Belatacept Therapy for the Failing Renal Allograft

[BMS PROTOCOL NUMBER: IM103-133]

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PROTOCOL SYNOPSIS

Protocol Title:	**Belatacept Therapy for the Failing Renal Allograft**
Site Numbers & Names:	Protocol IM103-133, Emory University
Research Hypothesis:	Belatacept will effectively inhibit sensitization (ie donor-specific allo-antibody production) in patients with a failing or failed renal allograft and as a result will facilitate re-transplantation. In addition treatment with belatacept will more favorably impact residual allograft function (ie preservation of GFR) in patients with IF/TA as compared to treatment with conventional immunosuppression thereby prolonging time to dialysis or need for re-transplant.

Study Schema: **Drugs / Doses /** **Length of Treatment)**	-Standard of care arm- Upon enrollment into the study- wean tacrolimus, or sirolimus dose to target level of 3-5 (or equivalent CNI or mTOR inhibitor level), and if applicable continue mycophenolate mofetil (MMF) or mycophenolic acid (MPA) (equivalent of at least 1g daily) or azathioprine, and/or prednisone (at least 5 mg daily) Upon initiation of dialysis or in subjects already requiring dialysis at time of enrollment- discontinue CNI or mTOR inhibitor over 5 days, if applicable MMF/MPA or azathioprine dose decreased by half then discontinued 2 weeks later, steroid withdrawal beginning 1 month after the initiation of dialysis with monthly reduction by half with plans to discontinue at 3 months after initiation of dialysis. -Belatacept arm- Upon enrollment into the study- initiate Belatacept, dosing 10mg/kg- day 0, 2 weeks, 4 weeks, 8 weeks, and 12 weeks; subsequent doses 5mg/kg qmonth through duration of trial or until re-transplantation, whichever is first. Dose of CNI or mTOR inhibitor will be reduced by 50% at time of first dose of belatacept. CNI or mTOR inhibitor will be discontinued at week 2 dose of belatacept. If applicable continue MMF or MPA (equivalent of at least 1g daily) or azathioprine, and/or prednisone Upon initiation of dialysis or in subjects already requiring dialysis at time of enrollment - wean remaining immunosuppression as above in standard of care arm except for belatacept which they will remain on for the duration of the study or until re-transplant.
Study Objectives: • **Primary:** • **Secondary:**	Primary: To prevent the formation of donor-specific alloantibody in patients with chronic allograft injury (grade II or III IF/TA), thereby facilitating re-transplantation by avoiding sensitization Secondary: To determine if treatment with belatacept better preserves GFR in those patients with marginal renal function as compared to those patients who continue calcineurin inhibitor therapy or mTOR inhibitor therapy and as a result delays time to initiation of dialysis.

Study Design:	Open-label, prospective, randomized, controlled trial
Accrual Goal: **(Total number of subjects)**	72 patients, randomized 1:1 to either treatment arm- Belatacept or control arm- (remaining on CNI or mTOR inhibitor as detailed above). This study will be performed in two phases: Phase I a total of 36 patients will be enrolled (18 in each arm). Phase II will contingent on preliminary safety review and study progress from phase I and funding availability and will enroll an equal number of patients (36)
Accrual Rate: **(Number of subjects expected per month)**	36 patients enrolled over 24 months (Phase I) 36 patients enrolled over 24 months (Phase II)
FPFV: **LPFV:** **Follow Up:** **(dd-mm-yy)**	Phase I Start: August 1, 2013 FPFV: November 1, 2013 LPLV: November 1, 2018 Enrollment period: November 1, 2013 – November 1, 2015 Follow-up: 36 months Phase II: timing TBD
Correlative Studies: **(PK/PD, etc.)**	Scheduled sample collection for measurement of allo-antibody using HLA-specific microparticles; serum chemistry including calculated GFR (creatinine measurement); complete blood count, viral titer monitoring
Inclusion Criteria:	Adult recipients (age $\geq$ 18yrs currently) of either living donor or deceased donor, non-HLA identical renal transplants who have a GFR$\leq$ 35 ml/min with a decline in GFR of $\geq$ 10% in the 12 months prior to enrollment with biopsy proven grade 2 or 3 IF/TA, OR eGFR $\leq$20 ml/min over the 6 month period prior to enrollment absent other causes for graft dysfunction, and deemed to have a failing allograft by the patient's transplant nephrologist, and who are being treated with a calcineurin-inhibitor or mTOR inhibitor, with or without MMF/MPA or azathioprine and/or prednisone as maintenance immunosuppression. Patients must be $\geq$ 1 year post-transplant and a re-transplant candidate.

Exclusion Criteria:	EBV(-) patients or history of PTLD Presence of donor-specific antibody at the time of enrollment Age>70 years Extra-renal organ transplant Biopsy proven acute rejection ≥ Banff grade Ia within the last year prior to enrollment Positive BK serum PCR ≥ 20,000 copies at the time of enrollment OR history of biopsy proven BK nephropathy within the last year prior to enrollment Patients who have a living donor identified and approved for transplant within 3 months Patients currently receiving belatacept as part of maintenance immunosuppression
Criteria for Evaluation: **(Efficacy, safety, stopping rules, etc.)**	A Data Monitoring Committee (DMC) will monitor emerging efficacy and overall safety data regularly to ensure that the benefits and risks of study participation remain acceptable. During its regular reviews, the DMC will also assess the rate progression to dialysis, development of allo-antibody, and serious adverse events (SAEs), including serious infections and malignancies. Based on the regular reviews of emerging data, the DMC may recommend to the sponsor alteration and/or termination of the trial or cessation of further enrollment into a treatment group.

Statistics:	There will be two main methods of analyzing the primary outcome at the end of the study. One will be a chi-squared test comparing the proportion of patients who developed donor-specific antibody in each study group. The second analysis will be a log-rank test comparing the survival curves (survival being defined as the time until development of donor specific antibody) between the two study groups. A separate set of similar analyses will evaluate both the need and time to initiating dialysis. Subjects requiring dialysis at the time of enrollment will be excluded from this analysis. In both calculations there are similar assumptions made; we will use a two-sided test with a significance level of 0.05 and the sample size for each arm will be 30 patients. Other measures that will be evaluated with standard statistical methods include the change in PRA, the level of allo-antibody intensity, GFR and change in GFR.

1 INTRODUCTION

1.1 Research Hypothesis

Treatment with belatacept will effectively inhibit sensitization (ie donor-specific antibody production) in patients with a failing or failed renal allograft and as a result will facilitate re-transplantation. In addition treatment with belatacept will more favorably impact residual allograft function (ie preservation of GFR) in patients with IF/TA as compared to treatment with conventional immunosuppression thereby prolonging time to dialysis or need for re-transplant.

1.2 Summary of Results of Investigational Program

Belatacept represents a new class of immunosuppressive therapy. As a soluble chimeric protein, belatacept was designed to selectively inhibit the co-stimulation of T-cells by targeting the blockade of key co-stimulatory signals required for T-cell activation. Belatacept was derived from the novel fusion protein CTLA4Ig (abatacept, BMS-188667) and differs from its parent molecule at 2 point mutations. Comprised of a modified extracellular domain of human CTLA4 fused to a fragment of the Fc domain of a human immunoglobulin (Ig) G1 antibody, belatacept contains 2 amino acid modifications. Like its predecessor, belatacept differs from existing immunosuppressants in the selective distribution of its molecular target and the specificity of its effect. Additionally, it has demonstrated a higher avidity for the blockade of specific humoral responses.

1.2.1 Pharmacology of Belatacept

T-cell activation requires 2 signals: T-cell receptor antigen binding and a subsequent co-stimulatory signal. The first signal, which is antigen specific, is delivered by engagement of the T-cell receptor with antigen presented in context with major histocompatibility complex molecules on the antigen presenting cell (APC). The second, or co-stimulatory signal, is delivered by engagement of a co-stimulatory ligand on the APC with a receptor on the T-cell. A key co-stimulatory signal is provided by the interaction of B7-1 (CD80) and B7-2 (CD86) on APCs with CD28 expressed on T-cells. In the absence of this second signal, the T-cell becomes anergic (unresponsive) or undergoes apoptosis. Engagement of this second signal allows for full T-cell activation

and initiation of the inflammatory cascade. When the T-cell becomes fully activated, CTLA4 (CD152) becomes expressed on the cell surface. CTLA4 has a substantially higher avidity (approximately 500- to 2,500-fold) than CD28 for CD80 and CD86. CD28/CTLA4 engagement blocks further activation of T-cells. The increased avidity of endogenous CTLA4, in comparison with CD28, affords a homeostatic mechanism to down-regulate T-cell activity. By binding avidly to CD80/86, the fusion protein CTLA4Ig (abatacept) blocks the interaction of the T-cell's CD28 with the APC's CD80/CD86, thus preventing T-cells from receiving the required second co-stimulatory signal. Belatacept has the same mechanism of action, but demonstrates a higher avidity for the CD86.

Belatacept's parent molecule, CTLA4Ig (abatacept), has been shown to be effective in a wide variety of preclinical models and in subjects with psoriasis and rheumatoid arthritis (RA). With respect to transplantation, CTLA4Ig (abatacept) demonstrated efficacy in rodent models of transplantation, but did not demonstrate substantial efficacy in a non-human primate renal transplant model (cynomolgus monkey). Therefore, belatacept, a 2 amino acid variant of CTLA4Ig, was developed. This alteration resulted in markedly increased binding avidity for B7 molecules, in particular B7-2 (CD86). Belatacept was subsequently shown to prevent allograft rejection in a non human primate renal transplant model in which CTLA4Ig was not effective (see Investigator Brochure for additional details).

1.2.2 Preclinical Toxicology of Belatacept

In a single-dose IV toxicity study, cynomolgus monkeys were treated with 0 (control), 9, 30, or 90 mg/kg of belatacept.[1] No drug-related toxicity was observed in monkeys given belatacept at doses of up to 90 mg/kg. At doses of 9 and 30 mg/kg, antibodies to belatacept developed 5 and 6 weeks after drug administration, respectively. In the presence of these antibodies, the rate of drug elimination from serum was increased.

In repeat-dose toxicity studies[2,3] conducted in cynologus monkeys, IV belatacept was well tolerated at doses up to 50 mg/kg every other day for 1 month (15 doses), and once weekly for 6 months (26 doses). Major nonclinical findings were reversible, related to the pharmacology of the drug, and consisted of minimal decreases in serum IgG levels. Minimal to moderate lymphoid depletion of germinal centers in the spleen and/or lymph nodes at all dose levels was noted. Functional activity of the immune system was demonstrated at all doses by a robust antibody response to the immunogenic KLH

following immunization after an 8-week dose-free recovery-period. Immunogenicity when observed followed the treatment period.

Although belatacept has demonstrated an increase in binding affinity in human and non-human primates for CD80 and CD86, the binding affinity for murine CD80 and CD86 is lower with belatacept as compared to abatacept.[4] In studies evaluating the in vivo activity of belatacept in various species, belatacept was found to be either as active as, or less active than, abatacept in rodents and rabbits. Thus, belatacept's increase in bioactivity seen in monkeys and humans do not directly translate to other species. As a result, the nonclinical safety assessment for belatacept was conducted in the cynomolgous monkey. To support this data, abatacept nonclinical safety assessments, including 6-month rodent toxicity, genetic toxicity, carcinogenicity, and reproductive toxicity studies were provided (see Investigator's Brochure for further details).

Currently, a complete battery of reproductive and developmental toxicity studies with belatacept is being conducted in rats and rabbits. Early results show that there were no effects of belatacept on reproductive function in either male or female rats, and no effect on early embryonic development at doses up to 200 mg/kg/day (human exposure multiple of 38-fold.[5] Please refer to the Investigator's Brochure for the most current information.

1.2.3 Other Toxicity Studies

1.2.3.1 Immunogenicity

Belatacept, a human protein, is immunogenic in mice, rats, rabbits, and monkeys based on the ability of each species to induce belatacept-specific antibodies.[1,2,3,6,7,8,9,10,11,12,13] However, as expected, belatacept-specific antibodies were generally detected only during the recovery period, suggesting that belatacept-specific antibodies were not formed until after belatacept serum levels had dropped below immunosuppressive levels. Thus, in each species tested, belatacept suppressed the antibody response against itself. Once belatacept specific antibodies were present, clearance of drug from the blood vascular compartment was often accelerated. However, exposure was maintained during the treatment period of each pivotal study. The appearance of belatacept-specific antibodies was not associated with any acute or target-organ toxicity.

1.2.4 Human Pharmacokinetics of Belatacept

In a Phase 1 study[14] assessing the pharmacokinetic (PK) of escalating single IV doses of belatacept in healthy volunteers, the Cmax appeared to increase proportionally to dose, and AUC(INF) appeared to increase in a more than dose-proportional manner. The observed T-HALF ranged between 86-222 hours at the dose levels tested. Following a single IV infusion of 1-20 mg/kg, CLT values ranged from 0.45-0.49 mL/h/kg. The VSS values were small, indicating that the drug (with high molecular weight) was confined mainly in the blood and in the extracellular space. Both CLT and VSS appeared to be dose independent between the 1 and 20 mg/kg dose levels. The PK of belatacept appears to be linear following IV administration in healthy subjects at dose levels of 1-20 mg/kg. The mean PK parameters in healthy patients are summarized in the table below.

