Belatacept Immunosuppression Therapy in Post-Transplant Kidney Recipients: Comparison of 4-Week and 8-Week Dosing Intervals

IRB00082511

Protocol Dated July 10th 2018

NCT02560558

Belatacept Immunosuppression Therapy in Post-Transplant Kidney Recipients: Comparison of every 1 month and every 2 months Dosing Intervals

PI: Raul Badell, MD
SubI: Andrew Adams, MD, PhD

1. Background and Rationale

Kidney transplantation is the preferred treatment for end-stage renal disease (ESRD) patients and is associated with increased quality of life and reduced mortality compared with dialysis. Nearly 17,000 kidney transplants are performed in the United States annually, and despite advances in improving early post-transplant outcomes, the need to improve long-term outcomes remains an important goal. Long-term immunosuppressive therapy is necessary to prevent rejection, but toxicity associated with immunosuppressive therapy can ultimately lead to decreased renal function and result in the need for re-transplantation. Traditional immunosuppressive regimens for kidney transplant consist of the calcineurin inhibitors (CNIs) cyclosporine A (CsA) and tacrolimus. These agents are associated with long-term renal toxicity and increase cardiovascular risk factors, including diabetes mellitus, hypertension, and hyperlipidemia.

The development of belatacept (trade name Nulojix), a member of a novel class of immunosuppressive medications known as selective T-cell costimulation blocking agents, represents a major advance in targeted immunosuppressive therapy. Immunosuppressive therapy with belatacept has been shown to improve renal function and has a favorable metabolic profile compared with CNIs. The mechanism of action of belatacept is more selective than that of previous immunosuppressants and its effect more specific; in animal models, belatacept more effectively blocks humoral responses that can lead to chronic injury and renal failure. During the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT), the overall incidence and severity of acute rejection was higher in patients treated with belatacept compared to the CsA treatment group; however, renal function as measured by the calculated glomerular filtration rate (cGFR) was up to 10 cc/min higher in the belatacept treatment group, which suggests that long-term graft survival and renal function may be improved compared to CsA (Vincenti F. et al AJT 2012).

Belatacept immunosuppressive therapy was implemented in the Emory Transplant Center (ETC) beginning in August of 2011. Current dosing protocol requires post-transplant kidney patients who are treated with belatacept to receive an infusion every 1 month, which presents logistical challenges due to the high cost of infusions, the limited capacity of the sites administering infusions, and inconvenience to patients. Definitive clinical evidence is lacking for equivalent treatment outcomes for patients who receive infusions at one month (q- 1M) intervals versus every two month (q-2M) intervals. Data from five year (Vincenti F, Blancho G, Durrbach A et al. J Am Soc Nephrol 2010) and ten year (personal communication, CP Larsen) follow up of the phase II clinical studies suggest that there are no significant differences in the patient outcomes for q-1Mversus q-2 Mdosing intervals. However, conclusions regarding differential

outcomes for the dosing interval regimens were limited by small sample size and deserve further investigation.

We hypothesize that immunologically low risk patients who are stable on belatacept therapy at least one year post transplant can be safely transitioned from an every 1 month to an every 2 months belatacept schedule, without a decrease in renal function or an increase in acute rejection. The Emory Transplant Center is uniquely qualified to perform this every two month study. We perform approximately 230 kidney transplants per year, utilizing belatacept as standard therapy in all eligible patients (Epstein Barr Virus (EBV) positive, etc). We have performed almost 500 kidney transplants on patients using belatacept as the primary immunosuppressant medication between August 2011 and the present (May 2015). Based on this clinical volume and high rate of belatacept use, we propose to screen approximately 18 patients per month and estimate enrolling an average of 12 patients per month into the study, specifically converting 6 patients per month from a q-1 month to a q-2 month schedule.

2. Study Objectives

2.1 Primary Objective

The primary objective of this non-inferiority trial involving immunologically low-risk patients is to show that the GFR 12 months post-randomization is the same for patients who receive belatacept at q-4 and q-8 dosing intervals.

