transplant recipients, since ACE inhibitors carry a number of limitations in the transplant setting, including significant reduction in renal function, anemia and hyperkalemia.

Preliminary data: B7-1 is expressed at significant levels in about 10% of kidney allograft biopsies with predominance in patients with proteinuria.

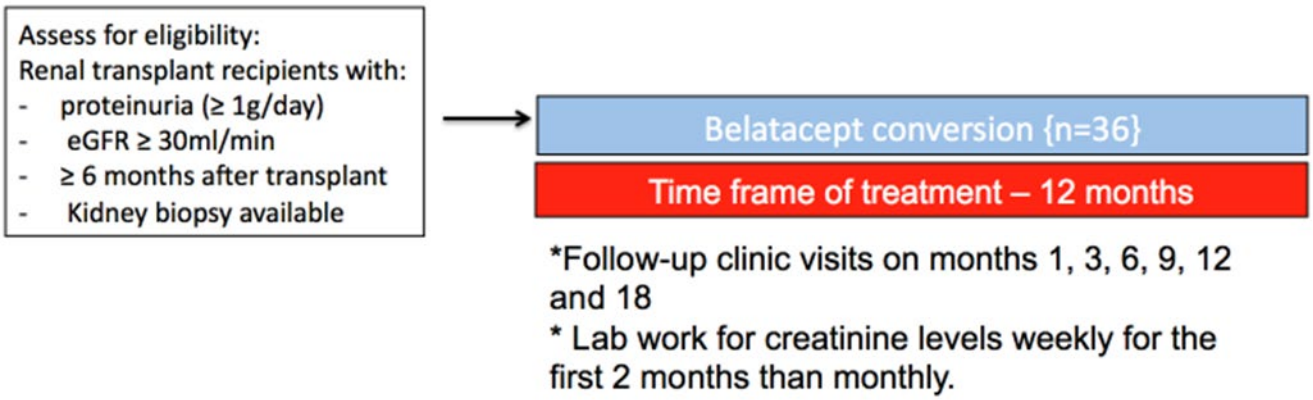
Hypothesis: We hypothesize that B7-1 targeting therapy may reduce proteinuria and improve graft survival in proteinuric transplant recipients that have B7-1 staining on allografts. In addition, the absence of calcineurin inhibitor (CNI) nephrotoxicity and the potential protective effect of Belatacept on DSA production may be of benefit in this subset of transplant patients.

Objectives:

Primary: Determine the effect of Belatacept conversion in reducing proteinuria by 25% at 12 months in renal transplant recipients (≥1gram/d) that are either B7-1-positive or negative on kidney biopsy.

Secondary: Assess the effect of Belatacept conversion in the percent change of renal function from baseline to 12 months; donor-specific anti-HLA antibodies presence and intensity (MFI); correlation of B7-1 positivity on immunofluorescence on biopsy with B7-1-expression in urine extracellular vesicles; adverse events; acute rejection episodes; blood pressure control; new onset diabetes; hyperlipidemia; graft survival; and patient survival.

Study design:



Inclusion Criteria:

1. Male or female adult kidney transplant recipients older than 18 years old
2. eGFR ≥30 ml/min
3. ≥6 months after transplantation
4. Proteinuria ≥1 gram/day in spot urine protein/creatinine ratio
5. Available biopsy specimen for B7-1 staining at recruitment time.
6. Ability to provide written informed consent for the study.
7. Maintenance immunosuppression of CNI (cyclosporine or tacrolimus), antiproliferative agent (azathioprine, MMF or MPA) with either steroids or not.
8. Must be EBV IgG positive

Exclusion Criteria:

1. Age <18 years

2. eGFR<30 ml/min
3. active acute cellular rejection (ACR; higher than borderline) or ACR in the previous 6 months; active acute antibody-mediated rejection.
4. recurrent FSGS
5. EBV IgG negative
6. patient on mTOR inhibitor (e.g. Everolimus, Sirolimus)
7. patient only on CNI (cyclosporine or tacrolimus) and steroids

Accrual Goal: 36 subjects, 3 study sites
Accrual Rate: approximately 2 subjects/month; total of 18 months enrollment; 18 months of follow-up
First Patient First Visit: 1-March-2015

Statistics: This is a Phase I clinical trial to test the safety and gain further insight into the potential effect of Belatacept in proteinuric kidney transplant patients. We plan to recruit 36 patients, based on the feasibility for recruitment in 3 transplant centers and prior literature on recommended sample sizes in a Phase I trial.

2. Background:

Although improvements in immunosuppression have led to a reduction in acute rejection rates, long-term allograft survival remains disappointing, with more than 50% of allografts lost 10 years after transplantation.

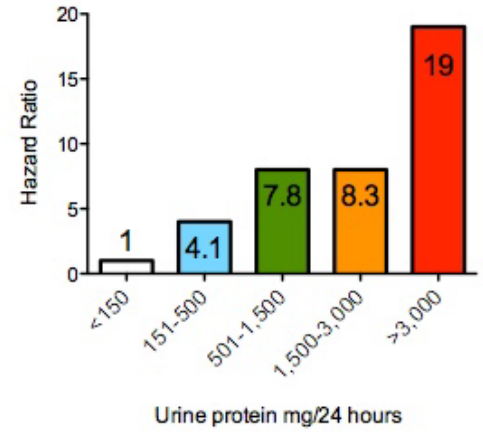


Figure 1. Risk of graft failure according to degree of proteinuria.

Proteinuria develops in about **30% of kidney transplant recipients** and is **strong predictor of graft loss** (1-3). The amount of proteinuria has a direct correlation with the risk of graft failure (**Figure 1**). More than 80% of patients with proteinuria greater than 1500 mg/d have evidence of allograft glomerular pathology. Among these, transplant glomerulopathy is the leading etiology in about 45% of cases followed by recurrent glomerular disease (25%) (4, 5). Patients with more than 1 gram/day of proteinuria after transplantation carry a dismal prognosis more than 50% of grafts lost after a mean follow up of 5 years (4). The proteinuria on these patients continues to progress and kidney function deteriorates until grafts are lost with no effective therapy to halt this progression, therefore the need to establish novel therapies for this subset of transplant patients.