Table 1.2.4A: Summary of Belatacept Pharmacokinetic Parameters in Healthy Subjects (6/group) (Study IM103001)

	Pharmacokinetic Results					
Treatment	**Cmax[a] µg/mL (% CV)**	**Tmax[b] h (Min, Max)**	**AUC(INF)[a] µg.h/mL (% CV)**	**T-HALF[a] h (SD)**	**CLT[c] mL/h/kg (SD)**	**VSS[c] mL/kg (SD)**
0.1 mg/kg i.v. infusion	2.32 (13.6)	1.0 (1.0, 1.0)	143 (14.4)	86.4 (14.7)	0.71 (0.12)	80.2 (14.8)
1 mg/kg i.v. infusion	28.2 (20.2)	1.0 (1.0, 2.0)	2232 (16.0)	137 (24.3)	0.45 (0.07)	79.6 (19.1)
5 mg/kg i.v. infusion	126 (14.9)	1.0 (1.0, 1.0)	10341 (21.8)	176 (25.8)	0.49 (0.11)	102.0 (15.4)
10 mg/kg i.v. infusion	260 (9.9)	1.0 (1.0, 1.0)	22049 (15.1)	197 (36.6)	0.46 (0.07)	98.8 (10.1)
20 mg/kg i.v. infusion	466 (10.3)	1.5 (1.0, 2.0)	41380 (4.1)	222 (37.1)	0.49 (0.02)	117 (12.6)

[a] Geometric mean.

[b] Median.

[c] Arithmetic mean.

AUC(INF) = area under the concentration-time curve from time zero extrapolated to infinity, CLT = total body clearance, Cmax = maximum plasma concentration, i.v. = intravenous, T-HALF= half-life, Tmax = time of maximum observed concentration, and VSS = steady-state volume of distribution.

In a Phase 1 study[15] assessing the single subcutaneous doses of belatacept in healthy volunteers, belatacept was dose dependent. From 50 to 100 mg, the Cmax increased slightly greater than the dose increment, whereas the AUC(INF) increased in a dose-related manner. From 100 to 150 mg, both Cmax and AUC increased in a proportion greater than the dose increment.

The Cmax and AUC(0-6h) values of belatacept following IV infusion to renal transplant subjects were dose proportional at 5 and 10 mg/kg. Accumulation index values < 1.5 indicated minimal belatacept accumulation after multiple dosing at the dosing intervals of 2-8 weeks. The steady state was reached after approximately 3 doses for every 4-week dosing or after 1-2 doses for every 8-week dosing. The steady-state Cmin levels at 5 mg/kg were 2-4 μg/mL for every 4-week dosing and 0.2-0.4 μg/mL for every 8-week dosing.

During the long term extension phase (LTE), belatacept exposure [area under the concentration-time curve in 1 dosing interval, AUC(TAU)] for subjects on the 4-week schedule was slightly higher (1.3-fold) than those [AUC(0-T)] on the 8-week schedule, indicating minimal accumulation upon 4-week multiple dosing. The mean steady-state VSS was 0.12 L/kg, indicating that this high molecular weight drug was confined mainly in the blood in the extracellular space. Mean T-HALF of belatacept in renal transplant subjects was 197 hours (~8 days). Belatacept geometric mean steady-state Cmin for subjects on the 4-week schedule was 5.7 μg/mL. In contrast, geometric mean belatacept trough level for subjects on the 8-week schedule was 0.25 μg/mL. Overall, belatacept PK in renal transplant recipients was comparable to that in healthy subjects.

In a multiple-dose Phase 2 study,[16] the PK profile was evaluated in subjects with RA. Both Cmax and AUC(TAU) values appeared to increase in ratio comparable to the dose increment ratio after first and last dose administration. Accumulation of belatacept was found to be minimal in the applied dosing schedule. The mean PK parameters are summarized in the table below.

Table 1.2.4B: Summary of Belatacept Pharmacokinetic Parameters in Subjects with Rheumatoid Arthritis (3/group) (Study IM103002)

	Pharmacokinetic Results					
	First Dose (Day 1)			Last Dose (Day 57)		
Treatment	Cmax[a] µg/mL (% CV)	AUC(TAU)[a] µg.h/mL (% CV)	T-HALF[b] h (SD)	Cmax[a] µg/mL (% CV)	AUC(TAU)[a] µg.h/mL (% CV)	T1/2[b] h (SD)
0.5 mg/kg i.v. infusion	10.4 (9)	683[c] (ND)	51.5 (37.1)	11.2 (6)	816[d] (NR)	64.3 (38.8)
2 mg/kg i.v. infusion	39.3 (17)	4021 (49)	105.8[d] (NR)	42.6[d] (NR)	5114[d] (NR)	178.8[d] (NR)
10 mg/kg i.v. infusion	305.8 (NR)	16379 (NR)	87.7 (NR)	268.4[c] (ND)	13972[c] (ND)	285.3[c] (ND)

1.2.5 Clinical Safety with Belatacept

1.2.5.1 Healthy Subjects

No deaths or discontinuations due to AE's were reported in healthy subjects treated with belatacept.[14,15,17] Medical events including skin infection (n=1) and pharyngitis (n=1) was reported in subjects treated with 50 and 75 mg of belatacept, respectively. Common AEs included headache and nasopharyngitis.

1.2.5.2 Post Transplant

Study IM103100

In a Phase 2 Study (IM103100) [18] the safety of belatacept vs. cyclosporine (CsA) was assessed as part of a quadruple therapy with mycophenolate mofetil, corticosteroids, and basiliximab in de novo renal transplant recipients.

Subjects treated with belatacept were randomized to 2 dosing groups: more intensive (MI) and less intensive (LI). For the MI regimen, subjects were dosed at 10 mg/kg on Days 1, 5, 15, 29, 43, 57, 71, 85, 113, 141, and 169, and then at 5 mg/kg every 4 or 8 weeks starting on Day 197. For the LI regimen, subjects were dosed at 10 mg/kg on Days 1, 15, 29, 57, and 85. Staring on Day 113, these subjects received 5 mg/kg belatacept every 4 or 8 weeks. PK parameters, such as AUC(0-6h), Cmax, and Cmin, were assessed, and the data are presented in Tables 5.2.5.1A, 5.2.5.1B, and 5.2.5.1C.

Overall, almost all subjects in each treatment group experienced at least 1 AE.[18]

Table 1.2.5.2A: Overall Incidence of Adverse Events During 12 Months Post-Transplant (As-Treated Population) - Study IM103100

	No. (%) of Subjects		
	Belatacept MI (N=74)	**Belatacept LI (N=71)**	**CsA (N=71)**
Adverse Events	73 (98.6)	69 (97.2)	68 (95.8)
Discontinued Due to Adverse Events	13 (17.6)	15 (21.1)	14 (19.7)
Related Adverse Events	43 (58.1)	40 (56.3)	50 (70.4)
Serious Adverse Events	50 (67.6)	52 (73.2)	42 (59.2)
Related Serious Adverse Events	21 (28.4)	23 (32.4)	21 (29.6)

CsA = cyclosporine, LI = less intensive, and MI = more intensive.

The most frequently reported AEs among patients who recieved belatacept post renal transplant are reported in the table below. Renal transplant rejection was reported more commonly with belatacept at high and low dose regimens when compared to CsA.

Table 1.2.5.2B: Most Frequent Adverse Events (At Least 10% in Any Group) During 12 Months Post-Transplant (As-Treated Population) - Study IM103100

MedDRA System Organ Class Preferred Term	No. (%) of Subjects Belatacept MI (N=74)	Belatacept LI (N=71)	CsA (N=71)
Subjects with Any Adverse Events	73 (98.6)	69 (97.2)	68 (95.8)
Blood & Lymphatic System Disorders	29 (39.2)	28 (39.4)	40 (56.3)
Leukopenia	14 (18.9)	12 (16.9)	21 (29.6)
Anemia	13 (17.6)	12 (16.9)	21 (29.6)
Cardiac Disorders	10 (13.5)	10 (14.1)	10 (14.1)
Endocrine Disorders	4 (5.4)	8 (11.3)	9 (12.7)
Gastrointestinal Disorders	45 (60.8)	45 (63.4)	42 (59.2)
Nausea	19 (25.7)	18 (25.4)	16 (22.5)
Diarrhea	17 (23.0)	18 (25.4)	17 (23.9)
Constipation	16 (21.6)	22 (31.0)	20 (28.2)
Vomiting	11 (14.9)	14 (19.7)	11 (15.5)
General Disorders & Administration Site Conditions	43 (58.1)	40 (56.3)	42 (59.2)
Edema Peripheral	23 (31.1)	20 (28.2)	21 (29.6)
Pyrexia	15 (20.3)	19 (26.8)	15 (21.1)
Pain	7 (9.5)	6 (8.5)	9 (12.7)
Fatigue	6 (8.1)	6 (8.5)	9 (12.7)
Edema	6 (8.1)	7 (9.9)	11 (15.5)
Immune System Disorders	22 (28.7)	29 (40.8)	16 (22.5)
Transplant Rejection	19 (25.7)	23 (32.4)	11 (15.5)
Infections & Infestations	54 (73.0)	52 (73.2)	53 (74.6)
Urinary Tract Infection	17 (23.0)	17 (23.9)	22 (31.0)
Cytomegalovirus Infection	11 (14.9)	10 (14.1)	13 (18.3)
Nasopharyngitis	9 (12.2)	10 (14.1)	11 (15.5)
Injury, Poisoning & Procedural Complications	44 (59.5)	45 (63.4)	45 (63.4)
Incision Site Complication	17 (23.0)	16 (22.5)	13 (18.3)
Post Procedural Pain	14 (18.9)	17 (23.9)	15 (21.1)
Graft Dysfunction	9 (12.2)	10 (14.1)	10 (14.1)

Table 1.2.5.2B: Most Frequent Adverse Events (At Least 10% in Any Group) During 12 Months Post-Transplant (As-Treated Population) - Study IM103100

MedDRA System Organ Class Preferred Term	No. (%) of Subjects Belatacept MI (N=74)	Belatacept LI (N=71)	CsA (N=71)
Investigations	26 (35.1)	22 (31.0)	29 (40.8)
Blood Creatinine Increased	13 (17.6)	10 (14.1)	13 (18.3)
Metabolism & Nutrition Disorders	36 (48.6)	35 (49.3)	42 (59.2)
Hypophosphatemia	14 (18.9)	24 (33.8)	15 (21.1)
Hyperlipidemia	9 (12.2)	8 (11.3)	6 (8.5)
Hypercholesterolemia	6 (8.1)	4 (5.6)	9 (12.7)
Hypokalemia	5 (6.8)	5 (7.0)	9 (12.7)
Musculoskeletal & Connective Tissue Disorders	26 (35.1)	20 (28.2)	20 (28.2)
Arthralgia	8 (10.8)	6 (8.5)	4 (5.6)
Back Pain	8 (10.8)	3 (4.2)	6 (8.5)
Nervous System Disorders	26 (35.1)	20 (28.2)	26 (36.6)
Headache	13 (17.6)	10 (14.1)	8 (11.3)
Tremor	8 (10.8)	10 (14.1)	14 (19.7)
Psychiatric Disorders	18 (24.3)	27 (38.0)	20 (28.2)
Insomnia	12 (16.2)	19 (26.8)	17 (23.9)
Renal & Urinary Disorders	28 (37.8)	27 (38.0)	25 (35.2)
Reproductive System & Breast Disorders	7 (9.5)	12 (16.9)	7 (9.9)
Respiratory, Thoracic & Mediastinal Disorders	23 (31.1)	24 (33.8)	29 (40.8)
Cough	7 (9.5)	8 (11.3)	11 (15.5)
Dyspnea	5 (6.8)	6 (8.5)	9 (12.7)
Skin & Subcutaneous Tissue Disorders	26 (35.1)	18 (25.4)	18 (25.4)
Vascular Disorders	27 (36.5)	29 (40.8)	29 (40.8)
Hypertension	16 (21.6)	17 (23.9)	22 (31.0)

CsA = cyclosporine, LI = less intensive, MI = more intensive, and MedDRA = Medical Dictionary of Regulatory Activities

SAEs were more frequently reported among belatacept-treated subjects; however, SAEs considered to be drug related by the investigators were similarly distributed across all 3 treatment groups.