2.2 Secondary Objective

- Assessing the incidence and severity of acute rejection 6 and 12 months post randomization
- Assessing the total cost associated with q-1M and q-2M dosing intervals
- Assessing the incidence of infection in the q-1M and q-2M patient groups
- Assessing the incidence of death and graft loss at 6 and 12 months
- Assessing the incidence of human leukocyte antigen (HLA) antibodies at randomization and at 6 and 12 months
- Assessing the frequency of clinic visits, hospitalizations, and transplant biopsies in the two patient groups

3. Assessment of Efficacy

3.1 Primary Outcome Measure

- This study will compare the primary outcome of mean eGFR between the standard q-1M control group and the q-2M treatment group, with the hypothesis that mean eGFR will not vary between the groups by more than a pre-specified acceptable difference, or equivalence margin. Difference in eGFR between the q-1M and q-2M treatment groups will be assessed monthly.

3.2 Secondary Outcome Measures

- The secondary outcome measure of rejection, death, graft lost, and HLA antibody production will be assessed at 6 and 12 months.
- Total cost, number of clinic visits, hospitalizations, and biopsies will be assessed at 12 months.

3.3 Safety

Patient safety will be assessed by monitoring the incidence of serious adverse events, infections, malignancies, morbidity, renal function, and rejection.

4. Safety Assessments

4.1 Adverse Events

During the study, safety assessments will include:

- Incidence of adverse events, serious adverse events, malignancies, opportunistic infections, and premature withdrawal due to adverse events
- Patient and Graft loss
- Changes in immunosuppressive regimen

4.2 Dose Adjustments of Concomitant Immunosuppression

Dose adjustment of mycophenolate mofetil or azathioprine (due to leucopenia or gastrointestinal toxicity), and prednisone may occur at the discretion of the investigator based on clinical indication.

4.3 Laboratory Tests

4.3.1 Laboratory Tests

Laboratory tests will be performed as noted in the Schedule of Events. The Emory Hospital Medical Laboratories will conduct these laboratory studies. Abnormal laboratory values will be addressed by standing protocols/operating procedures; that is through the patient's post-transplant coordinator, transplant nephrologist and/or primary nephrologist. These values will be monitored until they return to patient's baseline or other explanation is given

4.3.2 Biobanking and Mechanistic Studies

Samples for biobanking and mechanistic assays (e.g. CD86 saturation and belatacept peak and trough levels) will be drawn at specified intervals (see schedule of events) and stored by the Emory Transplant Clinic Biorepository. Given the possibility of the need for biological samples for unanticipated current, new and future immunologic assays, samples for this purpose may also be drawn at other times during the study period on select patients and will also be stored in the ETC biorepository. All samples will be used for assays performed by ETC investigators and Bristol-Myers Squibb. Banking of these samples is for purposes of this study, but may be used

for other potential future research uses. Study patients will have the option of requesting for the destruction of their samples if desired.

In general, the volume of blood donated for this study will be 40 mL or 3 mL/kg, whichever is less, for each time point. Under circumstances where the needs of a specific assay require larger amounts (e.g. multiple planned assays), a larger blood volume will be considered, up to a maximum of 150 mL for any single phlebotomy session and not to exceed 3mL/kg. The total amount of blood drawn will not exceed 450 mL, or 7mL/kg whichever is less, over any 6-week period in keeping with current NIH guidelines.

4.4 Study stopping rules

4.4.1 Study enrollment continuation with expedited review by the DSMB will occur for a threshold incidence of biopsy proven acute rejection of 10% on a rolling basis consistent with the following number of subjects with the event of rejection per enrolled patients (modified Simon's two-stage design strategy for 75-85% probability):

Number of subjects with Rejection (n)	Number of subjects enrolled in Q8 group
2	14
4	41
7	83

4.4.2 Study enrollment suspension pending expedited review by the DSMB will occur for a threshold incidence of biopsy proven acute rejection of 20% on a rolling basis consistent with the following number of subjects with the event of rejection per enrolled patients (modified Simon's two-stage design strategy for 75-90% probability):

Number of subjects with Rejection (n)	Number of subjects enrolled in Q8 group
3	14
5	35
15	83

5.0 Investigational Drug Supplies

All medications will be obtained from commercial pharmacies and billed to the subject's insurance provider. Therefore investigational drug services will not be utilized.

6.0 Safety Issues

Adverse events will be monitored and documented for the duration of the study and for 30 days after study completion.

6.1 Women of Childbearing Potential (WOCBP)

Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation. A spot urine pregnancy test will be performed only on WOCBP after the patient is enrolled in the study. If the spot urine pregnancy test is positive, it will be, confirmed by a serum human chorionic gonadotrophin laboratory test. A positive serum pregnancy test (>5 mIU/mL) will exclude a female patient from participation in this study.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means must agree to use birth control throughout their participation in the study.