KDIGO guidelines recommend ACEI/ARB in post-transplant proteinuric patients though there is no clear evidence that this approach improves renal transplant survival (6, 7). In contrary, ACEI/ARB have been associated with significant decrease in renal function, anemia and hyperkalemia post-transplantation. Novel therapies are urgently needed to reduce proteinuria and prevent graft loss in transplant recipients.

It has been recently published that **Abatacept is able to reduce proteinuria in patients with B7-1–positive glomerular disease** by stabilizing β1-integrin activation in podocytes (8). However, prevalence of positive B7-1 staining in renal allografts and a possible role of B7-1 target therapy in the treatment of proteinuria post-transplantation remains to be explored.

3. Preliminary Data:

Using a goat anti-human B7-1 (CD80) antibody, we performed immunostaining for B7-1 on frozen sections of **123 clinically indicated kidney transplant biopsies** obtained between 2011 and 2012. Fifteen patients had ≥1+ B7-1 staining on glomeruli at podocyte location **(Figure 2).** The predominant pathologic diagnosis among those with B7-1 positivity was **transplant glomerulopathy** (46%). In addition, 27% of patients with ≥1+ B7-1 staining in their biopsies had nephrotic range proteinuria (4 out of 15) and 50% of allograft biopsies obtained from patients with nephrotic syndrome stained positive for B7-1 (4 out of 8). In sum, **B7-1 is expressed at significant levels in about 10% of kidney allograft biopsies.**

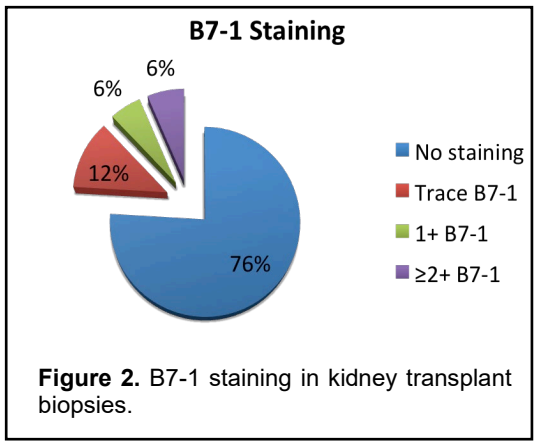


Figure 2. B7-1 staining in kidney transplant biopsies.

4. Hypothesis:
We hypothesize that B7-1 targeting therapy may reduce proteinuria and improve graft survival in proteinuric transplant recipients that have B7-1 staining on allografts. In addition, the absence of CNI nephrotoxicity and the potential protective effect of Belatacept on DSA production may be of benefit in this subset of transplant patients (9, 10).

5. Objectives:
Primary: Determine the effect of Belatacept conversion in reducing proteinuria by 25% at 12 months in renal transplant recipients that have more than 1 gram of proteinuria per day and are either B7-1-positive or negative on kidney biopsy.
Secondary: Assess the effect of Belatacept conversion in the percent change of renal function from baseline to 12 months; donor-specific anti-HLA antibodies presence and intensity (MFI); correlation of B7-1 positivity on immunofluorescence on biopsy with B7-1-expression in urine extracellular vesicles; adverse events; acute rejection episodes; blood pressure control; new onset diabetes; hyperlipidemia; graft survival; and patient survival.

6. Proposal:
We propose to perform a multi-center study in which adult kidney transplant recipients with proteinuria (≥1g/day) will be converted from CNI to Belatacept (**Figure 3**) once B7-1 staining has been performed on allograft biopsy (Dr Astrid Weins will be performing all stains). This is a Phase I study that will aim to enroll 36 patients in 18-month recruitment time involving 3 transplant sites. Other inclusion criteria include: eGFR >30 ml/min, greater than 6 months post-transplant and EBV IgG positive status. **Exclusion criteria** include: age <18 years, eGFR<30 ml/min, active acute cellular rejection (ACR; higher than borderline) or ACR in the previous 6 months, recurrent FSGS, EBV IgG negative status and on mTOR inhibitor as maintenance immunosuppression.

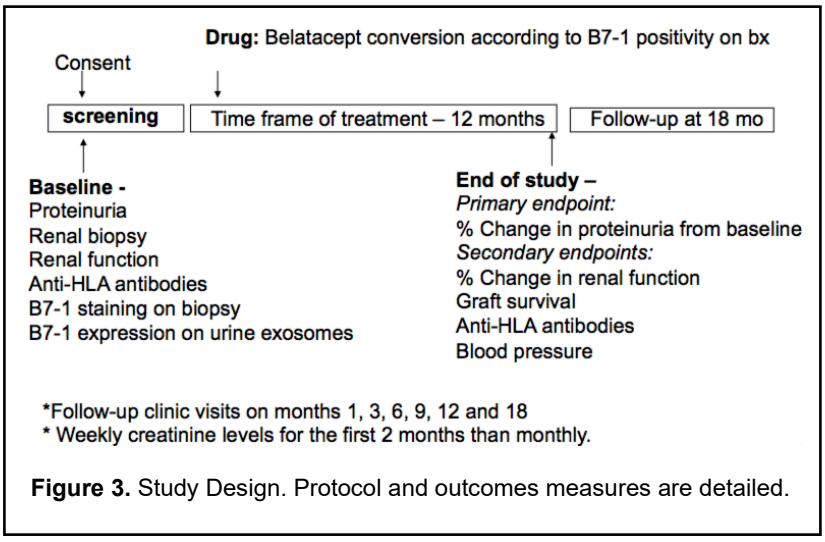


Figure 3. Study Design. Protocol and outcomes measures are detailed.

Patients that develop proteinuria after transplant are a heterogenous group with many potential

underlying etiologies including calcineurin inhibitor toxicity, transplant glomerulopathy, BK nephropathy or recurrent glomerular disease (4). Therefore, we decided to enroll 12 patients per center (3 centers total) to allow the inclusion of different etiologies of proteinuria and be a feasible study based on our inclusion criteria.