MedDRA System Organ Class Preferred Term	No. (%) of Subjects Belatacept MI (N=74)	Belatacept LI (N=71)	CsA (N=71)
Subjects with Any Serious Adverse Events	50 (67.6)	52 (73.2)	42 (59.2)
Blood & Lymphatic System Disorders	2 (2.7)	3 (4.2)	4 (5.6)
Gastrointestinal Disorders	7 (9.5)	7 (9.9)	5 (7.0)
General Disorders & Administration Site Conditions	5 (6.8)	8 (11.3)	7 (9.9)
Pyrexia	4 (5.4)	8 (11.3)	6 (8.5)
Immune System Disorders	20 (27.0)	23 (32.4)	13 (18.3)
Transplant Rejection	18 (24.3)	20 (28.2)	9 (12.7)
Infections & Infestations	17 (23.0)	12 (16.9)	18 (25.4)
Cytomegalovirus Infection	5 (6.8)	4 (5.6)	7 (9.9)
Pyelonephritis	4 (5.4)	1 (1.4)	2 (2.8)
Urinary Tract Infection	2 (2.7)	0	4 (5.6)
Injury, Poisoning & Procedural Complications	8 (10.8)	6 (8.5)	9 (12.7)
Investigations	8 (10.8)	2 (2.8)	4 (5.6)
Blood Creatinine Increased	8 (10.8)	2 (2.8)	4 (5.6)
Metabolism & Nutrition Disorders	1 (1.4)	2 (2.8)	4 (5.6)
Renal & Urinary Disorders	9 (12.2)	11 (15.5)	9 (12.7)
Respiratory, Thoracic & Mediastinal Disorders	6 (8.1)	3 (4.2)	4 (5.6)
Vascular Disorders	3 (4.1)	5 (7.0)	8 (11.3)

CsA = cyclosporine, LI = less intensive, MI = more intensive, and MedDRA = Medical Dictionary of Drug Regulatory Activities

Approximately 20% of subjects discontinued the study medication as a result of an AE, and the reported rates were comparable across all treatment groups.

Table 1.2.5.2C: Most Frequent (At Least 2% in Any Group) Adverse Events Leading to Discontinuation During 12 Months Post-Transplant (As-Treated Population) - Study IM103100

MedDRA System Organ Class Preferred Term	No. (%) of Subjects Belatacept MI (N=74)	Belatacept LI (N=71)	CsA (N=71)
Subjects Who Discontinued Due to Adverse Events	13 (17.6)	15 (21.1)	14 (19.7)
Immune System Disorders	10 (13.5)	11 (15.5)	7 (9.9)
Transplant Rejection	9 (12.2)	9 (12.7)	3 (4.2)
Kidney Transplant Rejection	1 (1.4)	2 (2.8)	2 (2.8)
Graft Loss	0	0	2 (2.8)
Injury, Poisoning & Procedural Complications	0	0	4 (5.6)
Investigations	0	0	2 (2.8)
Blood Creatinine Increased	0	0	2 (2.8)
Renal & Urinary Disorders	0	3 (4.2)	2 (2.8)
Proteinuria	0	2 (2.8)	0

CsA = cyclosporine, LI = less intensive, MI = more intensive, and MedDRA = Medical Dictionary of Regulatory Activities

One death was reported in the belatacept MI group. No deaths were reported in the belatacept LI group.

Study IM103100 Long Term Extension

Among the 164 patients who completed the 12-month phase, 128 patients continued in a long term extension (LTE) phase of the study; 102 and 26 patients were entered into the pooled (MI+LI) belatacept and CsA groups, respectively. As of 12-OCT-07, a LTE safety analysis determined that overall rates of AEs, SAEs and discontinuations were similar between belatacept and CsA treated subjects. The safety summary of patients entered in the LTE phase is summarized in Table 1.2.5.2D below.

Table 1.2.5.2D: Summary of Safety in Long-term Extension Phase (Intent-to-Treat Population)- IM103100

	No. (%) of Subjects	
	Belatacept (MI+ LI) (N=102)	**CsA (N=26)**
Death	3 (2.9)	2 (7.7)
SAEs	47 (46.1)	14 (53.8)
Related SAEs	27 (26.5)	7 (26.9)
Discontinued due to SAEs	6 (5.9)	1 (3.8)
AEs	92 (90.2)	24 (92.3)
Related AEs	60 (50.8)	16 (61.5)
Discontinued due to AEs	9 (8.8)	1 (3.8)

The most commonly reported AEs (≥ 10% in each arm) reported among the pooled belatacept patients (MI + LI) in the LTE were psychiatric disorders (22%), cough (17%), pyrexia (16%), bronchitis (14%), reproductive system and breast disorders (22%), cough (17%), influenza (12%) and hyperlipidemia (11%).

The most frequently reported SAEs (≥ 2/5% subjects) among pooled belatacept patients included neoplasms and malignancies (12%), infections and infestations (16%), and immune disorders (11%). The belatacept group reported congenital, familial and genetic disorders (4 subjects, 4%) more frequently than the CsA group.

During the LTE phase (as of 12-OCT-2007), 9 subjects discontinued belatacept (MI or LI). The most frequently reported AE leading to discontinuation among belatacept treated subjects was transplant rejection in 2 subjects (2%).

During the IM103100 LTE, 3 deaths (2 belatacept MI and 1 belatacept LI) were reported in the belatcept group. Of these, 2 deaths were considered unrelated to study drug (severe cardio-respiratory arrest and cardiac infarction). One death attributed to *P. carinii* pneumonia, was considered possibly related to the study drug.

Please refer to the most current Investigator's Brochure for further details.

Phase III Studies: IM103008 and IM103027

Two phase III, randomized, controlled studies were performed to assess the efficacy and safety of Belatacept in *de novo* kidney transplant patients. Study IM103008 (Study 1)

evaluated its use in recipients receiving standard criteria donor kidneys and study IM103027 (Study 2) evaluated its performance in recipients who were transplanted with kidneys from extended criteria donors. Belatacept was studied at the currently recommended dose and frequency in a total of 401 patients compared to a cyclosporine control regimen in a total of 405 patients. These two trials also included a total of 403 patients treated with a belatacept regimen of higher cumulative dose and more frequent dosing than currently recommended. All patients also received basiliximab induction, mycophenolate mofetil, and corticosteroids. Patients were treated and followed for 3 years.

CNS PTLD, PML, and other CNS infections were more frequently observed in association with a belatacept regimen of higher cumulative dose and more frequent dosing compared to the current recommended regimen; therefore, administration of higher than the recommended doses and/or more frequent dosing of belatacept will not be used in this trial. The average age of patients in these studies was 49 years, ranging from 18 to 79 years. Approximately 70% of patients were male; 67% were white, 11% were black, and 22% other races. About 25% of patients were from the United States and 75% from other countries.

The most commonly reported adverse reactions occurring in ≥20% of patients treated with the recommended dose and frequency of belatacept were anemia, diarrhea, urinary tract infection, peripheral edema, constipation, hypertension, pyrexia, graft dysfunction, cough, nausea, vomiting, headache, hypokalemia, hyperkalemia, and leukopenia. The proportion of patients who discontinued treatment due to adverse reactions was 13% for the recommended belatacept regimen and 19% for the cyclosporine control arm through three years of treatment. The most common adverse reactions leading to discontinuation in belatacept-treated patients were cytomegalovirus infection (1.5%) and complications of transplanted kidney (1.5%). Information on selected significant adverse reactions observed during clinical trials is summarized below.

Post-Transplant Lymphoproliferative Disorder

Reported cases of post-transplant lymphoproliferative disorder (PTLD) up to 36 months post transplant were obtained for belatacept by pooling both dosage regimens of belatacept in both studies (804 patients) with data from a third study in kidney transplantation (145 patients) which evaluated two belatacept dosage regimens similar, but slightly different, from those of Studies 1 and 2 (see table below). The total number of belatacept patients from these three studies (949) was compared to the pooled cyclosporine control groups from all three studies (476 patients).

Among 401 patients in Studies 1 and 2 treated with the recommended regimen of belatacept and the 71 patients in Study 3 treated with a very similar (but non-identical) belatacept regimen, there were 5 cases of PTLD: 3 in EBV seropositive patients and 2 in EBV seronegative patients. Two of the 5 cases presented with CNS involvement. Among the 477 patients in Studies 1, 2, and 3 treated with the belatacept regimen of higher cumulative dose and more frequent dosing than recommended, there were 8 cases of PTLD: 2 in EBV seropositive patients and 6 in EBV seronegative or serostatus unknown patients. Six of the 8 cases presented with CNS involvement. Therefore, administration of higher than the recommended doses or more frequent dosing of belatacept is not recommended.

One of the 476 patients treated with cyclosporine developed PTLD, without CNS involvement. All cases of PTLD reported up to 36 months post transplant in belatacept- or cyclosporine-treated patients presented within 18 months of transplantation. Overall, the rate of PTLD in 949 patients treated with any of the belatacept regimens was 9-fold higher in those who were EBV seronegative or EBV serostatus unknown (8/139) compared to those who were EBV seropositive (5/810 patients). Therefore belatacept is recommended for use only in patients who are EBV seropositive.

Summary of PTLD Reported in Studies 1, 2, 3 Through Three Years of Treatment

	NULOJIX Non-Recommended Regimen* (N=477)			NULOJIX Recommended Regimen† (N=472)			Cyclosporine (N=476)		
Trial	EBV Positive (n=406)	EBV Negative (n=43)	EBV Unknown (n=28)	EBV Positive (n=404)	EBV Negative (n=48)	EBV Unknown (n=20)	EBV Positive (n=399)	EBV Negative (n=57)	EBV Unknown (n=20)
Study 1									
CNS PTLD	1	1							
Non-CNS PTLD		1		2				1	
Study 2									
CNS PTLD	1	1		1	1				
Non-CNS PTLD					1				
Study 3									
CNS PTLD		2							
Non-CNS PTLD			1						
Total (%)	**2 (0.5)**	**5 (11.6)**	**1 (3.6)**	**3 (0.7)**	**2 (4.1)**	**0**	**0**	**1 (1.8)**	**0**

* Regimen with higher cumulative dose and more frequent dosing than the recommended NULOJIX regimen.
† In Studies 1 and 2 the NULOJIX regimen is identical to the recommended regimen, but is slightly different in Study 3.

EBV Seropositive Subpopulation

Other Malignancies

Malignancies, excluding non-melanoma skin cancer and PTLD, were reported in Study 1 and Study 2 in 3.5% (14/401) of patients treated with the recommended belatacept regimen and 3.7% (15/405) of patients treated with the cyclosporine control regimen. Non-melanoma skin cancer was reported in 1.5% (6/401) of patients treated with the recommended belatacept regimen and in 3.7% (15/405) of patients treated with cyclosporine.

Progressive Multifocal Leukoencephalopathy

Two fatal cases of progressive multifocal leukoencephalopathy (PML) have been reported among 1096 patients treated with a belatacept-containing regimen: one patient in

clinical trials of kidney transplant (Studies 1, 2, and 3 described above) and one patient in a trial of liver transplant (trial of 250 patients). No cases of PML were reported in patients treated with the recommended belatacept regimen or the control regimen in these trials.

The kidney transplant recipient was treated with the belatacept regimen of higher cumulative dose and more frequent dosing than currently recommended, mycophenolate mofetil (MMF), and corticosteroids for 2 years. The liver transplant recipient was treated with 6 months of a belatacept dosage regimen that was more intensive than that studied in kidney transplant recipients, MMF at doses higher than the recommended dose, and corticosteroids.

Bacterial, Mycobacterial, Viral, and Fungal Infections

Adverse reactions of infectious etiology were reported based on clinical assessment by physicians. The causative organisms for these reactions are identified when provided by the physician. The overall number of infections, serious infections, and select infections with identified etiology reported in patients treated with the belatacept recommended regimen or the cyclosporine control in Studies 1 and 2 are shown below. Fungal infections were reported in 18% of patients receiving belatacept compared to 22% receiving cyclosporine, primarily due to skin and mucocutaneous fungal infections. Tuberculosis and herpes infections were reported more frequently in patients receiving belatacept than cyclosporine. Of the patients who developed tuberculosis through 3 years, all but one belatacept patient lived in countries with a high prevalence of tuberculosis

Overall Infections and Select infections with Identifies Etiology by Treatment Group following One and Three Years of Treatment

	Up to Year 1		Up to Year 3†	
	NULOJIX Recommended Regimen N=401 n (%)	Cyclosporine N=405 n (%)	NULOJIX Recommended Regimen N=401 n (%)	Cyclosporine N=405 n (%)
All infections‡	287 (72)	299 (74)	329 (82)	327 (81)
Serious infections§	98 (24)	113 (28)	144 (36)	157 (39)
CMV	44 (11)	52 (13)	53 (13)	56 (14)
Polyoma virus¶	10 (3)	23 (6)	17 (4)	27 (7)
Herpes#	27 (7)	26 (6)	55 (14)	46 (11)
Tuberculosis	2 (1)	1 (<1)	6 (2)	1 (<1)

* Studies 1 and 2 were not designed to support comparative claims for NULOJIX for the adverse reactions reported in this table.

† Median exposure in days for pooled studies: 1203 for NULOJIX recommended regimen and 1163 for cyclosporine in Studies 1 and 2.

‡ All infections include bacterial, viral, fungal, and other organisms. For infectious adverse reactions, the causative organism is reported if specified by the physician in the clinical trials.

§ A medically important event that may be life-threatening or result in death or hospitalization or prolongation of existing hospitalization. Infections not meeting these criteria are considered non-serious.

¶ BK virus-associated nephropathy was reported in 6 NULOJIX patients (4 of which resulted in graft loss) and 6 cyclosporine patients (none of which resulted in graft loss) by Year 3.