If a subject becomes pregnant while receiving belatacept this event will be reported in accordance with SAE reporting.

If a WOCBP indicates plans to pursue pregnancy, or reports an unanticipated pregnancy, the subject will be withdrawn from further participation in the study, but followed for safety and pregnancy outcome.

6.2 Clinical Adverse Events

Because Belatacept is an FDA approved medication and we only propose to decrease the dosing frequency from every 1months to every 2 months, only the clinical adverse events of worsening kidney function, graft loss, kidney transplant rejection, increased donor-specific antibody formation, infection, and cancer will be assessed and recorded unless the event meets the definition of a serious adverse event. We will also record any adverse events that may occur as a result of blood draws specifically done for the study.

6.3 Rejection

The occurrence of rejection requires special consideration:

- In the standard of care q-1M dosing group, any grade of rejection will be treated in accordance to our established ETC protocol for the treatment of rejection (Appendix 1).
- In the treatment arm, q-2M dosing group, any grade of rejection will be treated in accordance to our established ETC protocol for the treatment of rejection (Appendix 1). However, depending on the grade of rejection, study subjects will either remain in the q-2M treatment group or be converted over to the standard of care q 1M group.
    - If the rejection is graded as borderline or 1A: the patient will remain in the q-2M treatment arm with close follow up and surveillance consistent with routine practice.
    - If the rejection grade is 1B or greater, then the patient will be converted back to q-1M standard of care dosing but will remain in the study.
    - If the rejection is antibody mediated rejection (AMR), then the patient will be converted back to q-1M standard of care dosing but will remain in the study.

Rejection Grade	**Group**	
	Q-1M	Q-2M
Borderline or 1A	Remain inQ-1M	Remain in Q-2M
1B or Greater	Remain in Q-1M	Convert to Q-1M
AMR	Remain in Q-1M	Convert to Q-1M

6.4 Severity

Severity of the adverse event will be defined as follows:
Mild – Discomfort noticed but no disruption of normal daily activity

Moderate – Discomfort sufficient to reduce or affect daily activity

Severe – Inability to work or perform normal daily activity

Life Threatening – Represents an immediate threat to life.

6.5 Determination of Relationship of Adverse Event to Belatacept Dosing

There will be three categories of possible relationship between the adverse event and belatacept dosing. Determination of drug-relatedness of the adverse event to belatacept dosing will be determined by the investigator.

Possible (must have first two)
A possible relationship will be assigned to an adverse event when the connection with belatacept administration appears unlikely but cannot be ruled out with certainty. An adverse event will be considered possible if:
1. It follows a reasonable temporal sequence from administration of belatacept

2. It cannot be reasonably explained by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject

3. It follows a known pattern of response to belatacept

Remote (must have first two)
An adverse event will be considered remote if:

1. It does not follow a reasonable temporal sequence from administration of belatacept
2. It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It does not follow a known pattern of response to belatacept.
4. It does not reappear or worsen when belatacept is re-administered.

Unrelated
An adverse event will be considered unrelated if it is judged to be clearly and incontrovertibly due only to extraneous causes such as disease, environment, etc. while not meeting the criteria for drug relationship as listed above for remote, possible, or probable.

6.6 Serious Adverse Event

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution and meets at least one of the following criteria:

- Is fatal (results in death);
- Is life-threatening;
- Requires in-patient hospitalization or prolongs existing hospitalization;
- Results in persistent or significant disability/incapacity;

- Results in a congenital anomaly/birth defect;
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

The clinical judgment of the investigator shall be used in deciding whether a certain situation may warrant consideration as a serious adverse event but may not meet the above criteria. This medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definitions above.

6.7 Reporting of Serious Adverse Events

All adverse events considered serious, and unexpected shall be reported to

- Emory University IRB within 10 business days if unanticipated and related to Belatacept
- DSMB within 7 days

6.7.1 SAE Reporting Contacts

Organization	
Emory University IRB	fax number: 404-727-1358
DSMB members	see Appendix 2

6.8 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board will be established to monitor the safety of the patients during this trial. The initial meeting of the DSMB will occur prior to the start of the study in which study start will be defined as the date on which the first patient enrolled in the study. Subsequent meetings will occur three months from study start and then every six months thereafter. The DSMB will be composed of 3 official members who are members of the Transplant Nephrology, Transplant Surgery, or the Nephrology community. DSMB members must be independent of this study and may not serve as investigators or participate in the care of subjects enrolled in this study. See Appendix 2 for DSMB membership and Appendix 3 for DSMB charter.