By including both B7-1 positive and B7-1 negative patients with proteinuria in the study, we will have the best chance of success and it would also allow for future testing for other potential prognostic markers in this population. One of the main reasoning's behind this is that the B7-1 staining is undergoing further optimization by Dr. Astrid Weins and a NIH task force, and therefore, restricting our recruitment may limit interpretation of the data in case the staining changes. This has been previously shown to be most productive approach in biomarker-driven interventions in the cancer field (11). In addition, the exact mechanism in which is B7-1 targeting reduce proteinuria is still debated. By including both B7-1 positive and B7-1 negative patients with proteinuria, we will be able to assess overall risk factors and have a control group with no B7-1 staining treated with Belatacept. A historical control group with patients that fit the inclusion criteria and were managed as standard of care at our institution will also be included for comparison.

The **primary endpoint** of the study will be a 25% reduction in proteinuria from baseline to 12 months. This endpoint was extrapolated from studies with ACE inhibitors showing significant benefit in patients with kidney disease and proteinuria that reached this endpoint (12). **Secondary end-points** include: percent change of renal function from baseline to 12 months; donor-specific anti-HLA antibodies presence and intensity (MFI); correlation of B7-1 positivity on immunofluorescence on biopsy with B7-1-expression in urine extracellular vesicles; adverse events; acute rejection episodes; blood pressure control; new onset diabetes; hyperlipidemia; graft survival; and patient survival. At 18 months, we will perform a chart review to check if patient remained or not on Belatacept, their renal function, proteinuria and biopsy-proven rejection events since trial termination.

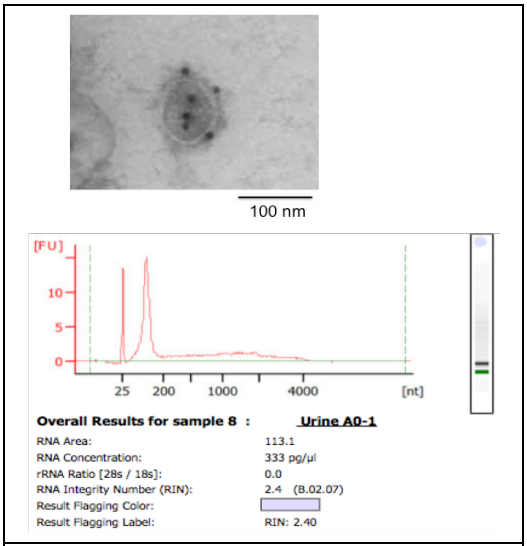


Figure 4. A, Electron Microscopy of urinary exosomes from a kidney transplant recipient labeled with exosomal marker, CD63. B, High sensitivity RNA analysis of urinary EVs. Urinary EVs were isolated from urine (average 35 ml) of a kidney transplant recipient followed by RNA isolation Agilent Bioanalyzer RNA for qualitative and quantitative analysis of RNA.

Developing **a urinary biomarker to non-invasively detect patients with B7-1 expression on allografts** is another goal of this study. This will not only allow monitoring of treatment effectiveness and serving as secondary end-points but will also permit non-invasively screening for B7-1 positivity in patients in the future. Briefly, we will isolate RNA from urinary extracellular vesicles (EVs) of transplanted patients and detect B7-1 mRNA using "Droplet Digital" PCR system. EVs such as exosomes (40-100 nm in diameter) and microvesicles (100-1000 nm) are nanometer-sized vesicles released by cells including kidney podocytes to mediate cell-to-cell communication by delivering proteins and genetic materials such as mRNAs and microRNAs (13). We hypothesize that podocytes expressing B7-1 will shed EVs into the urine that will carry B7-1 mRNA. Dr. Jamil Azzi's laboratory at the Transplantation Research Center (Co-Investigator) optimized the isolation of high quality and quantity of RNA from urinary EVs of transplant patients (Figure 4).

Enrolled patients will have serum and urine collected at time of conversion and 12 months post-conversion. Urine will be processed for extracellular vesicles (EVs) and mRNA isolation. Samples will be stored at minus 80 degrees Celsius freezer until analysis. Future alternative approaches for characterization of B7-1 expression on kidney allografts involve determination of urinary B7-1 mRNA

by PCR and laser micro-dissection of glomerulus on biopsy sample followed by measurement of B7-1 by QT-PCR.

Sample size calculation: This is a Phase I clinical trial to test the safety and gain further insight into the potential effect of Belatacept in proteinuric patients. We plan to recruit 36 patients, based on the feasibility for recruitment in 3 transplant centers and prior literature on recommended sample sizes in Phase I trials.(14, 15).

Impact: Causes of long-term graft loss are heterogenous and it is clear that the one-size-fits-all approach in transplantation is deemed for failure. Therefore, we believe that the identification of abnormal B7-1 expression in proteinuric kidney transplant recipients may permit the application of a personalized target therapy that will have a higher likelihood of success, avoiding the use of costly ineffective agents, minimizing their adverse effects and potentially improving long-term graft survival. Lastly, prior work from our laboratory has shown some promising results in B7 targeting in experimental models of chronic allograft rejection (16, 17) and more recent work supports an effective role of B7 targeting in suppressing humoral response through significant reduction in T follicular helper cells (18). Both findings support additional pathophysiological mechanisms involving not only podocytes but the immune system in contributing to obtain favorable results in this proposed study.

Ethical considerations:
All study investigators and study staff must follow all appropriate requirements, including Good Clinical Practice (GCP), International Conference on Harmonization (ICH), Code of Federal Regulations (CFR), and the Partners Human Research Committee (PHRC) Institutional Review Board (IRB). The study will be conducted in compliance of the protocol. The protocol, all amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study. Study personnel must be qualified by education, training and experience to perform their respective tasks, and will not utilize personnel for whom sanctions have been invoked or where there has been scientific misconduct or fraud.
Appropriate study personnel will obtain signed and dated informed consent from each study participant. [Investigators will ensure that subjects, or their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding this clinical research study in which they voluntarily participate. The approved consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki. All relevant safety information regarding the dose/schedule of study drug, or any other drugs/procedures in this clinical study must be explained in the informed consent document. Informed consent will also delineate which authorities may have direct access to study records and documents. Consent will also clearly state that although Dr. Leonardo Riella is the study sponsor, Bristol-Myers Squibb (BMS) is the study funding source and is also supplying study drug for this study.