Most herpes infections were non-serious and 1 led to treatment discontinuation.

Infections Reported in the CNS

Following three years of treatment in Studies 1 and 2, cryptococcal meningitis was reported in one patient out of 401 patients treated with the belatacept recommended regimen (0.2%) and one patient out of the 405 treated with the cyclosporine control (0.2%). Six patients out of the 403 who were treated with the belatacept regimen of higher cumulative dose and more frequent dosing than recommended in Studies 1 and 2 (1.5%) were reported to have developed CNS infections, including 2 cases of cryptococcal meningitis, one case of Chagas encephalitis with cryptococcal meningitis, one case of cerebral aspergillosis, one case of West Nile encephalitis, and one case of PML (discussed above).

Infusion Reactions

There were no reports of anaphylaxis or drug hypersensitivity in patients treated with belatacept in Studies 1 and 2 through three years. Infusion-related reactions within one hour of infusion were reported in 5% of patients treated with the recommended dose of belatacept, similar to the placebo rate. No serious events were reported through Year 3. The most frequent reactions were hypotension and hypertension.

Proteinuria

At month 1 after transplantation in Studies 1 and 2, the frequency of 2+ proteinuria on urine dipstick in patients treated with the belatacept recommended regimen was 33% (130/390) and 28% (107/384) in patients treated with the cyclosporine control regimen. The frequency of 2+ proteinuria was similar between the two treatment groups between one and three years after transplantation (<10% in both studies). There were no differences in the occurrence of 3+ proteinuria (<4% in both studies) at any time point, and no patients experienced 4+ proteinuria. The clinical significance of this increase in early proteinuria is unknown.

New-Onset Diabetes After Transplantation

The incidence of new-onset diabetes after transplantation (NODAT) was defined in Studies 1 and 2 as use of an antidiabetic agent for ≥30 days or ≥2 fasting plasma glucose values ≥126 mg/dL (7.0 mmol/L) post-transplantation. Of the patients treated with the belatacept recommended regimen, 5% (14/304) developed NODAT by the end of one year compared to 10% (27/280) of patients on the cyclosporine control regimen. However, by the end of the third year, the cumulative incidence of NODAT was 8% (24/304) in patients treated with the belatacept recommended regimen and 10% (29/280) in patients treated with the cyclosporine regimen.

Hypertension

Blood pressure and use of antihypertensive medications were reported in Studies 1 and 2. By Year 3, one or more antihypertensive medications were used in 85% of belatacept-

treated patients and 92% of cyclosporine-treated patients. At one year after transplantation, systolic blood pressures were 8 mmHg lower and diastolic blood pressures were 3 mmHg lower in patients treated with the belatacept recommended regimen compared to the cyclosporine control regimen. At three years after transplantation, systolic blood pressures were 6 mmHg lower and diastolic blood pressures were 3 mmHg lower in belatacept-treated patients compared to cyclosporine-treated patients. Hypertension was reported as an adverse reaction in 32% of belatacept-treated patients and 37% of cyclosporine-treated patients.

Dyslipidemia

Mean values of total cholesterol, HDL, LDL, and triglycerides were reported in Studies 1 and 2. At one year after transplantation these values were 183 mg/dL, 50 mg/dL, 102 mg/dL, and 151 mg/dL, respectively, in 401 patients treated with the belatacept recommended regimen and 196 mg/dL, 48 mg/dL, 108 mg/dL, and 195 mg/dL, respectively, in 405 patients treated with the cyclosporine control regimen. At three years after transplantation, the total cholesterol, HDL, LDL, and triglycerides were 176 mg/dL, 49 mg/dL, 100 mg/dL, and 141 mg/dL, respectively, in belatacept-treated patients compared to 193 mg/dL, 48 mg/dL, 106 mg/dL, and 180 mg/dL in cyclosporine-treated patients. The clinical significance of the lower mean triglyceride values in NULOJIX-treated patients at one and three years is unknown.

Other Adverse Reactions

Adverse reactions that occurred at a frequency of ≥10% in patients treated with the belatacept recommended regimen or cyclosporine control regimen in Studies 1 and 2 through three years are summarized by preferred term in decreasing order of frequency within the table below.

Adverse Reactions Reported by ≥10% of Patients Treated with Either the Belatacept Recommended Regimen or Control in Studies 1 and 2 Through Three Years*,†

Adverse Reaction	NULOJIX Recommended Regimen N=401 %	Cyclosporine N=406 %
Infections and Infestations		
Urinary tract infection	37	36
Upper respiratory infection	15	16
Nasopharyngitis	13	16
Cytomegalovirus infection	12	12
Influenza	11	8
Bronchitis	10	7
Gastrointestinal Disorders		
Diarrhea	30	36
Constipation	33	35
Nausea	24	27
Vomiting	22	20
Abdominal pain	19	16
Abdominal pain upper	9	10
Metabolism and Nutrition Disorders		
Hyperkalemia	20	20
Hypokalemia	21	14
Hypophosphatemia	19	13
Dyslipidemia	19	24
Hyperglycemia	16	17
Hypocalcemia	13	11
Hypercholesterolemia	11	11
Hypomagnesemia	7	10
Hyperuricemia	5	12
Procedural Complications		
Graft dysfunction	25	34
General Disorders		
Peripheral edema	34	42
Pyrexia	28	26
Blood and Lymphatic System Disorders		
Anemia	45	44
Leukopenia	20	23
Renal and Urinary Disorders		
Hematuria	18	18
Proteinuria	16	12
Dysuria	11	11
Renal tubular necrosis	9	13
Vascular Disorders		
Hypertension	32	37
Hypotension	18	12
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	24	18
Dyspnea	12	15
Investigations		
Blood creatinine increased	15	20
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	17	13
Back pain	13	13
Nervous System Disorders		
Headache	21	18
Dizziness	9	10
Tremor	8	17
Skin and Subcutaneous Tissue Disorders		
Acne	8	11
Psychiatric Disorders		
Insomnia	15	18
Anxiety	10	11

* All randomized and transplanted patients in Studies 1 and 2.

† Studies 1 and 2 were not designed to support comparative claims for NULOJIX for the adverse reactions reported in this table.

Selected adverse reactions occurring in <10% from NULOJIX-treated patients in either regimen through three years in Studies 1 and 2 are listed below:

Immune System Disorders: Guillain-Barré syndrome

Infections and Infestations: see Table 3

Gastrointestinal Disorders: stomatitis, including aphthous stomatitis

Injury, Poisoning, and Procedural Complications: chronic allograft nephropathy, complications of transplanted kidney, including wound dehiscence, arteriovenous fistula thrombosis

Blood and Lymphatic System Disorders: neutropenia

Renal and Urinary Disorders: renal impairment, including acute renal failure, renal artery stenosis, urinary incontinence, hydronephrosis

Vascular Disorders: hematoma, lymphocele

Musculoskeletal and Connective Tissue Disorders: musculoskeletal pain

Skin and Subcutaneous Tissue Disorders: alopecia, hyperhidrosis

Cardiac Disorders: atrial fibrillation

1.2.5.3 Rheumatoid Arthritis

Twelve subjects reported SAEs, and none was considered drug related by the investigators. Sixteen subjects reported SAEs, and only 1 was considered possibly drug related by the investigators (elbow infection in an abatacept subject in the 2 mg/kg group). No deaths were reported during the treatment period or the follow-up period (through Day 169). All AEs and SAEs reported in belatacept-treated subjects that were not also reported in the renal transplant patients are listed in the updated Investigator's Brochure. Please refer to that document for further details.

1.2.6 Clinical Efficacy of Belatacept

In study IM103100 the efficacy of belatacept in post transplant patients was assessed. The trial evaluated the incidence of clinically-suspected and biopsy-proven acute rejection (CSBPAR) in patients at 6 months post-transplantation. Secondary variables including biopsy-proven acute rejections (BPARs), CSBPAR, death, and/or graft loss were assessed at 1 year.

1.2.6.1 Acute Rejection

CSBPAR at 6 months, occurred infrequently across all treatment groups (Table 1.2.6). The incidence rate of CSBPAR was slightly lower in the belatacept groups than in the CsA group. The distribution of events by severity (as indicated by histological grade) was similar across the 3 treatment groups. Identical results were observed at 12 months. The criteria for non-inferiority to CsA were easily satisfied for both belatacept groups; however, the number of events was too small to support any further conclusions regarding the relative efficacy of the 3 regimens.

The secondary endpoint of BPAR occurred 2 to 4 times more frequently than the primary endpoint of CSBPAR, indicating that most BPAR episodes were subclinical (ie, not associated with an increase in serum creatinine of $\geq$ 0.5 mg/dL). These episodes of subclinical rejection were observed on biopsies taken to satisfy the protocol requirements, according to local practice, or for other reasons than an increase in serum creatinine of $\geq$ 0.5 mg/dL.

BPAR occurred most frequently in the belatacept LI group. As the rate of CSBPAR was comparable across treatment groups, the difference in the rate of BPAR was due to an increase in the number of subclinical rejection episodes in the belatacept LI treatment

arm. Reallocation to 8-week treatment was associated with an increased frequency of subclinical rejection. Overall, the histologic severity grade of acute rejection episodes appeared to be similar across the 3 treatment groups.

Table 1.2.6: Acute Rejection - Study IM103100

Banff Grade for Acute Rejections	Belatacept MI (N=74)	Belatacept LI (N=71)	CsA (N=73)
CSBPAR (ITT Analysis) at Month 6 (Primary Endpoint) [1]			
Mild Acute (IA)	2 (2.7%)	0	1 (1.4%)
Mild Acute (IB)	0	0	1 (1.4%)
Moderate Acute (IIA)	2 (2.7%)	3 (4.2%)	2 (2.7%)
Moderate Acute (IIB)	1 (1.4%)	1 (1.4%)	2 (2.7%)
Total	5 (6.8%)	4 (5.6%)	6 (8.2%)
Difference in Event Rates (Belatacept - CsA) with Asymptotic 95% CI (%)	-1.5 (-10.0, 7.0)	-2.6 (-10.9, 5.7)	---
BPAR (ITT Analysis) at Month 6			
Mild Acute (IA)	2 (2.7%)	3 (4.2%)	3 (4.1%)
Mild Acute (IB)	0	1 (1.4%)	1 (1.4%)
Moderate Acute (IIA)	6 (8.1%)	8 (11.3%)	7 (9.6%)
Moderate Acute (IIB)	3 (4.1%)	5 (7.0%)	2 (2.7%)
Total	11 (14.9%)	17 (23.9%)	13 (17.8%)
Difference in Event Rates (Belatacept - CsA) with Asymptotic 95% CI (%)	-2.9 (-14.9, 9.0)	6.1 (-7.1, 19.4)	---
BPAR (ITT Analysis) at Month 12			
Mild Acute (IA)	3 (4.1%)	4 (5.6%)	3 (4.1%)
Mild Acute (IB)	1 (1.4%)	4 (5.6%)	1 (1.4%)
Moderate Acute (IIA)	5 (6.8%)	8 (11.3%)	7 (9.6%)
Moderate Acute (IIB)	5 (6.8%)	5 (7.0%)	2 (2.7%)
Total	14 (18.9%)	21 (29.6%)	13 (17.8%)
Difference in Event Rates (Belatacept - CsA) with Asymptotic 95% CI (%)	1.1 (-11.4, 13.6)	11.8 (-2.0, 25.5)	---

[1] The results for CSBPAR were the same at Month 12.

BPAR = biopsy-proven acute rejection, CI = confidence interval, CsA = cyclosporine, CSBPAR = clinically-suspected and biopsy-proven acute rejection, ITT = intent to treat, LI = less intensive, and MI = more intensive.

1.2.6.2 Chronic Allograft Nephropathy

Biopsy specimens were also examined for chronic allograft nephropathy (CAN) including arteriolar hyalinosis, interstitial fibrosis, glomerulosclerosis and tubular atrophy. By Month 12, CAN was approximately 30% to 50%, in relative terms, less common with belatacept than with CsA.

Table 1.2.6.2: Biopsy-proven Chronic Allograft Nephropathy - Study IM103100

Biopsy-proven Chronic Allograft Nephropathy	Belatacept MI (N=74)	Belatacept LI (N=71)	CsA (N=73)
Month 3	3 (4.1%)	2 (2.8%)	9 (12.3%)
Difference in Event Rates (Belatacept - CsA) with Asymptotic 95% CI (%)	-8.3 (-17.1, 0.5)	-9.5 (-18.0, -1.0)	---
Month 6	6 (8.1%)	3 (4.2%)	11 (15.1%)
Difference in Event Rates (Belatacept - CsA) with Asymptotic 95% CI (%)	-7.0 (-17.3, 3.3)	-10.8 (-20.3, -1.4)	---
Month 12	15 (20.3%)	11 (15.5%)	22 (30.1%)
Difference in Event Rates (Belatacept - CsA) with Asymptotic 95% CI (%)	-9.9 (-23.8, 4.1)	-14.6 (-28.1, -1.2)	---

Note: Biopsy-proven chronic allograft nephropathy was assessed by the central pathologist; Day 1 baseline biopsies were included. In an analysis restricted to subjects with at least 1 post-baseline biopsy, the rates of biopsy-proven chronic allograft nephropathy at 12 months were 29%, 20%, and 44% for the belatacept MI, belatacept LI, and CsA groups, respectively.