DSMB recommendations to modify or prematurely terminate the study shall require a unanimous vote of all voting DSMB members.

To reduce the risk of disclosure of study information to non-DSMB members, board members shall not copy, disseminate, communicate, or allow access to information pertaining to this study. Any copies of materials prepared for distribution to DSMB members will be clearly labeled as confidential. All materials will be identified only with subjects' unique study identification number and personal information that could lead to the identification of the study subject will not be made available to the DSMB membership. All communications and confidential study data will be stored in a secured area by DSMB members.

6.9 DSMB Data Reviews

The initial meeting of the DSMB will commence after the study has been open for 3 months. Subsequent data reviews will occur every 6 months thereafter, until the last study subject has completed study follow-up.

DSMB meetings will be held via teleconference.

Written DSMB reports will be issued following each data review. These reports will be forwarded to the IRB for review with protocol renewals.

7. Study design and methods

After randomization into either the q-1M or q-2M dosing groups, belatacept will be administered at a dose of 5 mg/kg, the same dose the patient was taking at the beginning of the study. The visit window for the q1M group will be per standard of care and the visit window for the q2M group will be +/- 5 days. See the attached dosing schedule and budget for the schedule of drug administration and lab tests. Q-2M patients will have lab tests every two weeks starting at week 4 of the study (the first time point when the q-1M patients receive belatacept and theq-2M patients do not). The q-2M group will have labs performed every two weeks from week 4 through week 16. With the exception of every two week labs for the q-2M group from week 4 through week 16 and frequency of belatacept administration, both groups of patients will be treated the same in all ways. Labs will be monthly otherwise. For study purposes, patients will receive a chemistry profile at every lab draw and antibody assessment (PRA/DSA) labs at enrollment, and 6 and 12 months. Otherwise they will be managed per standard of care as clinically indicated. For mechanistic studies, blood and serum will be drawn and stored on select study patients.

8. Study Population

The trial population consists of adults ≥18 years of age who are first-time transplant recipients of either living donor or deceased donor renal transplants. Patients of all races and ethnicities will be included.

This is an intention to treat, randomized, controlled trial. There will be a total of 166 subjects, randomized in equal numbers, 83 patients in each arm. We anticipate needing to consent/enroll 200 patients to achieve 166 randomized subjects accounting for an approximate 15% screen failure rate. All patients will be actively followed in the study for 12 months following enrollment. The study is projected to last 2 years.

Before any study procedures are performed, the details of the study will be described to subjects, and they will be given a written informed consent document to read. Patients who consent to participate in the study will sign and date the informed consent document in the presence of study personnel. Only patients who have given informed written consent will be included in this study.

8.1 Inclusion criteria

1. Adult (age ≥18 years currently),
2. first-time renal transplant recipients of either living donor or deceased donor,
    a. who were initiated on belatacept at the time of transplant and

   b. are at least one year post-transplant and off CNI therapy for at least 6 months.
3. patients at low immunologic risk, defined as
   a. patients with a first transplant who have an antibody screen < 50 against class I and class II antigens,
   b. no donor specific antibody (DSA),
   c. who have not had more than one episode of rejection (grade 1A or greater), and
   d. no episodes of rejection within the last 6 months prior to enrollment, and
   e. no rejection with a grade of IIB or above.
4. Immunosuppression consisting of belatacept (5mg/kg q 1M), cellcept (at least 1000 mg daily) or equivalent azathioprine dose, and prednisone 5 mg daily.

8.2 Exclusion criteria

1. Not first renal transplant, or multi-organ transplant recipient
2. History of greater than one episode of biopsy-proven acute rejection (grade 1A or greater), or of rejection of Banff 97 grade IIB or greater, or rejection within the last 6 months.
3. Pregnancy (women of childbearing potential must use adequate contraception during study)
4. GFR less than 35.
5. Serum creatinine at enrollment over 30% higher than 3 months (±4 weeks) prior to randomization
6. HbA1C greater than 8 within 3 months of enrollment (diabetic patients only)
7. Recent history of significant proteinuria (protein/Cr ratio >1)
8. Non-standard belatacept dosing (e.g. dose other than 5 mg belatacept/kg body weight)
9. Cellcept dose (or azathioprine equivalent) less than 500 mg po bid.
10. Prednisone dose greater than 5 mg po qd within 3 months of enrollment
11. Patients not currently taking prednisone
12. Active infection, or antibiotic or antiviral drug therapy within 1 month of randomization
13. Evidence of CMV viremia or clinical CMV infection within last 3 months.
14. BK PCR log greater then 4.3 (copy number greater than 20,0000) within 3 months of randomization
15. Known hepatitis B surface antigen-positive or PCR-positive for hepatitis B (testing not required)
16. Known HIV (testing not required)
17. Presence of donor specific antibody by Luminex single antigen assessment, or antibody screen above 50%.
18. History of substance abuse or psychiatric disorder not compatible with study adherence and follow up.