7. Eligibility:
7.1 Inclusion Criteria:
- Deceased or living donor adult kidney transplant recipients older than 18 years old
- eGFR >30 ml/min
- >6 months after transplantation
- Proteinuria >1 gram/day in spot urine protein/creatinine ratio
- Available biopsy specimen for B7-1 staining at recruitment time.
- Ability to provide written informed consent for the study.
- Must be EBV IgG positive

7.2 Exclusion Criteria:
- Age <18 years
- eGFR<30 ml/min
- Active acute cellular rejection (ACR; higher than borderline) or ACR in the previous 6 months; active acute antibody-mediated rejection.
- Recurrent FSGS
- EBV IgG negative

- Patient on mTOR inhibitor (e.g. Everolimus, Sirolmus)
- Age and Reproductive Status:

7.3 Age and Reproductive Status

- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

- Women must not be breastfeeding

- WOCBP and male subjects with reproductive potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug and for four (4) months post-treatment completion.

- Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception.

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.
At a minimum, subjects must agree to the use of one method of highly effective contraception as listed below:

7.4 HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena by WOCBP subject or male subject's WOCBP partner
- Female partners of male subjects participating in the study may use hormone-based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

7.5 LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide

- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*.

* A male and female condom must not be used together

8. Study Drug: Belatacept (Treatment with Belatacept will continue for 12 months)****:**
Belatacept conversion dosing: 5 mg/kg IV on days 1, 15, 29, 43 and 57, followed by an infusion every 28 days thereafter. Calcineurin inhibitors (CNI) Taper: CNI dose will remain the same for week 1 and then will be tapered by 25% each week and discontinued at the end of week 4 (day 29).

Infusion pre-medications: none
Duration of Infusion: 30 minutes
Observation period post-infusion: none

Standard of Care (SOC) Dosing of Belatacept:
5 x the patient's weight (in kg) = mg of Belatacept. Dose then needs to be rounded to the nearest 12.5 mg increment. Example: 74 kg patient x 5 = 370 mg; rounded to the nearest 12.5 mg increment = 375 mg. At the end of 12 months, study subjects have completed the study drug protocol and they have the option to continue on Belatacept treatment, paid for by their medical insurance, or they can switch back to a CNI.

**Please see additional important study drug information on pages 11-12.

8.1 Potential Risks of Belatacept

8.1.1 Acute Rejection

Acute rejection is expected to be the principle risk in this study. In quantitative terms, the magnitude of renal function benefit necessary to offset the risk of incremental acute rejection (up to 10% based upon historical experience in the conversion setting) is not well characterized. Further, opinion among treating clinicians may vary based upon a number of factors, including individual patient needs and the clinician's assessment of the relative importance of rejection versus renal function as predictors of long-term outcomes. Thus, it is anticipated that a comprehensive review of the totality of safety and efficacy data will be necessary in order to characterize the clinical importance of acute rejection. The long-term data is reassuring since even patients that developed an episode of acute rejection had improved renal function when compared to CNI regimen at 5 years post-transplant.

*8.1.2 Post-transplant Lymphoproliferative Disorder (PTLD)**- Black Box Warning***

WARNING:POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER, OTHER MALIGNANCIES, AND SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.

- **Increased risk for developing post-transplant lymphoproliferative disorder (PTLD), predominantly involving the central nervous system (CNS). Recipients without immunity to Epstein-Barr virus (EBV) are at a particularly increased risk; therefore, use in EBV seropositive patients only. Do not use NULOJIX in transplant recipients who are EBV seronegative or with unknown serostatus.**
- **Only physicians experienced in immunosuppressive therapy and management of kidney transplant patients should prescribe NULOJIX.**
- **Increased susceptibility to infection and the possible development of malignancies may result from immunosuppression.**
- **Use in liver transplant patients is not recommended due to an increased risk of graft loss and death.**

PTLD is a known complication of immunosuppression in renal transplant recipients. In the core

Belatacept studies in adults, the overall 3-year incidence rate of PTLD in Belatacept was consistent with published reports, the highest risk of PTLD with Belatacept was observed in EBV-negative subjects in whom a 13-fold increased risk of PTLD relative to EBV-positive patients was observed (9.9% in EBV-negative patients vs 0.7% in EBV-positive patients). Based upon these findings, Belatacept is contraindicated for use in patients with EBV serostatus negative or unknown. While there was also an increased risk in EBV-positive subjects with Belatacept compared to CsA within the studies, the absolute risk in this population was low. In addition to EBV-negative serostatus, CMV disease, and use of lymphocyte depleting therapy (LDT) for treatment of AR were also associated with an increased risk of PTLD in the core Belatacept studies. PTLD in Belatacept-treated patients was unusual in that a majority of cases presented in the CNS. The overall proportion of CNS PTLD in the Belatacept groups (MI and LI combined) was 9/14 (64%), which is higher than the proportion of CNS PTLD reported in the literature: 11% to 13% 32 PTLD should be considered in subjects who develop new neurologic signs or symptoms.
In the Phase 2 Belatacept conversion study, there were no cases of PTLD.

8.1.3 Malignancy
An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. In the Phase 3 studies, overall malignancy rates were similar across all treatment groups, with the exception of PTLD.
In the Phase 2 Belatacept conversion study, the overall rates of malignancies were similar in patients converted to Belatacept and those who remained on CNI treatment.