CI = confidence interval, CsA = cyclosporine, LI = less intensive, and MI = more intensive.

1.2.6.3 Subject and Graft Survival

Death and/or graft loss occurred infrequently in all treatment groups, and was least frequently reported in the belatacept LI group. Most graft losses occurred for technical, rather than immunological, reasons.

Table 1.2.6.3: Subject and Graft Survival - Study IM103100

	Belatacept MI (N=74)	Belatacept LI (N=71)	CsA (N=73)
Deaths at Month 12 (ITT Analysis)			
Total No. of Deaths	1 (1.4%)	0	4 (5.5%)
Reasons:			
Cardiac	0	0	2 (2.7%)
Infection / Sepsis	1 (1.4%)	0	0
Pulmonary Embolism	0	0	1 (1.4%)
Other – Unknown	0	0	1 (1.4%)
Graft Loss at Month 12 (ITT Analysis)			
Total No. of Graft Losses	3 (4.1%)	1 (1.4%)	3 (4.1%)
Reasons:			
Renal Vein or Renal Artery Thrombosis	1 (1.4%)	1 (1.4%)	2 (2.7%)
Other - Infarction (Etiology Unknown, Possibly Ongoing Rejection)	1 (1.4%)	0	0
Other - PTLD as Treatment of PTLD	1 (1.4%)	0	0
Other - Combination - Persistent DGF; Acute Rejection; Infection	0	0	1 (1.4%)

Note: After the cutoff date for the 12-month analysis, 1 additional death was reported (Subject IM103100-13-16 in the belatacept MI group died due to multiple organ failure).

CsA = cyclosporine, DGF = delayed graft function, ITT = intent to treat, LI = less intensive, MI = more intensive, and PTLD = post-transplant lymphoproliferative disorder.

1.2.6.4 Renal Function

Renal function was assessed by measurement of iohexol clearance. Iohexol clearance was greater in the belatacept groups than in the CsA group at all time points. Serum creatinine and creatinine-based estimates of renal function were also assessed. These measures are known to be less sensitive and more variable than true measures of GFR. However, assessments of renal function by these measures generally favored belatacept.

Mean systolic blood pressure (SBP) was slightly higher with CsA (133 mm Hg) than with belatacept by Month 12 (SBP: 130 and 129 mm Hg in the MI and LI groups, respectively). Antihypertensive medication use was also somewhat more common with CsA use than with belatacept use.

At Month 12, mean total cholesterol was slightly lower with both the belatacept MI and LI groups, respectively, than with CsA (198 and 201 mg/dL vs. 212 mg/dL), as were both the mean non-high density lipoprotein (non-HDL) fraction (145 and 144 mg/dL vs. 151 mg/dL) and the mean HDL fraction (53 and 56 mg/dL vs. 59 mg/dL). Lipid-lowering medications were used more frequently with CsA (53%) than with belatacept (32%-36%).

At Month 12, mean HbA1c was slightly lower with belatacept (5.8% in both groups) than with CsA (6.2%). The incidence of new-onset PTDM was slightly lower with belatacept than with CsA (2 and 0 subjects in the MI and LI groups, respectively vs. 3 subjects).

1.2.6.5 IM103100 Long Term Extension

Of the 164 subjects who completed the 12-month phase, 128 subjects (102/113 subjects from the MI + LI belatacept group and 26/51 subjects in the CsA group) consented to continue in the long term extension (LTE) phase of the study.

During the LTE phase, a low rate of acute rejection, death, or graft loss was reported in belatacept subjects. Two cases of acute rejection (CSBPAR) were reported in the belatacept group (1 each in the MI/8-week and LI/8-week groups). Six cases of BPAR, including 2 cases of CSPAR, were reported in the combined belatacept group. All of these cases were mild or moderate in severity. The incidence of CAN was reported in 25 cases in the combined belatacept group and 9 cases in the CsA group.

In the LTE phase, mean calculated GFR (MDRD formula) was reportedly higher in the belatacept group. At Months 12 and 60, GFR was reported as 75.8 and 77.2 mL/min/1.73 m^2, respectively in the combined belatacept group and 74.4 and 59.3 mL/min/1.73 m^2, respectively, in the CsA group.

Five deaths were reported: 3 in the combined belatacept group (2 died with a functioning graft) and 2 in the CsA group (both died with a functioning graft). The causes of death reported among the belatacept subjects were myocardial infarction (LI), cardiopulmonary arrest (MI) and pneunomia (MI).

1.3 Overall Risk/Benefit Assessment

1.3.1 Potential Benefits

The field of transplantation is moving towards optimizing immunosuppression to avoid the toxicities of the current immunosuppressive regimens while at the same time achieving acceptable efficacy. Belatacept is being developed as an immunosuppressive agent for kidney transplant to provide comparable efficacy to the current standard immunosuppressive class, CNIs, with an improved safety profile. At present, CNI-based regimens are suboptimal for several reasons. First, CNIs are frequently not initiated until after there is sufficient clinical evidence of allograft function. This potential for delayed administration in a critical immunologic window may lead to increased acute rejection rates. Polyclonal antilymphocyte preparations may be used as an immunosuppressive bridge until a CNI may be safely administered; however, these preparations have short-term adverse effects (infection) as well as long-term sequelae (PTLD). These adverse effects must be factored into the risk burden of a CNI-based regimen.

Second, the adverse cardiovascular and metabolic effects of CNI-based regimens further weigh on the benefit-risk ratio of these agents. Since CNIs are well known to cause or exacerbate conditions such as hypertension, hypercholesterolemia, or diabetes mellitus, renal transplant recipients are vulnerable to these adverse effects of CNIs. Unfortunately, while alternative CNI-free regimens have been previously tested, none have been proven to offer a favorable benefit-risk relationship. Therefore, CNIs remain the cornerstone for immunosuppression in these subjects despite their known liabilities.

An alternative strategy to promote improvement in kidney transplant function has been the use of mTOR inhibitors, sirolimus or everolimus, instead of CNI or in combination

with low dose CNI. While conceptually this strategy had promise, in practice this has not borne true. Attempts to wean patients from CNI and convert to mTOR-based therapy have been hampered by an increase in acute rejection upon removing CNI. In addition to the detrimental effects of acute rejection, including a higher incidence of new donor specific antibody formation, patients required higher doses of mTOR inhibitor leading to an increased incidence of adverse events/side effects including hyperlipidemia, mouth ulcers, edema, anemia, proteinuria resulting in intolerability of the regimen and a high rate of discontinuation. Belatacept, an immunosuppressive agent with a novel mechanism of action, is a promising non-nephrotoxic candidate for use in renal transplant recipients. Unlike CNIs or mTOR inhibitors, belatacept acts selectively rather than through ubiquitous pathways to afford immunosuppression. This targeted mechanistic approach may provide immunosuppressive efficacy while circumventing the intrinsic toxicities of CNIs. Consistent with this notion, existing data show comparable rates of acute rejection, with favorable trends in subject and graft survival, GFR, CAN, and cardiovascular adverse effect profile.

Two dose regimens of belatacept are being studied in Phase 3. Both regimens are based on the regimens successfully studied in Phase 2, with minor modifications to increase the likelihood of a favorable outcome.

1.3.2 Potential Risks

Post-Transplant Lymphoproliferative Disorder

Reported cases of post-transplant lymphoproliferative disorder (PTLD) up to 36 months post transplant were obtained for belatacept by pooling both dosage regimens of belatacept in both studies (804 patients) with data from a third study in kidney transplantation (145 patients) which evaluated two belatacept dosage regimens similar, but slightly different, from those of Studies 1 and 2 (see table below). The total number of belatacept patients from these three studies (949) was compared to the pooled cyclosporine control groups from all three studies (476 patients).

Among 401 patients in Studies 1 and 2 treated with the recommended regimen of belatacept and the 71 patients in Study 3 treated with a very similar (but non-identical) belatacept regimen, there were 5 cases of PTLD: 3 in EBV seropositive patients and 2 in

EBV seronegative patients. Two of the 5 cases presented with CNS involvement. Among the 477 patients in Studies 1, 2, and 3 treated with the belatacept regimen of higher cumulative dose and more frequent dosing than recommended, there were 8 cases of PTLD: 2 in EBV seropositive patients and 6 in EBV seronegative or serostatus unknown patients. Six of the 8 cases presented with CNS involvement. Therefore, administration of higher than the recommended doses or more frequent dosing of belatacept is not recommended.

One of the 476 patients treated with cyclosporine developed PTLD, without CNS involvement. All cases of PTLD reported up to 36 months post transplant in belatacept- or cyclosporine-treated patients presented within 18 months of transplantation. Overall, the rate of PTLD in 949 patients treated with any of the belatacept regimens was 9-fold higher in those who were EBV seronegative or EBV serostatus unknown (8/139) compared to those who were EBV seropositive (5/810 patients). Therefore belatacept is recommended for use only in patients who are EBV seropositive.

Malignancy

Malignancies, excluding non-melanoma skin cancer and PTLD, were reported in Study 1 and Study 2 in 3.5% (14/401) of patients treated with the recommended belatacept regimen and 3.7% (15/405) of patients treated with the cyclosporine control regimen. Non-melanoma skin cancer was reported in 1.5% (6/401) of patients treated with the recommended belatacept regimen and in 3.7% (15/405) of patients treated with cyclosporine.

Infection

Adverse reactions of infectious etiology were reported based on clinical assessment by physicians. The causative organisms for these reactions are identified when provided by the physician. The overall number of infections, serious infections, and select infections with identified etiology reported in patients treated with the belatacept recommended regimen or the cyclosporine control in Studies 1 and 2 are shown above. Fungal

infections were reported in 18% of patients receiving belatacept compared to 22% receiving cyclosporine, primarily due to skin and mucocutaneous fungal infections. Tuberculosis and herpes infections were reported more frequently in patients receiving belatacept than cyclosporine. Of the patients who developed tuberculosis through 3 years, all but one belatacept patient lived in countries with a high prevalence of tuberculosis

Other Potential Risks

Other potential risks include those events that may theoretically be associated with belatacept, or that have been observed more frequently in belatacept-treated subjects in a single clinical trial. These events include graft thrombosis, infusional reactions, proteinuria, pulmonary edema, and autoimmune disorders. None of these events have been consistently associated with belatacept treatment. These events are undergoing augmented surveillance in the clinical trials.

1.3.3 Summary of Risk/Benefit Assessment

Belatacept, an immunosuppressive agent with a novel mechanism of action, is a promising non-nephrotoxic candidate for use in renal transplant recipients. Clinical data from approximately 1000 belatacept-treated patients in 3 trials in de novo renal transplantation indicate that belatacept results in similar rates of adverse events, serious adverse events, infections and malignancies to a CNI-based regimen. Overall rates of infection and malignancy were similar in belatacept and CNI-treated subjects.

Appropriate screening for TB, per local guidelines, is required before treatment with belatacept.

Although rare, PTLD and CNS PTLD have been observed more frequently in belatacept-treated subjects. A thorough analysis indicates that the elevated risk of PTLD, an expected event in transplant patients, appears to be restricted to EBV-negative recipients, with no increase in risk in EBV-positive recipients treated with belatacept.

Therefore, the current study offers a favorable benefit/risk relationship to study subjects, and the potential to provide important data for the development of new immunosuppressive regimens that have improved safety and tolerability when compared to existing therapies.

End stage renal disease is a major health problem affecting over 350,000 people in the US alone. Kidney transplantation is now the ideal treatment for renal failure, with nearly 17,000 transplants performed annually. While early outcomes have improved dramatically over the past 30 years, long-term results continue to be disappointing. Ten years after transplant nearly all renal allografts have histologic evidence of chronic injury with accompanying impaired renal function. Many patients with failing allografts ultimately return to dialysis. Fortunately, a significant proportion of these patients are re-transplant candidates. Indeed 10-15% of all renal transplants are performed in recipients of prior renal allografts. There is an ongoing debate regarding the management of patients with a failed kidney transplant. Those patients who require dialysis and are maintained on immunosuppression continue to be subjected to increased risks of infection, cardiovascular disease, malignancies, etc. In fact several studies have shown a significantly increased risk of infection and death for those who continue immunosuppression after graft failure. Thus most centers favor tapering immunosuppressive therapy off once a patient requires dialysis. Unfortunately, this puts the patient at risk for developing allo-antibody which may limit options for re-transplant. The development of an immunosuppressive strategy to minimize the complications of persistent therapy while preventing sensitization could greatly enhance the likelihood of re-transplantation.

1.4 Study Rationale

Kidney transplantation is an accepted form of treatment for end stage renal disease. Indeed transplant recipients not only live longer than those patients who remain on dialysis, their quality of life is superior and the therapy is cost effective. Unfortunately, ten years after transplant nearly all renal allografts have histologic evidence of chronic injury and over 60% have evidence of severe chronic allograft nephropathy, grade III interstitial fibrosis/tubular atrophy (IF/TA). Many of these patients ultimately return to dialysis. Given the increased risks of infection, cardiovascular disease and malignancy most patients have their immunosuppression discontinued when they start dialysis. Unfortunately this puts the patient at increased risk for developing allo-antibody which limits options for re-transplant. Indeed a significant proportion of these patients will be re-listed for a subsequent transplant. Belatacept has a unique mechanism of action as an immunosuppressive agent. Given its favorable side-effect profile, lack of nephrotoxicity and effectiveness in preventing T-cell dependent antibody production including allo-antibody, belatacept represents an ideal agent to test in this patient population.