9. Study Procedures and Assessments

See Appendix 3.

10. Statistical Analysis

All analyses will be conducted on the intent-to-treat (ITT) population. The distribution of continuous outcome measures will be examined, and non-parametric equivalents of the two-sample t-test will be used to assess the statistical significance of non-normally distributed outcomes.

Statistical significance of the mean difference in eGFR between the q-4 and q-8 treatment groups at 12 months post-randomization will be assessed using the two-sample independent t-test statistic. The incidence of clinically suspected or biopsy-proven acute rejection (and date of acute rejection) will be collected based upon final ETC biopsy-proven acute rejection. We will describe acute rejection rates at 6 and 12 months post-randomization for the overall cohort and for the q-1M and q-2M treatment groups by calculating time to acute rejection. Kaplan-Meier analyses examining time to acute rejection will be used for comparisons by treatment group, with the log-rank test used to assess statistical significance. Potential differences in the severity of acute rejection between the treatment groups will be assessed by comparing the proportions of grade IIA and lower rejections and grade IIB and higher rejections between the treatment groups. Statistical significance of acute rejection severity will be assessed using the two-sample independent t-test statistic.

The incidence of infection in the q-4 and q-8 treatment groups will be collected based on labs performed at regular intervals throughout the study duration. Differences in the incidence of infection by treatment group will be assessed using the two-sample t-test statistic. The incidence of death and graft loss will also be determined, and the death rate and graft loss rates will be calculated at 6 and 12 months post-randomization. Kaplan-Meier analyses examining time to death and time to graft loss will be used for comparisons by treatment group, with the log-rank test used to assess statistical significance.

The incidence of HLA donor specific antibodies (DSA) (e.g. presence or absence of HLA DSA) at 6 and 12 months post-randomization will be compared by treatment group, with statistical significance assessed using the two-sample independent t-test statistic. The frequency of clinic visits, hospitalizations, and transplant biopsies will be calculated for each patient and descriptive statistics (e.g. mean and standard deviation) reported by treatment group. Differences in the frequency of these outcomes at 12 months post-randomization will be compared by treatment groups using the two-sample t-test statistic.

The total cost associated with the q-1M and q-2M dosing intervals will be compared between the two treatment groups by calculating the mean total cost of infusions received by each subject. The time and cost associated with roundtrip travel to the ETC will be estimated using the distance between the residential addresses of subjects and the ETC. Statistically significant differences in the preceding secondary endpoints will be assessed using the two-sample

independent t-test statistic. Potential differences in patient compliance will be assessed using the two-sample independent t-test statistic to compare the proportions of missed infusion appointments between the q-1M and q-2M dosing treatment groups.

Equivalence testing is used to assess whether "practical equivalence" of the outcome of interest has been achieved between two groups. This study will compare the primary outcome of mean eGFR between the standard q-1M control group and the q-2M treatment group, with the hypothesis that mean eGFR will not vary between the groups by more than a pre-specified acceptable difference, or equivalence margin. In the context of equivalence testing, statistical power represents the probability of detecting a difference at least as large as the equivalence margin.

The mean eGFR at one year post-transplant for patients receiving belatacept at the Emory Transplant Center has been found to be 60.2 ml/min/1.73 m^2 with a standard deviation of 14.5 ml/min/1.73 m^2. When patients with an eGFR less than or equal to 35 ml/min/1.73 m^2 are excluded, the mean eGFR at one year post-transplant has been found to be 61.5 ml/min/1.73 m^2 with a standard deviation of 13.1 ml/min/1.73 m^2. Based on this inclusion criterion, the table below details several scenarios of potential sample size for different equivalence margins in order to attain 80% power for a significance level (alpha) of 0.05.