8.1.4 Infection
Increased susceptibility to infection, including serious and fatal infections may result from the use of Belatacept, as with all immunosuppressive therapies. Overall incidences of infections, including serious fungal and viral infections, were similar across all therapies in the Phase 3 IM103008 and IM103027 studies. The most common serious infections across treatment groups were urinary tract infection (UTI) and cytomegalovirus (CMV) infections.
One (1) case of progressive multifocal leukoencephalopathy (PML) has been reported in the Belatacept renal transplantation program, in a subject receiving the MI regimen in study IM103027. PML should be considered in subjects who develop new neurologic signs or symptoms.
Tuberculosis (TB) has been more frequently reported in Belatacept-treated patients than CsA-treated patients. There were a total of 13 TB cases (12 with Belatacept and 1 with CsA) reported in the Phase 3 studies over 36 months. Nearly all cases of TB were reported in subjects who currently or previously resided in countries with a high prevalence of TB. It is recommended that all patients be screened for TB and treated for any evidence of latent disease prior to initiation of Belatacept therapy.
In the Phase 2 Belatacept conversion study, the overall rates of serious infections were similar in patients converted to Belatacept and those who remained on CNI treatment. The most common serious infections across treatment groups were urinary tract infection (UTI) and gastrointestinal infections. There were higher rates of adverse events due to non-serious viral and fungal infections in patients converted to Belatacept. There was one case of TB in a Belatacept-treated subject.

8.1.5 Other Potential Risks
Other potential risks include clinically relevant peri-infusion-related reactions, early post-transplant proteinuria, congestive heart failure or pulmonary edema, and autoimmune disorders. These events have been observed infrequently in Belatacept-treated subjects but are being closely monitored in all Belatacept clinical trials.

8.1.6 Non-investigational Product
Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.
In this protocol, non-investigational product(s) is/are: Tacrolimus (TAC), Cyclosporine A (CsA), Mycophenolate Mofetil (MMF) or Mycophenolic Acid (MPA) and corticosteroids.

8.1.7 Description of the Dosage Form

Belatacept for Injection, 250 mg/Vial

Belatacept for Injection, 250 mg/Vial, is a sterile non-pyrogenic lyophilized powder. Each vial contains 275 mg of Belatacept, 550 mg of sucrose, 38.0 mg of sodium phosphate monobasic monohydrate, 6.4 mg of sodium chloride, and 1 N sodium hydroxide/1 N hydrochloric acid solution sufficient to adjust pH to 7.5. A 10% overfill is included in each vial to account for vial needle syringe (VNS) holdup.

8.1.8 Drug Product Preparation

Constitution and dilution of Belatacept for Injection 250 mg/Vial must be performed using silicone-free disposable syringes. Suitable fluids for constitution of the lyophile include sterile water for injection (SWFI), 0.9% sodium chloride injection (NS) or 5% dextrose injection (D5W). Prior to IV administration, the constituted solution is further diluted with NS or D5W to Belatacept concentrations between 2 mg/mL and 10 mg/mL. The infusion is to be administered through a sterile, non-pyrogenic, low protein binding in-line filter. Additionally, care must be taken to ensure the sterility of the prepared solution, as the drug product does not contain antimicrobial preservatives or bacteriostatic agents.

8.1.9 Constitution of the Lyophile

Each 250 mg vial of Belatacept for Injection should be constituted with 10.5 mL of a suitable constitution fluid (SWFI, NS or D5W) to provide a solution with a Belatacept concentration of approximately 25 mg/mL. Belatacept for injection, 250 mg/Vial, is not stored under vacuum. To avoid excessive foam formation in the vial, slowly inject the constitution fluid into the vial with the stream directed toward the vial wall and not into the lyophilized cake. The vial should be gently swirled and inverted until the lyophile dissolves. Although some foam may remain on the surface of the constituted solution, a sufficient excess of Belatacept is included in each vial to account for withdrawal losses, thus, 10.0 mL of a 25 mg/mL Belatacept solution can be withdrawn from each vial. Constituted solutions of Belatacept may foam, therefore, shaking should be avoided.

8.2.0 Preparation of the Infusion

Prior to IV administration, the constituted Belatacept solution (25 mg/mL) should be further diluted with either NS or D5W to final Belatacept concentrations ranging from 2 mg/mL to 10 mg/mL. Lyophiles constituted with SWFI may be further diluted with either NS or D5W. Lyophiles constituted with NS should be further diluted with NS and lyophiles constituted with D5W should be further diluted with D5W.

8.2.1 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g. required diluents, administration sets).

8.2.2 Recommended Storage Conditions

Belatacept for Injection 250 mg/Vial should be stored refrigerated at 2° - 8° C (36□-46□F) and protected from long-term exposure to light. The reconstituted solution should be transferred from the vial to the infusion bag or bottle immediately. After further dilution with NS or D5W to Belatacept concentrations between 2 mg/mL and 10 mg/mL, the solutions may be stored in plastic, non-siliconized, IV bags or glass bottles. If not used immediately, the infusion solution may be stored under refrigerated conditions at 2° - 8° C (36□-46□F) and protected from light for up to 24 hours (a maximum of 4 hours

of the total 24 hours can be at room temperature: 20□ - 25□C [68□-77□F] and room light). Regardless of storage condition, the Belatacept infusion must be completed within 24 hours of constitution of the lyophile.

8.2.3 Drug ordering and accountability (BMS will be shipping drug directly to study sites as needed)

8.2.3.1 Initial Orders

Following submission and approval of the required regulatory documents, a supply of Belatacept may be ordered from BMS by completing a Drug Request Form. (please see MOP) The first request may take place upon site activation.

Belatacept vials (40 mL) are shipped in quantities of five. The initial order should be limited to 25 vials (5 cartons of 5 vials each). Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. Shipments will be made from BMS (There will be no weekend or holiday delivery of drugs).

It is possible that sites may have more than one Belatacept clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.

8.2.3.2 Re-Supply

Drug re-supply request form should be submitted electronically or by fax at least 5 business days before the expected delivery date. Deliveries will be made Tuesday through Friday. When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from [BMS or other third-party vendor] receipt of request. Drug is not patient specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

9. Study assessments and procedures [Please see: Schedule of Events (SOE) on page 19]:

9A. Belatacept Infusions

See SOE, on page 19, for complete Belatacept infusion schedule.