The current study proposes a randomized clinical trial of first-time renal transplant recipients who now have impaired renal function (eGFR≤35 with a decline in GFR of ≥ 10 % in the year prior to enrollment with biopsy proven grade II or III IF/TA OR a GFR ≤ 20 in the 6 month period prior to enrollment absent other causes for graft dysfunction and deemed to have a failing allograft by the patient's transplant nephrologist. Patients must be re-transplant candidates and have completed or be actively undergoing the evaluation process for re-listing. Patients will be randomized to a belatacept-based immunosuppressive regimen or standard of care with a calcineurin inhibitor-based or sirolimus therapy. Endpoints include rate of donor-specific antibody production as well as renal function and rate/time to dialysis. We hypothesize that belatacept will effectively inhibit sensitization (ie donor-specific antibody production) in patients with a failing or failed renal allograft and as a result will facilitate re-transplantation. In addition treatment with belatacept will more favorably impact residual allograft function (ie preservation of GFR) in patients with IF/TA as compared to treatment with conventional immunosuppression thereby prolonging time to dialysis or need for re-transplant.

2 STUDY OBJECTIVES

2.1 Primary Objective

To prevent the formation of donor-specific alloantibody in patients with chronic allograft injury, thereby facilitating re-transplantation by avoiding sensitization

Primary Endpoint: The rate of donor-specific antibody formation 36 months following randomization.

2.2 Secondary Objectives

To determine if treatment with belatacept better preserves GFR in those patients with marginal renal function as compared to those patients who continue calcineurin inhibitor therapy and as a result delays time to initiation of dialysis. Subjects already requiring dialysis at the time of enrollment will be excluded from this analysis.

Secondary Endpoints:

-Rate of change in GFR compared to participants maintained on CNI-based or mTOR-based regimen. Subjects already requiring dialysis will be excluded from this endpoint analysis.

-Time to dialysis measured from the time of randomization to initiation of dialysis compared to participants maintained on CNI-based or mTOR-based regimen.

Subjects already requiring dialysis at the time of enrollment will be excluded from this endpoint analysis.

- Overall level of alloantibody as indicated by PRA.
- Incidence of infectious complications.

3 ETHICAL CONSIDERATIONS

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

All potential serious breaches must be reported to Bristol-Myers Squibb (BMS) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

3.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided

to subjects. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

3.3 Informed Consent

Investigators must ensure that subjects (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) before clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

This is an open-label, prospective, randomized, controlled clinical trial. First-time renal transplant recipients who now have impaired renal function (estimated GFR $\leq$35 with a decline in renal function of $\geq$ 10% in the year prior to enrollment with biopsy proven grade II or III IF/TA) OR a GFR of $\leq$ 20 over the 6 month period prior to enrollment absent other causes for graft dysfunction and deemed to have a failing allograft by the patient's transplant nephrologist will be identified for randomization to either treatment (belatacept-based) or to continue standard of care (CNI-based or mTOR-based) regimen. There will be a total of 72 subjects, randomized in equal numbers, 36 patients in each arm. Patients must be candidates for re-transplantation. Those subjects who are EBV seronegative or have a history of PTLD will be excluded. Follow up will be planned for 36 months after randomization. The study will proceed in two sequential phases with distinct funding periods. Phase I will enroll 18 patients in each arm, 36 total patients. After discussions with BMS we will proceed with phase II, contingent on funding

availability and preliminary results from phase I. Phase II will enroll an additional 36 patients for a total of 72 patients, 36 in each arm.

Study Design

-Standard of care arm-

GFR≤35 - wean tacrolimus or sirolimus dose to target level of 3-5 (or equivalent CNI or mTOR inhibitor level), and if applicable continue MMF or MPA (equivalent of at least 1g daily) or azathioprine, and/or prednisone

Upon initiation of dialysis or in subjects already requiring dialysis at time of enrollment - discontinue CNI or mTOR inhibitor over 5 days, if applicable MMF, MPA or azathioprine dose decreased by half then discontinued 2 weeks later, steroid withdrawal beginning 1 month after the initiation of dialysis with monthly reduction by half with plans to discontinue at 3 months after initiation of dialysis.

-Belatacept arm-

GFR ≤35- initiate Belatacept; dose of CNI or mTOR inhibitor will be decreased by half at time of first dose. CNI or mTOR inhibitor will be discontinued at time of second dose of belatacept (week 2). Belatacept dosing 10mg/kg- day 0, 2 weeks, 4 weeks, 8 weeks, and 12weeks; subsequent doses 5mg/kg q month through duration of trial or until retransplantation, whichever is first. If applicable continue MMF or MPA (equivalent of at least 1g daily) or azathioprine and/or prednisone

Upon initiation of dialysis or in subjects already requiring dialysis at time of enrollment- wean remaining immunosuppression (if applicable) as above in standard of care arm except for belatacept which they will remain on for the duration of the study or until re-transplant. If a subject progresses to dialysis dependence while still receiving belatacept at the 10 mg/kg dosing, the subject will continue to receive 10 mg/kg dose as scheduled through week 12 (5 total doses) and then decrease to 5 mg/kg IV q month for the duration of study participation.

At the time of anticipated enrollment study patients will be greater than one (1) year post-transplant and likely have already had their immunosuppression reduced. Indeed, they probably do not require the same level of immunosuppression as they did in the immediate post-transplant period. Thus the protocol is written to accept patients receiving CNI or mTOR monotherapy, or a CNI or mTOR based regimen with the equivalent of at least 1g daily of MMF or comparable dose of MPA or azathioprine, and/or corticosteroid. (i.e. Total immunosuppression may be less intense than currently recommended in the prescribing instructions for Belatacept. We would allow participants receiving reduced dose MMF (500mg BID) or equivalent and/or weaned off corticosteroids for any reason, or patients weaned off MMF or equivalent being

maintained on prednisone. This allows for inclusion of additional patients without subjecting them to increased immunosuppression.

4.2 Study Population

The study population includes kidney transplant recipients who now have impaired renal allograft function or failed allograft requiring initiation of dialysis.

For entry into the study, the following criteria MUST be met.

4.2.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Before any study procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if subjects consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.

2) Target Population

a) The subject is a kidney transplant recipient (non-HLA identical donor) who now has impaired renal allograft function with at least one of the following:

i) Estimated GFR $\leq$ 35 with a decline in GFR of $\geq$ 10% in the 12 months prior to enrollment and must have biopsy proven grade II or III interstitial fibrosis/tubular atrophy (IF/TA)

ii) Estimated GFR persistently $\leq$ 20 ml/min over the 6 month period prior to enrollment absent other causes for graft dysfunction, and deemed to have a failing allograft by the patient's transplant nephrologist

b) $\geq$ 1 year post-transplant

c) The subject must be a re-transplant candidate

d) The subject must be on an immunosuppression regimen meeting one of the following criteria:

i) A CNI (tacrolimus or cyclosporine) or mTOR inhibitor (sirolimus or everolimus) and at least one of the following:

(1) MMF at a dose of at least 1 gm/day or comparable dose of MPA or azathioprine

(2) Prednisone at a dose of at least 5 mg/day

ii) A CNI (tacrolimus or cyclosporine) or mTOR inhibitor (sirolimus or everolimus) alone for 3 months or more, with no clinically significant changes in PRA during that time, as determined by the Emory HLA lab.

3) Age and Sex

a) Men and women, ages 18 to 70, inclusive.

4.2.2 Exclusion Criteria

1) Sex and Reproductive Status

a) WOCBP who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for up to **8 weeks** after the last dose of study drug.

b) Women who are pregnant or breastfeeding.

c) Women with a positive pregnancy test.

d) Sexually active fertile men not using effective birth control if their partners are WOCBP.

2) Target Disease Exceptions

a) Subjects who are EBV seronegative.

b) Subjects with any prior solid organ (e.g., heart, liver, pancreas) or cell (e.g., islet, bone marrow) transplant other than a renal allograft. Exception may be made for recipient of a simultaneous kidney-pancreas transplant who had previously experienced graft loss of the pancreas allograft due to thrombosis or rejection.

c) Subjects with presence of donor specific antibody at the time of enrollment

d) Subjects who have a recent history (within 1 yr) of biopsy proven acute rejection $\geq$ Banff grade Ia

e) Subjects who have a living donor identified for re-transplant within 3 months

3) Medical History and Concurrent Diseases

a) Subjects with a history of PTLD

b) Subjects at risk for tuberculosis (TB)

c) Subjects with a history of cancer within the past 3 years, other than non-melanoma skin cancer(s)

4) Physical and Laboratory Test Findings

a) Subjects with a positive BK serum PCR $\geq$ 20,000 copies at the time of enrollment OR history of biopsy-proven BK nephropathy within the year prior to enrollment.

b) Subjects with a mammogram that is suspicious for malignancy and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory, or other diagnostic evaluations. All women 50 years or older must have a screening mammogram, or provide results of a screening mammogram performed within 1 year of enrollment. If the screening mammogram was not performed within 1 year of enrollment, but the subject is deemed a suitable study candidate, the baseline mammogram may be obtained within 8 weeks after enrollment. Women of any age who have first degree relatives with a history of breast carcinoma or who have other risk factors of

breast carcinoma must undergo increased surveillance for breast cancer according to local practice.

c) Subjects who have difficult intravenous access or other reasons that would likely preclude the ability to receive long-term intravenous infusions

5) Allergies and Adverse Drug Reactions

a) Hypersensitivity to any medications that will be used in the protocol

6) Prohibited Treatments and/or Therapies

a) Subjects who have used any investigational drug within the 30 days prior to anticipated enrollment

b) Subjects currently receiving belatacept as part of their maintenance immunosuppressive regimen

7) Other Exclusion Criteria

a) Prisoners, or subjects who are involuntarily incarcerated.

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

4.2.3 Discontinuation of Subjects from Treatment

Subjects MUST discontinue study treatment and withdraw from the study for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality, 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
  - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
  - The investigator must immediately notify BMS if a study subject becomes pregnant. The mechanism for reporting pregnancy is described in Section 7.6.
- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Subjects who discontinue from the study for any reason other than withdrawal of consent will be asked to continue in the study under a reduced follow-up plan.

4.3 Data Safety Monitoring Plan

An Independent Data Monitoring Committee (DMC) will monitor emerging efficacy and overall safety data regularly to ensure that the benefits and risks of study participation remain acceptable. The DMC will assess the incidence of acute rejection, development of donor-specific antibody, graft loss, infectious complications, death, PTLD, and other serious adverse events (SAEs) in this study. In addition, other safety and efficacy variables (to be defined in the DMC charter) will be monitored by the DMC in order to minimize potential risks to study participants.

The first review of data by the DMC will occur either after 10 subjects have been enrolled and randomized or approximately 6 months after the first subject is enrolled, whichever comes first. The second review of the data by the DMC will occur either after 30 subjects have been enrolled or 6 months after the first patient is enrolled, whichever comes first. Subsequent reviews of data by the DMC will occur every 3 months during the remainder of the first year and approximately every 6 months thereafter.

Based on regular reviews of the emerging data, the DMC may recommend alteration and/or termination of the trial or cessation of further enrollment. Meeting structure, schedule, procedures, and communication between the Sponsor and the DMC, the content and format of DMC reports, and other relevant details will be determined in consultation with the DMC members and will be detailed in a separate charter.

5 TREATMENTS

5.1 Study Treatment: Belatacept

An investigational product, also known as investigational medicinal product in some regions, is defined as follows: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. In this protocol, the investigational product is Belatacept.

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons as components of a given standard of care are considered noninvestigational products.

5.1.1 Identification, Packaging and Labeling

Study Treatments

Table 5.1: Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Belatacept for Injection 250mg/vial	250 mg	Vial/Commercial presentation	Commercial carton	White to off white, whole or fragmented cake in a vial	Store refrigerated, 2-8 degrees Celsius. Protect from light.

5.1.2 Storage, and Handling

The investigational product should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations.

The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity).

5.1.3 Preparation

Belatacept (Nulojix) will be prepared as per package insert.

5.2 Drug Ordering and Accountability

5.2.1 Initial Orders

The BMS project manager should be contacted for study drug requirements. Study drug requests need 10 business days of processing time.

5.2.2 Re-Supply

The BMS project manager should be contacted for re-supply of study drugs. The re-supply requests need 10 business days of processing time.