Calculated GFR is a continuous variable and will be assessed at monthly intervals (increasing to every two weeks from week 4 to 16 in the q-2M group) throughout the study. The secondary time points of rejection, death, graft lost, and HLA antibody production will be assessed at 6 and 12 months. Total cost, clinic visits, hospitalizations, biopsies and patient satisfaction will be assessed at 12 months.

Assuming a standard deviation of 13.1 ml/min/1.73 m^2:

Equivalence margin (ml/min/1.73 m^2)	N per group	Sample Size (total N)
5.0	119	238
5.5	98	196
6.0	83	166
6.5	71	122
7.0	61	122

For example, assuming the standard deviation for eGFR at one year post-transplant is 13.1 ml/min/1.73 m^2, 166 patients total (83 per treatment group) are required to be 80% sure that a

two-sided 95% confidence interval will exclude a difference in mean eGFR between the treatment groups of more than 6.0 ml/min/1.73 m^2.

This study also aims to compare the secondary outcome of acute rejection rate between the q-1M and q-2M dosing interval groups. The one-year post-transplant acute rejection rate among patients treated with belatacept is expected to be 1-2%; based on this assumption, the table below details several scenarios of potential sample size for absolute differences in acute rejection rate in order to attain 80% power for a significance level of 0.05.

AR rate for reference group (q-4)	AR rate for intervention group (q-8)	Absolute difference	N per group	Sample Size (total N)
1%	4%	3%	137	274
1%	5%	4%	77	154
1%	6%	5%	49	98
1%	8%	7%	25	50
2%	5%	3%	270	540
2%	7%	5%	97	194
2%	8%	6%	68	136
2%	9%	7%	50	100

Outcome data will be presented to the safety monitoring board for review. The board will consist of a transplant nephrologist, a transplant surgeon and one other medical personnel with sufficient transplant knowledge to monitor the progress of the study; these individuals will not be affiliated with the study. The board will be notified of all serious adverse events, as well as data pertinent to patient recruiting and outcome.

References

1. Costimulation Blockade with Belatacept in Renal Transplantation. Vincenti F, Larsen C, Durrback A et al. N Engl J Med 2005; 353:770-78.
2. Three-Year Outcomes from BENEFIT, a Randomized, Active-Controlled, Parallel-Group Study in Adult Kidney Transplant Recipients. Vincenti F, Larsen CP, Alberu J, et al. American Journal of Transplantation 2012;: 210-217.
3. 3. Five-Year Safety and Efficacy of Belatacept in Renal Transplantation. Vincenti F, Blancho G, Durrbach A, et al. J Am Soc Nephrol 2010; 21, 1587-1596.

Appendix 1

ETC Rejection Protocol

Borderline	• Mini Pulse • No change in maintenance immunosuppression
ACR 1A	• Steroid Pulse • 6 week prednisone taper • Rebiopsy in 1 month if SCr not improved
ACR 1B, 2A	• Thymoglobulin (7 days) • 6 week prednisone taper • If on belatacept and Prograf, reduce Prograf goal trough to 3-5 ng/ml. Then taper per protocol. • For patients on belatacept and weaned from Prograf, no change in maintenance immunosuppression.
ACR 2B	• Thymoglobulin (10 days) • 6 week prednisone taper • If on belatacept and Prograf, reduce Prograf goal trough to 3-5 ng/ml. Then taper per protocol. • For patients on belatacept and weaned from Prograf, no change in maintenance immunosuppression.
ACR 3	• Thymoglobulin (14 days) • 6 week prednisone taper • If on belatacept and Prograf, reduce Prograf goal trough to 3-5 ng/ml. Then taper per protocol. • For patients on belatacept and weaned from Prograf, no change in maintenance immunosuppression.
AMR	Plasmapheresis/ IVIG

ACR – acute cellular rejection, AMR – antibody mediated rejection

Appendix 2

DSMB Membership

Chair:
Kenneth E. Kokko MD/PhD
Associate Division Director - Nephrology
Fellowship Director - Nephrology
Medical Director of Renal Transplant Program
University of Mississippi
601-984-5670
Email: kkokko@umc.edu

Membership:
Avinash Agarwal, MD
Assistant Professor of Surgery
University of Virginia
PO Box 800709
Charlottesville, VA 22908
Phone 434-924-9370
Fax 434-924-5539
Email: aagarwal@virginia.edu

Wasim A. Dar MD, PhD, FACS
Assistant Professor of Surgery
The University of Texas Health Science Center at Houston
Department of Surgery
Division of Immunology and Organ Transplantation
6431 Fannin Street, MSB 6.240
Houston, TX 77030
Email: wasim.a.dar@uth.tmc.edu

Appendix 3

DSMB Charter for the Belatacept Immunosuppression Therapy in Post-Transplant Kidney Recipients: Comparison of every 1 month and every 2 month Dosing Intervals study.