9A.1 Belatacept Infusion reactions**

In the event of new, serious, and unexpected toxicity potentially related to Belatacept, study drug administration should be interrupted. The investigator must immediately notify the medical monitor (MM). The subject will be considered eligible to receive further study drug treatment only after discussion with the medical monitor.

9B. Early Withdrawal of Study Drug Regimen – safety follow-up schedule:

Subjects in whom Belatacept dosing is discontinued should be placed on a conventional immunosuppressive regimen. To ensure the safety of immunosuppression conversion, repeated blood work for creatinine and drug levels will be performed a 1 week, 2 weeks and 4 weeks post-conversion. A safety follow-up clinic visit 1 month post-conversion will be scheduled.

9C. Study Stopping Rules

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE); abnormal laboratory test results such as refractory neutropenia after immunosuppression adjustment (absolute neutrophil count below 500), refractory life-threatening infection; occurrence of PTLD; refractory acute cellular rejection confirmed by kidney biopsy; or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for

treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Missing 2 consecutive Belatacept infusions, unless the subject is receiving lymphocyte-depleting therapy or has approval by the medical monitor to remain in the study. Documentation will be required.
- Subjects receiving a maintenance dialysis regimen and deemed by the investigator to have functional graft loss and therefore do not require immunosuppression.

If PTLD or refractory rejection develops in two or more subjects of the study, the trial will be interrupted.

9.1 Site Labs - See SOE, on page 19, for complete labs schedule

Blood Pressure - sitting
Urinalysis with sediment
Urine: protein, Urine: creatinine on spot sample; Urine protein/creatinine ratio (calculation)
Serum Creatinine

9.2 Central Labs: Mechanistics (See SOE, on page 19, for complete Central Labs schedule)

9.2.1 Anti-HLA antibody: recipient's serum will be tested for the presence of anti-HLA antibodies through Luminex single antigen bead assay. In this assay, patient's serum is incubated with microbeads coated with purified HLA proteins and then a fluorescent anti-IgG is used for antibody detection. Mean fluorescence intensity and donor-specificity of the antibodies present will be determined by correlating with known HLA antigens from donor.

9.2.2 Urine B7-1 quantitative: we will isolate RNA from urinary extracellular vesicles (EVs) of transplanted patients and detect B7-1 mRNA using "Droplet Digital" PCR system.

9.2.3 B7-1 biopsy staining: Using a goat anti-human B7-1 (CD80) antibody, we will perform immunostaining for B7-1 on frozen sections of allograft biopsies.

10. Safety and Reporting:

10.1 Data Safety and Monitoring Board (DSMB)
A Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the Principal Investigator of this study, to monitor participant safety, data quality and evaluate the progress of the study. The Chair of the DSMB will also act as the study's Medical Monitor (MM). Please see the DSMB Charter, starting on Page 17 of this Protocol.

10.2 Definitions
10.2.1 Adverse Event (AE):
An AE is any *unfavorable* medical occurrence in a human subject enrolled in this study regardless of its causal relationship to study treatment. This may include:
- Abnormal sign (e.g. finding on physical exam or laboratory finding);
- Symptom;
- Disease.

10.2.2 Serious Adverse Event (SAE):
An SAE is an adverse event which meets *any* of the following criteria:
- Results in death;
- Is life threatening (places subject in immediate risk of death from the event as it occurred);
- Requires patient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect;

- Any clinically significant event that based on the judgment of the Investigator may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.3 Reporting Requirements

10.3.1 Adverse Event Reporting Requirements:

Adverse events should be reported on an ongoing basis in the appropriate eCRF in StudyTRAX.

Study sites should follow their IRB guidelines for reporting these events and document in their Study Binders.

10.3.2 Serious Adverse Event Reporting Requirements:

Serious Adverse Events should be reported to the sponsor within 5 working days/7 calendar days of the date that the Study Investigator becomes aware of the event. Please report in the appropriate eCRF AND complete and scan Adverse Event Form (AEF) found in the Manual of Procedures (MOP). Please send the scanned Adverse Event Form to the following email address: lriella@bwh.harvard.edu.

Study sites should follow their IRB guidelines for reporting these events and document in their Study Binders.

10.3.3 **Non-SAEs Reporting Requirements:**

The following are not considered SAEs for this study, however they should still be documented in the subject binder and eCRF when appropriate (i.e. surgical procedure, adverse event):

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

10.4 IND Safety Reporting Requirements:

Per 21 CFR 312.32(c)(1)(i), the Sponsor (Dr. Riella) will notify the FDA, Medical Monitor (MM)/DSMB Chair, Partners Human Research Committee (PHRC), BMS (drug manufacturer), and all participating investigators in an IND Safety Report when an event meets ALL of the following criteria:

- suspected adverse reaction (reasonable possibility of relationship to study drug)
- serious
- unexpected

Fatal or life-threatening events will be reported as soon as possible, but no later than 7 days of occurrence.

Serious and unexpected events will be reported as soon as possible, but no later than 15 days of occurrence.

Study sites should follow their IRB guidelines for reporting these events and document in their Study Binders.

10.5 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or

may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify Dr. Riella of this event and complete and send an Adverse Event Form (AEF) to Dr. Riella within 24 hours of discovery by investigator. [Dr. Riella will then report this AEF to BMS (drug manufacturer) within 24 hours of his knowledge of this event.]

In most cases, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, the Sponsor will consult with BMS representative, and the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Adverse Event Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor within 24 hours of discovery by investigator. Information on this pregnancy will be collected on the Adverse Events Form (AEF).

Please send the completed and scanned Adverse Event Form to all of the following email addresses: lriella@bwh.harvard.edu .

[Dr. Riella will then report this AEF to BMS (drug manufacturer) within 24 hours of his knowledge of this event.]

10.6 Overdose

All occurrences of overdose must be reported as SAEs (see Section 10.3.2 for reporting details).
An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 10.3.2 for reporting details.).

10.7 Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.
Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 10.9 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN),
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 10.9 for reporting details).

Potential drug induced liver injury is defined as: [can be defined based on specific study]

10.8 Data Monitoring Committee, Data and Protocol Compliance Monitoring, and Other External Committees Please see MOP for information, including how often a site must complete their electronic clinical research forms (eCRFs), query resolution guidelines, regulatory binder requirements, and how the study data, and protocol compliance, will be monitored by the Sponsor (Dr. Riella/designated study managers).