5.3 Method of Assigning Subjects to a Treatment

Subjects will be randomized in equal numbers to the following treatment groups:

1) CNI (tacrolimus or cyclosporine) or mTOR inhibitor (sirolimus or everolimus) based regimen (with or without MMF/MPA/azathioprine and/or steroids)

2) Belatacept based regimen (with or without MMF/MPA/azathioprine and/or steroids)

At the time of enrollment, immediately after written informed consent is obtained and before performing any study-related procedures, each subject will be assigned a unique sequential subject number for identification throughout the study. This subject number will not be reused for any other participant during the study. Once the subject has met all the entry criteria (inclusion and exclusion), the subject will be randomized to one of the two described treatment regimens. Adverse event reporting for all subjects will begin at the time of randomization.

5.4 Selection and Timing of Dose for Each Subject

Patients will be randomized as described above. In the standard of care arm patients will remain on CNI or mTOR inhibitor therapy. The tacrolimus or sirolimus dose will be weaned to achieve trough levels of 3-5 (if on equivalent medication, dose will be adjusted to achieve similar potency levels). If on MMF they will continue on MMF, equivalent of at least 1 gram daily, or if on MPA or azathioprine, a comparable dose. If on steroids they will continue on corticosteroids. If on both MMF/MPA/azathioprine and steroids they will continue on both. Upon initiation of dialysis or in subjects already requiring dialysis at the time of enrollment, the CNI (tacrolimus or cyclosporine) or mTOR inhibitor (sirolimus or everolimus) will be discontinued over a 5 day period. The MMF, MPA or azathioprine dose will be decreased by 50% and then discontinued 2 weeks later. Steroid dose will be weaned by 50% at one month after returning to dialysis, with a subsequent 50% reduction at 2 months and discontinuation at 3 months.

In those patients randomized to receive belatacept, the CNI (tacrolimus or cyclosporine) or mTOR inhibitor (sirolimus or everolimus) will be weaned in the following fashion: dose of CNI or mTOR inhibitor will be reduced by 50% at time of first dose of belatacept. CNI or mTOR inhibitor will be discontinued at week 2 dose of belatacept. Subjects will receive Belatacept 10mg/kg IV on the first study day, at 2 weeks,1 month, 2

months, and 3 months. Subsequent belatacept doses will be 5mg/kg IV every month through the duration of the trial or until re-transplantation occurs, whichever is first. A month will be defined as one true calendar month. There will be a ±2 days window for the 2nd (2 week) belatacept infusion, and a ±5 days window for subsequent infusions. If on MMF subjects will continue their MMF (equivalent of at least 1g daily) or if on MPA or azathioprine, a comparable dose. If on steroids they will continue on corticosteroids. If on MMF/MPA/azathioprine and steroids they will continue on both. Upon initiation of dialysis or in subjects already requiring dialysis at the time of enrollment, the MMF or azathioprine dose will be decreased by 50% and then discontinued 2 weeks later. Steroid dose will be weaned by 50% at one month after returning to dialysis, with a subsequent 50% reduction at 2 months and discontinuation at 3 months. Belatacept will be continued at 5mg/kg IV monthly (± 5 days) for the duration of the study or retransplantation whichever occurs first. If a subject progresses to dialysis dependence while still receiving belatacept at the 10 mg/kg dosing, the subject will continue to receive 10 mg/kg dose as scheduled through month 3 (5 total doses) and then decrease to 5 mg/kg IV q month for the duration of study participation.

Infusion doses will be based on the subject's actual body weight at enrollment, and will not be modified during the course of the study, unless there is a change of body weight greater than ±10%. Study drug should be administered to the subject at a relatively constant rate over approximately 30 minutes. Once subjects have initiated hemodialysis, study infusion visits will be scheduled on non-dialysis days. If patients perform peritoneal dialysis, study infusion visits will be scheduled without regard to dialysis schedule.

5.4.1 Dose Modifications

In the absence of AEs deemed at least possibly related to study drug treatment, subjects will complete their scheduled infusions as prescribed by the protocol. 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. The subject will be considered eligible to receive further study drug treatment only after discussion with the medical monitor. Under no circumstances should the dose of belatacept be modified. Subjects in whom belatacept dosing is discontinued should be placed on the standard of care regimen.

5.5 Blinding/Unblinding

Not Applicable

5.6 Concomitant Treatments

5.6.1 Prohibited and/or Restricted Treatments

Use of immunosuppressive agents and corticosteroids must be limited to those specified in the protocol. For full prescribing information, see the package inserts.

5.6.2 Other Restrictions and Precautions

Vaccination

There is limited information available regarding the effectiveness of immunizations in non-human primates and humans that have been treated with belatacept. No data are available on the effect of therapeutic vaccinations in subjects receiving belatacept. Due to the risk of infection, vaccination of subjects with any live vaccine is absolutely contraindicated during the course of the study, as is the administration of LIVE oral polio or varicella vaccine to household contacts. The Centers for Disease Control recommend that subjects should not be administered a live virus vaccination for at least 3 months after discontinuing high-dose corticosteroid therapy (defined as > 20 mg/day of prednisone for > 2 weeks). In view of the long half-life of belatacept, study subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication.

Peri-infusional Reactions

The infusion of protein biologic agents can be associated with hypersensitivity or acute allergic reactions. Subjects should be monitored frequently during and following study drug administration. Appropriate emergency equipment should be present at the treatment facility in the event of a serious anaphylactic reaction.

Other Potential Risks

Proteinuria and pulmonary edema was reported more frequently as an AE among belatacept-treated subjects in clinical trials. Proteinuria, pulmonary edema, and congestive heart failure have been identified as events of special interest future trials.

5.7 Treatment Compliance

All medications specified in this protocol must be administered as described within the protocol. Belatacept will be exclusively administered at the study site. Compliance for the other medications will be discussed with the subjects at each study visit and will be documented by the study coordinator. Patients in the standard of care arm will have periodic CNI (tacrolimus or cyclosporine) or mTOR inhibitor (sirolimus or everolimus) levels evaluated to document compliance.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Time and Events Schedule

Baseline and study evaluations are summarized in table 6.1

All assessments will be performed or administered prior to study drug administration unless otherwise indicated.

If a subject needs to withdraw from the study, the next scheduled set of assessments will be performed early. The reason for study discontinuation will be documented.

6.1

Belatacept-Treatment Group Pre-Dialysis																				
Visit #	Screen	2	3	4	5	6	7-8	9	10-11	12	13-14	15	16-20	21	22-26	27	28-32	33	34-38	39
time points		0	2 wks	1 mo	2 mo	3 mo	4-5 mo	6 mo	7-8 mo	9 mo	10-11 mo	12 mo	13-17 mo	18 mo	19-23 mo	24 mo	25-29 mo	30 mo	31-35 mo	36 mo
			± 2 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days
Eligibility Assessments																				
Informed Consent	X																			
Inclusion/Exclusion Criteria	X																			
Medical History	X																			
Safety Assessments																				
Physician Visit	X			X	X	X		X		X		X		X		X		X		X
Physical Examination	X			X	X	X		X		X		X		X		X		X		X
Vital Signs	X	X	X	X	X	X	XX	X	XX	X	XX	X	XXXXX	X	XXXXX	X	XXXXX	X		X
Assessment of Signs and Symptoms		X	X	X	X	X	XX	X	XX	X	XX	X	XXXXX	X	XXXXX	X	XXXXX	X	XXXXX	X
Adverse Events Assessments		X	X	X	X	X	XX	X	XX	X	XX	X	XXXXX	X	XXXXX	X	XXXXX	X	XXXXX	X
Laboratory Tests	X	X		X	X	X		X		X		X		X		X		X		X
EBV/CMV titer	X																			
Neurologic Evaluation	X			X	X	X		X				X		X		X		X		X
Efficacy Assessments																				
DSA/PRA	X	X		X	X	X		X		X		X		X		X		X		X
Mechanistic																				
Sample storage	X	X	X	X	X	X	XX	X	XX	X	XX	X	X[15]	X	X[15]	X	XXXXX	X	XXXXX	X
Clinical Drug Supplies																				
Randomize		X																		
Belatacept Infusion[3]		X[1]	X	X	X	X	X[2]X	X	XX	X	XX	X	XXXXX	X	XXXXX	X	XXXXX	X	XXXXX	X
Tac/CsA dosing		X[4]	X[5]																	
Concomitant immunosuppression[6]		X	X	X	X	X	XX	X	XX	X	XX	X	XXXXX	X	XXXXX	X	XXXXX	X	XXXXX	X

6.1

Belatacept-Treatment Group Post-Dialysis																				
Visit #	Screening	Initiation of Dialysis	1	2	3	4	5	6	7	8-9	10	11-12	13	14-18	19	20-24	25	26-30	31	32-36	37
time points			2 wks	1 mo	2mo	3mo	4mo	5mo	6mo	7-8mo	9mo	10-11 mo	12 mo	13-17 mo	18 mo	19-23 mo	24 mo	25-29 mo	30 mo	31-35 mo	36 mo
			± 2 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days
Eligibility Assessments																					
Informed Consent	X																				
Inclusion/Exclusion Criteria	X																				
Medical History	X																				
Safety Assessments																					
Physician Visit	X	X			X	X	X	X	X		X				X				X		X
Physical Examination	X	X		X	X	X	X	X	X		X		X		X		X		X		X
Vital Signs	X	X		X	X	X	X	X	X	X	X	XX	X	XXXXX	X	XXXXX	X	XXXXX	X	XXXXX	X
Assessment of Signs and Symptoms		X	X	X	X	X	X	X	X	X	X	XX	X	XXXXX	X	XXXXX	X	XXXXX	X	XXXXX	X
Adverse Events Assessments		X	X	X	X	X	X	X	X	X	X	XX	X	XXXXX	X	XXXXX	X	XXXXX	X	XXXXX	X
Laboratory Tests	X	X		X	X	X	X	X	X		X		X		X		X		X		X
EBV/CMV titer	X	X		X		X			X				X		X		X		X		X
Neurologic Evaluation	X	X				X					X		X		X		X		X		X
Efficacy Assessments															X						
DSA/PRA	X	X			X	X	X	X	X				X				X		X		X
Mechanistic															X						
Sample storage	X	X		X	X	X	X	X	X	X	X	XX	X	X[15]		XXXXX	X	XXXXX	X	XXXXX	X
Clinical Drug Supplies															X						
Randomization		X																			
MMF weaning[7]		X	X																		

Prednisone weaning[8]				X	X	X															
Belatacept Infusion[9]		X	X	X	X	X	X	X	X	X	X	XX	X	XXXXX	X	XXXXX	X	XXXXX	X	XXXXX	X
Tac/CsA dosing			X[5]																		
Concomitant immunosuppression[6]			X	X																	

6.1

Standard of Care Pre-Dialysis												
Visit #	Screen	2	3	4	5	6	7	8	9	10	11	12
time points		0	1mo	2mo	3mo	6mo	9mo	12mo	18mo	24mo	30 mo	36 mo
			± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days
Eligibility Assessments												
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Medical History	X											
Safety Assessments												
Physician Visit	X		X	X	X	X	X	X	X	X	X	X
Physical Examination	X			X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Signs and Symptoms		X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessments		X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests	X	X	X	X	X	X	X	X	X	X	X	X
EBV/CMV titer	X											
Neurologic Evaluation	X		X		X	X		X		X		X
Efficacy Assessments												
DSA/PRA	X	X	X	X	X	X	X	X	X	X	X	X
Mechanistic												
Sample storage	X		X	X	X	X	X	X	X	X	X	X
Clinical Drug Supplies												
Randomize		X										
Tac/CsA level[10]		X	X	X	X	X	X	X	X	X	X	X
Concomitatnt immunosuppression[11]		X	X	X	X	X	X	X	X	X	X	X

6.1

Standard of Care Post-Dialysis																
Visit #	Screen	Initiation of Dialysis	2	3	4	5	6	7	8	9	10	11	12	13	14	15
time points			1mo	2mo	3mo	4mo	5mo	6mo	9mo	12mo	15mo	18mo	21mo	24mo	30mo	36mo
			± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days
Eligibility Assessments																
Informed Consent	X															
Inclusion/Exclusion Criteria	X															
Medical History	X															
Safety Assessments																
Physician Visit	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Signs and Symptoms	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessments	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
EBV/CMV titer																
Neurologic Evaluation	X				X			X		X		X		X	X	X
Efficacy Assessments																
DSA/PRA	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mechanistic																
Sample Storage	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Drug Supplies																
Randomization	X															
Tac/CsA weaning[12]	X															
MMF weaning[13]		X	X													
Prednisone weaning[14]			X	X	X											

Table 6.1

SOE footnotes

[1] Belatacept dose 10 mg/kg IV administered at study day 0, week 2, month 1, 2, 3

[2] Belatacept dose 5 mg/kg IV q month administered beginning study month 4 and continuing through end of study treatment period

[3] Infusion dose based on subject's actual body weight at enrollment and will not be modified during the course of the study unless there is a change of body weight greater than ± 10%

[4] at first dose of belatacept, reduce CNI or mTOR inhibitor dose by 50%

[5] at second dose of belatacept (week 2) discontinue CNI or mTOR inhibitor

[6] Continue concomitant immunosuppression (MMF/MPA/AZA and/or prednisone) at current dose until initiation of dialysis

[7] Decrease MMF/MPA/AZA dose by 50% at initiation of dialysis. Discontinue MMF/MPA/AZA 2 weeks after initiation of dialysis

[8] Reduce prednisone dose by 50% one month after initiation of dialysis, by half again at 2 months after initiation of dialysis. Discontinue prednisone at 3 months after initiation of dialysis

[9] After initiation of hemodialysis, infusion visits will be scheduled on non-dialysis days

[10] Maintain target tacrolimus trough of 3-5 ng/ml (or equivalent CNI or mTOR inhibitor trough) until initiation of dialysis

[11] Continue concomitant immunosuppression (MMF/MPA/AZA and/or prednisone) at current dose until initiation of dialysis

[12] Discontinue CNI or mTOR inhibitor over 5 days after initiation of dialysis

[13] Decrease MMF/MPA/AZA dose by 50% at initiation of dialysis. Discontinue MMF/MPA/AZA 2 weeks after initiation of dialysis

[14] Reduce prednisone dose by 50% one month after initiation of dialysis, by 50% again at 2 months after initiation of dialysis. Discontinue prednisone at 3 months after initiation of dialysis

6.2 Screening Evaluation

Obtain written consent and enroll the subject. Consent will be obtained prior to any change in medical therapy or any procedure performed solely for the purpose of this study.