Introduction: This charter describes the roles and responsibilities of the Board.

Organization: The DSMB is an external expert group which, on a regular basis, reviews accumulating study data, evaluates the treatments for excess adverse effects, determines whether the basic study assumptions remain valid, judges whether the overall integrity and conduct of the study remain acceptable, and makes recommendations to the principal investigator.

Composition: The DSMB members are selected by the principal investigator and consist of 3 voting members:

Dr. Kenneth E. Kokko, (DSMB Chair) nephrologist and Associate Division Director of Nephrology, University of Mississippi

Dr. Avinash Agarwal, transplant surgeon and Assistant Professor of Surgery, University of Virginia

Dr. Wasim A. Dar, transplant surgeon and Assistant Professor of Surgery, Division of Immunology and Organ Transplantation, The University of Texas Health Science Center at Houston

DSMB members are independent, neither participating in the study as investigators nor having any other conflicts of interest (e.g. financial) with either the study sponsor or an intellectual conflict, such as participation in a leadership position in a similar outcome study.

Roles and Responsibilities: The independent DSMB will monitor the study safety on a regular basis accumulating safety data with the first meeting to occur prior to first patient enrollment. and will evaluate the safety parameters of the ongoing study 3 months after first patient enrollment and then every 6 months and at completion of the study. The frequency of the DSMB may be increased, for example, when safety issues arise.

Goal: The DSMB is independent of all aspects of the trial. The major role is to monitor on a regular basis the continuing safety of subjects participating in the study. The DSMB is an independent body.

The DSMB will:

- Protect the welfare of the patient.
- Monitor interim safety data.
- Identify safety issues and suggest solutions regarding study design and conduct.
- Review the study protocol and any protocol amendments
- Review the methods of data collection and safety monitoring making recommendations for additions or adjustments to ensure the timely delivery of such data.

- Review and approve the DSMB charter that defines the safety and related parameters to be reviewed by the DSMB, the frequency of DSMB monitoring reviews, methods for review, and establish criteria for making recommendations to the principal investigator.
- Conduct a futility analysis based at the time when approximately 30% of the study subjects complete the 6-month data collection.
- Based on the data reviewed at each meeting, the DSMB will advise one of the following actions to the principal investigator:
  - Continue the study according to the protocol and any related amendments.
  - Modify the study protocol. Modifications may include, but are not limited to: changes in inclusion/exclusion criteria, frequency of visits or safety monitoring, and alterations in study procedures.
  - Discontinue the study overall or end participation in particular subgroup.

Stopping Rules

The study as a whole may be stopped by the Investigator and DSMB if there are reasons for which continuation of study is no longer justified, such as:

- Unacceptable delay of study completion,
- Low recruitment rate,
- A large number of study participants with premature termination,
- Changed benefit-risk ratio according to the efficacy and/or safety results from this or parallel studies

Study enrollment suspended pending expedited review by the DSMB when:

- 5 of 10 patients in treatment arm (every 2-Month Belatacept infusion) experience acute rejection

Study enrollment continuation with expedited review by the DSMB when:

- 3 of 5 patients in treatment arm (every 2-Month Belatacept infusion) experience acute rejection

In case of premature termination of the entire study, the PI will ensure that IRB/ appropriate Regulatory Authorities are notified within 15 days.

The Sponsor-Investigator

The principal investigator is responsible to the DSMB to:

- Provide regular updates to the DSMB regarding the trial progress, including any protocol amendments or issues that could potentially affect the safety of the subjects or the overall integrity of the study.
- Document and communicate the decisions to the remainder of the Study Team for

implementation.

- Communicate all pertinent regulatory information to all Regulatory Authorities as appropriate.
- Securely archive all DSMB documentation following the completion of the study and termination of the DSMB activities.

DSMB Procedures

Scheduled meetings

- A full DSMB meeting will be held prior to the start of the study/first patient enrolled. After the initial meeting, safety review of data by the full DSMB will occur 3 months after the first patient is enrolled and then every 6 months thereafter.
- Further reviews may be requested by the DSMB Chair or the principal investigator at any time.
- Serious adverse events (including narratives) will also be provided for DSMB review.
- Ad hoc review will be done no later than 4 days following the request.
- DSMB meetings may be face-to-face or via telephone conference at the DSMB Chair's discretion.