11.Statistics: This is a phase I clinical trial to test the safety and gain further insight to the potential effect of Belatacept in proteinuric patients. We plan to recruit 36 patients, based on the feasibility for recruitment in 3 transplant centers and prior literature on recommended sample sizes in Phase I trials.

The primary endpoint of the study will be a 25% reduction in proteinuria from baseline to 12 months. This endpoint was extrapolated from studies with ACE inhibitors showing significant benefit in patients with kidney disease and proteinuria that reached this endpoint (12). For comparison, we will also have a historical control group with patients that fit the inclusion criteria and were managed as standard of practice on our institution. A logistic regression model will be used to control for key variables such as baseline ACEI/ARB use, level of proteinuria, age and gender.

For the primary endpoint: Percentage of those patients who have a ≥25% reduction in proteinuria from baseline to 12 months will be reported separately for each group. We will compare these percentages between the two groups using Fisher's exact test. In addition, means and standard deviations of the actual reduction will be reported separately for each group and will be compared between the two groups using a non-parametric test (Wilcoxon rank-sum). These results will also be compared to historical controls. A logistic regression model will be used to control for key variables such as baseline ACEI/ARB use, level of proteinuria, age and gender.

For the secondary endpoints: Descriptive statistics (means, standard deviations and/or percentages) will be reported on percent change of renal function from baseline to 12 months; donor-specific anti-HLA antibodies presence and intensity (MFI); adverse events; acute rejection episodes; blood pressure control; new onset diabetes; and hyperlipidemia. Spearman correlations will be calculated between B7-1 positivity on immunofluorescence on biopsy with B7-1-expression in urine extracellular vesicles. Kaplan-Meyer plots will be used to study graft survival and patient survival and a proportional hazards model will be used here to compare survival between treated and historical controls, controlling for the baseline covariates above.

References:

1. Amer H, Cosio F. Significance and management of proteinuria in kidney transplant recipients. Journal of the American Society of Nephrology : JASN. 2009;20(12):2490-2.
2. Halimi J-M. Low-grade proteinuria and microalbuminuria in renal transplantation. Transplantation. 2013;96(2):121-30.
3. Shamseddin M, Knoll G. Posttransplantation proteinuria: an approach to diagnosis and management. Clinical journal of the American Society of Nephrology : CJASN. 2011;6(7):1786-93.
4. Amer H, Fidler M, Myslak M, Morales P, Kremers W, Larson T, et al. Proteinuria after kidney transplantation, relationship to allograft histology and survival. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2007;7(12):2748-56.
5. El-Zoghby Z, Stegall M, Lager D, Kremers W, Amer H, Gloor J, et al. Identifying specific causes of kidney allograft loss. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2009;9(3):527-35.
6. Hiremath S, Fergusson D, Doucette S, Mulay AV, Knoll GA. Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence. Am J Transplant. 2007 Oct;7(10):2350-60. PubMed PMID: 17845569.
7. Opelz G, Zeier M, Laux G, Morath C, Dohler B. No improvement of patient or graft survival in transplant recipients treated with angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers: a collaborative transplant study report. J Am Soc Nephrol. 2006 Nov;17(11):3257-62. PubMed PMID: 17035607.
8. Yu C-C, Fornoni A, Weins A, Hakroush S, Maiguel D, Sageshima J, et al. Abatacept in B7-1-positive proteinuric kidney disease. The New England journal of medicine. 2013;369(25):2416-23.
9. Good-Jacobson KL, Song E, Anderson S, Sharpe AH, Shlomchik MJ. CD80 expression on B cells regulates murine T follicular helper development, germinal center B cell survival, and plasma cell generation. Journal of immunology. 2012 May 1;188(9):4217-25. PubMed PMID: 22450810. Pubmed Central PMCID: 3331930.
10. Njau MN, Kim JH, Chappell CP, Ravindran R, Thomas L, Pulendran B, et al. CD28-B7 interaction modulates short- and long-lived plasma cell function. Journal of immunology. 2012 Sep 15;189(6):2758-67. PubMed PMID: 22908331.
11. Mandrekar SJ, Sargent DJ. Predictive biomarker validation in practice: lessons from real trials. Clinical trials. 2010 Oct;7(5):567-73. PubMed PMID: 20392785. Pubmed Central PMCID: 3913192.
12. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney international. 2004 Jun;65(6):2309-20. PubMed PMID: 15149345.
13. Lai CP, Breakefield XO. Role of exosomes/microvesicles in the nervous system and use in emerging therapies. Frontiers in physiology. 2012;3:228. PubMed PMID: 22754538. Pubmed Central PMCID: 3384085.
14. Browne RH. On the use of a pilot sample for sample size determination. Statistics in medicine. 1995 Sep 15;14(17):1933-40. PubMed PMID: 8532986.
15. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. Journal of clinical epidemiology. 2012 Mar;65(3):301-8. PubMed PMID: 22169081.
16. Azuma H, Chandraker A, Nadeau K, Hancock WW, Carpenter CB, Tilney NL, et al. Blockade of T-cell costimulation prevents development of experimental chronic renal allograft rejection. Proceedings of the National Academy of Sciences of the United States of America. 1996 Oct 29;93(22):12439-44. PubMed PMID: 8901600. Pubmed Central PMCID: 38010.
17. Chandraker A, Azuma H, Nadeau K, Carpenter CB, Tilney NL, Hancock WW, et al. Late blockade of T cell costimulation interrupts progression of experimental chronic allograft rejection. The Journal of clinical investigation. 1998 Jun 1;101(11):2309-18. PubMed PMID: 9616202. Pubmed Central PMCID: 508820.

18. Kim EJ, Kwun J, Gibby AC, Hong JJ, Farris AB, 3rd, Iwakoshi NN, et al. Costimulation blockade alters germinal center responses and prevents antibody-mediated rejection. Am J Transplant. 2014 Jan;14(1):59-69. PubMed PMID: 24354871.