Quorum

A quorum of 2 voting DSMB members are required at scheduled meetings, phone conferences, and unscheduled meetings. A recommendation to continue the protocol without modification can be made by 2 voting DSMB members, however all 3 members must be present for any decisions to modify the protocol or prematurely stop the trial.

Appendix 4

Data Safety Monitoring Plan (DSMP)

Belatacept Q2M Dosing study Monitoring Plan

Scheduling visits:

- The research coordinator will inform the independent monitor of the first patient enrollment so that study monitor can plan to hold the first monitor visit within 2 weeks.
- Monitor visits will be scheduled in advance with research coordinator.
- Monitor visit confirmation to be sent via email or fax at least 24 business hours ahead of visit, noting scheduled hours and which charts to be reviewed.
- Scheduled visits cancelled or revised by monitor will require monitor to notify Elizabeth Ferry via email (Elizabeth.ferry@emoryhealthcare.org)
- Monitor is responsible for initiating all discussions on scheduling visits and for insuring that they are arranged in a timely manner and with an appropriate frequency.

During visit:

- Monitor will complete sign in log located in E426 above fax machine. Incomplete sign in log may result in delay of Emory authorizing DocsGlobal timesheet.
- Monitor will discuss missing source data or repeating identical queries with coordinator. Items unable to be resolved quickly will be entered into monitoring letter. Items resolved will not be entered into monitoring letter.
- Monitor will set aside time at each visit to review queries with coordinator. Queries resolved during review with coordinator will not be entered into monitoring letter.
- Previously monitored visits completed by another monitor will not be re-monitored.
- Regulatory monitoring will occur in conjunction with our regulatory coordinator, Dasia Webster.
- Investigational Drug Services monitoring visits will be scheduled by the monitor via Emory University's Investigational Drug Services online calendar at www.ocr.emory.edu/ids

Reports and Communication

- Monitor reports are to be as succinct as possible.
- Monitor and coordinators will respond to email communications within 48-72 hours.
- All communication will be in email or written hard copy. Any communication in hard copy form will be received by this site within 48-72 business hours.

Supervisory Details

- The monitor will bring his/her own laptop to the site in order to review medical records.
- It is expected that the monitor already has tools in place which can be generalized to this study.
- It is expected that the monitor will review the protocol prior to starting. Up to one hour of prep time will be reimbursed by site.

- Any compensation for work done off site will be cleared through Elizabeth Ferry prior to being done.
- Failure of the monitor to show up for a scheduled visit may be grounds for dismissal.

Belatacept Dosing Q 1 Months

event/study	V1 M0	V2 M1	 M1.5	V3 M2	 M2.5	V4 M3	 M3.5	V5 M4	V6 M5	V7 M6	V8 M7	V9 M8	V10 M9	V M
Belatacept infusion	X	X		X		X		X	X	X	X	X	X	
PRA - HLA Ab screen	X									X				
DSA I/II - SAB	X													
Hgb A1c (diabetic patients only)	X													
CP Basic	X	X		X		X		X	X	X	X	X	X	

Belatacept Q-1Month vs Q 2 Month Intervals

Belatacept Dosing Q 2 Months

event/study	V1 M0	V2 M1	V3 M1.5	V4 M2	V5 M2.5	V6 M3	V7 M3.5	V8 M4	V9 M5	V10 M6	V11 M7	V12 M8	V13 M9	V M
Belatacept infusion	X			X				X		X		X		
PRA - HLA Ab screen	X									X				
DSA I/II – SAB	X													
Hgb A1c (diabetic patients only)	X													
CP Basic	X	X	X	X	X	X	X	X	X	X	X	X	X	

Mechanistic Studies

event/study	0	M1	M1.5	M2	M2.5	M3	M3.5	M4	M5	M6	M7	M8	M9	M
PBMC/CPT processing & storage (Q1 M & Q2 M)														
Serum storage (Q1M) for belatacept trough levels														
Serum storage (Q2M) for belatacept trough levels														
CD86 Saturation 2 per patient (50 total: 15 Q1M, 15Q2M, 10 normal, 10 CNI														
Belatacept concentration/trough levels (30 total: 15 Q1M + 15 Q2M)														

Appendix5

Schedule of Events