DSMB Charter
Principal Investigator: Leonardo Riella, MD, PhD
Brigham and Women's Hospital

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the Principal Investigator of this Investigator-Initiated study, to monitor participant safety, data quality and evaluate the progress of the study.

Membership
DSMB Chair: Andrew Siedlecki, MD [BWH Renal Division]
Jean Francis, MD (Boston University)
Paulo Martins, MD PhD (UMass)

DSMB Responsibilities
The DSMB responsibilities are to:

evaluate the progress of the trial, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome;

consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial; review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;

protect the safety of the study participants;

make recommendations to the Principal Investigator, and, if required, to the Food and Drug Administration (FDA) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;

The DSMB will discharge itself from its duties when the study is complete.

Board Process
At each meeting, the DSMB will discuss the protocol, suggested modifications, and establish guidelines to study monitoring by the Board. The a designated DSMB Chairperson, in consultation with the Principal Investigator and study staff, will prepare the agenda to address the review of study materials, and the reporting of adverse events.

Meetings of the DSMB will take place quarterly, until the completion of the study. An emergency meeting of the DSMB may be called at any time should participant safety questions or other unanticipated problems arise.

Meetings shall be closed to the public because discussions may address confidential participant data. Meetings are attended by the Principal Investigator and members of his/her staff. Meetings may be convened as conference calls as well as in-person.

Meeting Format

DSMB meetings will consist of open and closed sessions. Discussion held in all sessions is confidential. The Principal Investigator and key members of the study team attend the open sessions.

Open session discussion will focus on the conduct and progress of the study, including participant accrual, protocol compliance, and problems encountered.

The closed session will be attended by the DSMB members.

Each meeting must include a recommendation to continue or to terminate the study made by a formal DSMB majority or unanimous vote. Should the DSMB decide to issue a termination recommendation, the full vote of the DSMB is required. In the event of a split vote, majority vote will rule, and a minority report should be appended. The DSMB Chair provides the tiebreaking vote in the event of a 50-50 split vote.

A recommendation to terminate the study may be made by the DSMB at any time by majority vote. In the event that the DSMB requires the study to be terminated, the PI will be immediately informed about their decision.

Meeting Materials

DSMB interim report templates will be prepared by the study staff, to be reviewed by the DSMB members at the first meeting. Interim data reports generally consist of two parts:

Part 1 - Open Session Report and
Part 2 - Closed Session Report

Format and content of the reports for both the open and closed sessions and plans for interim analyses should be finalized and approved at the initial DSMB meeting, although changes throughout the trial may be requested by the Board.

The reports will list and summarize safety data and describe the status of the study. All meeting materials should be sent to the DSMB members at least 1 business day prior to the meeting.

Part 1 - Open Session Reports: Open session reports generally include administrative reports by site that describe participants screened, enrolled, completed, and discontinued, as well as baseline characteristics of the study population. Other general information on study status may also be presented. Listings of adverse events and serious adverse events as well as any other information requested by the DSMB may also be in the open session report, but none of the data should be presented in an unblinded manner. The DSMB may direct additions and other modifications to the reports on a one-time or continuing basis.

Part 2 – Closed Session Report: Closed session reports generally present the same information as presented in the open session but by blinded treatment group. The reports may also contain data on study outcomes, including safety data, and depending on the study, perhaps efficacy data. The Closed Session reports should be destroyed at the conclusion of the meeting. If the meetings are held by telephone, printed copies of the closed reports should be destroyed immediately following the meeting. If a study has an interim analysis, it is also discussed in the closed session.

Reports from the DSMB
A formal report containing the recommendations for continuation or modifications of the study will be prepared by the DSMB Chairperson. Once approved by the DSMB members, the DSMB Chair will forward the formal DSMB recommendation to the Principal Investigator, within 2 weeks of the DSMB meeting. It is the responsibility of the Principal Investigator to distribute the DSMB recommendation to all co-investigators and to ensure that copies are submitted to all the IRBs associated with the study.

Confidentiality
All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

B7-1 Study: Schedule of Events (SOE)

Study Visits	Screening	Day 1 60 days	Day 15 ± 5 days	Day 29 M 1 ± 5 days	Day 43 ± 5 days	Day 57 M2 ± 5 days	Day 85 M3 ± 5 days	Day 113 M4 ± 5 days	Day 141 M5 ± 5 days	Day 169 M6 ± 5 days	Day 197 M7 ± 5 days	Day 225 M8 ± 5 days	Day 253 M9 ± 5 days	Day 281 M10 ± 5 days	Day 309 M11 ± 5 days	Day 337 M12 ± 5 days	M18 ± 5 days
Procedures																	
Full Medical History	X																
Physical Exam	X																
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chart Review Only																X	X[F]
Serum or Urine Pregnancy Test (WOCBP only*)	X*																
EBV Serology[a]	X																
Spot Urine Protein/ Creatinine Ratio[a]	X			X			X			X			X			X	
Urine[a,b]	X			X			X			X			X			X	
Cholesterol Panel[a]	X															X	
Serum Glucose[a]	X			X			X			X			X			X	
Serum Creatinine[a]	X			X			X			X			X			X	
anti-HLA Antibody[c]	X[a]															X	
B7-1 biopsy staining[c]	X																
Research Urine[c]	X															X	
Research Blood[c]	X															X	
Belatacept Infusions[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CNI Taper		X[d]	X[d]	X[e]													
AE/SAE Reporting		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

KEY:

[a] Standard of Care (SOC)

[b] Urine = urinalysis w/sediment **AND** Spot Urine = Urine:Creatinine & Urine:Protein; AND Urine Protein/Creatinine ratio = calculation needed

[c] Central Lab = send to BWH (transplant research center, 221 Longwood ave)

[d] CNI dosing to be tapered 25% of baseline dose PER WEEK (weekly reduction NOT represented on this SOE), dates of reduction must be documented in eCRFs.

[e] Last day of CNI; CNI completely stopped after this day.

[f] Collect information about last blood pressure, medications, serum creatinine and urine protein/creatinine