Review inclusion and exclusion criteria with patient; determine if they remain a candidate for the trial

Obtain a serum or urine pregnancy test

EBV serology done at any previous time point will be accepted for eligibility criteria and will be documented. If serology results are not available then serum will be sent for EBV antibody quantification. Both EBV and CMV viral titers will be checked prior to randomization. If the EBV viral load is positive in an EBV seropositive individual, the subject will have the EBV viral load repeated and the subject may be considered for enrollment when the result is undectable. If CMV titer is positive, the subject will be appropriately treated and reconsidered for enrollment once the viral load is undetectable for >1 month period.

Obtain blood sample for donor specific antibody evaluation and overall allo-antibody levels. Donor specific antibody/anti-HLA antibody will be evaluated using the FlowPRA assay in the Emory University Hospital Clinical HLA Laboratory. The Emory Medical laboratory is a CLIA certified facility. If allo-antibody is detected then antigen specificity will be assessed using single-antigen HLA beads. Results from donor HLA typing will be used to determine if new anti-HLA antibody is donor specific constituting a new DSA.

Obtain a complete medical history and physical examination including a neurologic exam.

Obtain body weight (clothes on, shoes off) and height, measure vital signs (BP, HR, temp, respiration)

All women 50 years or older must have a screening mammogram, or provide results of a screening mammogram performed within the last year. Women of any age who have first degree relatives with a history of breast carcinoma or who have other risk factors of breast carcinoma must undergo increased surveillance for breast cancer according to local practice

Check and record all medications

Obtain baseline laboratory tests including serum Cr and related estimated GFR

6.3 Post-Enrollment/Randomization

Prior to the first treatment time point, confirm all inclusion/exclusion criteria. Randomize when all entry criteria are satisfied. Randomization may take place prior to the first post-screening visit if required due to scheduling constraints.

Obtain vital signs, monitor for any adverse events, check and record any changes in medications immediately prior to first treatment session

For subsequent study assessments see respective charts for either belatacept-treated arm or standard of care group.

If during the course of immunosuppressive withdrawal, the kidney allograft becomes a source of symptoms (swelling, fever, local pain, and/or hematuria) or infection then trial participants will be treated according to standard of care as deemed appropriate by the treating physician including, if appropriate, a limited course of oral or intravenous corticosteroids or if required allograft nephrectomy. Study participants will remain on their treatment protocol (i.e. continue to receive belatacept or wean quickly off the corticosteroid treatment back to no immunosuppression in the standard of care arm). For the purposes of statistical analyses participants will be treated in an intent to treat fashion.

Study participants will have the option to consent for storage of a banked blood sample for future mechanistic assays. If the subject consents to blood for storage, an additional 10 ml sample of blood will be collected at enrollment and every 3 months during pre-dialysis period, upon initiation of dialysis, and every 3 months during post-initiation of dialysis period as noted on the schedule of events.

Banked samples will be stored in the PI's research lab. Samples may remain stored indefinitely. Subjects will have the ability request destruction of samples at any time.

6.4 Study Materials

Bristol-Myers Squibb (BMS) will provide belatacept for this study.

6.5 Safety Assessments

All subjects who are randomized and remain in the study will be evaluated for safety. Safety assessments include monitoring of adverse events, clinically significant changes in vital signs, physical examination, neurologic assessment, or laboratory test abnormalities. The investigator will determine the severity of each adverse event as mild, moderate, severe, or very severe. All adverse events will be documented. In addition the investigator will determine the relationship of the adverse event to the administration of belatacept.

All serious adverse events (SAEs) must be reported as described in Section 7.3.1. All nonserious adverse events must be collected as well and documented according to the procedures of the investigational site. They do not need to be sent to BMS.

If the patient is a WOCBP, pregnancy tests (blood or urine; minimum sensitivity 25 IU/L of HCG) must be performed within 72 hours before the first infusion. If the patient becomes pregnant at any point during the study, she will exit the study and belatacept treatment will be discontinued.

Laboratory tests may be performed as part of routine standard of care as directed by the investigator. Laboratory specimens should be obtained before belatacept infusions. Additional tests may be ordered if deemed necessary for monitoring the patient's safety.

PTLD Safety Surveillance

Specific surveillance for PTLD will be conducted for all subjects in this study. The PTLD safety surveillance should be implemented as soon as IRB/IEC approvals and subject consent are obtained.

Neurologic Examinations

To assess for PTLD, neurologic examinations will be conducted periodically for the duration of the subject's participation in the study. The neurologic history will include the subject's description of any new neurologic symptoms, such as:

- changes in personality
- changes in memory
- headaches
- pain
- seizures
- impairment of consciousness
- difficulty swallowing
- changes in vision, hearing, or language function
- changes in coordination or gait
- weakness
- sensory alterations
- sphincter disturbance, or
- involuntary movements.

In addition, the following will be recorded:

- time course of any new symptoms (onset and duration)
- corroboration of any complaints with other individuals
- medical illnesses, and
- medication use.

The neurologic examination will include assessment of:

- mental status
- gait
- speech
- cranial nerves
- cerebellar function
- sensory function
- motor function.

Any new or worsening findings should be reported as adverse events and evaluated with a follow up neurologic examination, additional modalities, and/or neurologic consultation as appropriate.

EBV Titers

Subjects receiving belatacept who are on dialysis will have samples sent for EBV viral titers periodically for the duration of the study. Positive titers will be confirmed and subjects will exit the study and belatacept treatment will be discontinued if they have persistent positive titers. Again only patients who are seropositive for EBV will be enrolled in the study.

Subjects with Suspected PTLD

CNS imaging and/or neurologic consultation should be considered for any subject with a new or worsening neurologic finding. For subjects who undergo biopsy for suspicion of PTLD, the biopsy specimen will be evaluated for CD3, CD20, CD79 and EBER. Management of belatacept and other immunosuppressants in subjects with suspected PTLD should be discussed with the BMS Medical Monitor. BMS should be informed of all confirmed cases of PTLD.

6.6 Efficacy Assessments

6.6.1 Primary Efficacy Assessment

The primary endpoint is the incidence of donor-specific allo-antibody formation in patients treated with belatacept vs standard of care arm. Serum samples from study subjects will be evaluated periodically (see table 6.1) for the presence of donor-specific alloantibody using standard flow cytometric techniques.

6.6.2 Secondary Efficacy Assessments

Secondary endpoints will include assessment of renal function including estimated GFR and rate of change in GFR, the need for and time to initiation of dialysis, the overall level of alloantibody as indicated by PRA and the incidence of infectious complications. GFR will be calculated based upon serum creatinine using the Diet in Renal Disease (study) formula as suggested by Levey et al. Subjects already requiring initiation of dialysis at

the time of enrollment will be excluded from the need for and time to initiation of dialysis analysis.

$$GFR=170 \times (SCr/0.95)^{(-0.999)} \times (Age)^{(-0.176)} \times (0.762 \text{ if the patient is female}) \times (1.180 \text{ if the patient is black}) \times (BUN)^{(-0.170)} \times (Alb)^{(0.318)}$$

GFR-glomerular filtration rate (ml/min), SCr-serum creatinine (mg/dL), Age in years, BUN- blood urea nitrogen (mg/dL), Alb-serum albumin (g/dL)

Laboratory efficacy parameters will be evaluated utilizing the main laboratory results

7 ADVERSE EVENT REPORTING

7.1 Adverse Events

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

7.1.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (eg, medical, surgical) to prevent one of the other serious

outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

All pregnancies, regardless of outcome, must be reported to BMS, **including pregnancies that occur in the female partner of a male study subject. <u>All</u> pregnancies must be followed to outcome.** See Section 7.6 for instructions on reporting pregnancies.

Although overdose and cancer are not always serious by regulatory definition, these events should also be reported to BMS.

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

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. 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 (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

7.1.2 Nonserious Adverse Events

Nonserious adverse events are all adverse events that are not classified as SAEs.

7.2 Assignment of Adverse Event Intensity and Relationship to Investigational Product

All adverse events, including those that are serious, will be graded by the physician investigator as follows:

- Mild (Grade 1): awareness of event but easily tolerated

- Moderate (Grade 2): discomfort enough to cause some interference with usual activity
- Severe (Grade 3): inability to carry out usual activity
- Very Severe (Grade 4): debilitating; significantly incapacitates subject despite symptomatic therapy.

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used:

- **Related:** There is a reasonable causal relationship to investigational product administration and the adverse event.
- **Not Related:** There is not a reasonable causal relationship to investigational product administration and the adverse event.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

7.3 Collection and Reporting

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

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the event was administered, it should be recorded in the medical record. The investigator must supply BMS and the IRB/IEC with any additional information requested, notably for reported deaths of subjects.

7.3.1 Serious Adverse Events

Following the randomization of the subject, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. Collection of all SAEs must continue for **8 weeks** after the last administration of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should notify BMS of any SAE occurring

after this time period that is believed to be related to the investigational product or protocol-specified procedure.

All SAEs, whether considered related or unrelated to belatacept, must be reported to BMS (by the investigator or designee) within 24 hours of study personnel becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

All SAEs should be faxed or emailed to BMS at:

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

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

MedWatch SAE forms should be sent to the FDA at:

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

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

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

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

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent immediately to BMS. As follow-up information becomes available it should be sent immediately using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

7.3.2 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union, an event meeting these criteria is termed a Suspected Unexpected Serious Adverse Reaction (SUSAR). BMS will send investigators an expedited safety report (ESR) to notify them of such an event.

Other important findings that BMS may report as ESRs include increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety findings from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or the decision by BMS to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, BMS will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, BMS will report suspected serious adverse reactions (whether expected or unexpected) to the relevant health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

7.3.3 Nonserious Adverse Events

The collection of nonserious adverse event (NSAE) information will begin at randomization. This NSAE information will also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

All identified NSAEs will be recorded and described in the medical record. If an ongoing NSAE worsens in its intensity, or if its relationship to the investigational product changes, a new NSAE entry for the event should be completed. NSAEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for NSAEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with NSAEs at study completion should receive post-treatment follow-up as appropriate.

7.4 Laboratory Test Abnormalities

All laboratory test values captured during treatment must be documented appropriately, including the following:

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

When reporting laboratory abnormalities, the clinical term rather than the laboratory term should be used by the reporter (eg, document “anemia,” not “low hemoglobin value”).

7.5 Overdose

An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

7.6 Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in such a manner that the risk of failure is minimized. (See Section 4.2.1 for the definition of WOCBP.) Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and of the potential risk factors for an unintentional pregnancy.

7.6.1 Requirements for Pregnancy Testing

All WOCBP MUST have a negative pregnancy test within 72 hours before receiving belatacept. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive Belatacept and must not continue in the study.

In addition, all WOCBP must be instructed to contact the investigator and/or other study personnel immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.

7.6.2 Reporting of Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during 8 weeks after administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify BMS of this event and record the pregnancy on the Pregnancy Surveillance Form (not on an SAE form). Initial information on a pregnancy must be reported immediately to BMS, and information on the outcome provided once it is available. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures.

Note: Any pregnancy that occurs in a female partner of a male study subject must be reported.

Protocol-required procedures for study discontinuation and follow-up must be performed for the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate

pregnancy follow-up procedures should be considered if indicated. Information regarding the course of the pregnancy, including perinatal and neonatal outcome, must be reported.

7.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded in the medical record.

Subjects who prematurely withdraw or are terminated from study participation, for reasons other than withdrawal if consent, will be asked to continue in a reduced safety follow-up schedule. The study team will contact the patient every 3 months for the duration of the trial to assess patient survival, dialysis status, and serious adverse event occurrences.

7.8 Influenza Guidelines

Per current CDC influenza recommendations for persons with immunosuppression, including those caused by medications, subjects should be counseled to obtain influenza vaccination in accordance with CDC guidelines (http://www.cdc.gov/flu/professionals/vaccination/index.htm).
In addition, they will be advised to promptly contact a healthcare provider upon onset of any fevers or flu like symptoms in order to determine whether early or empirical antiviral therapy is indicated in accordance with CDC guidelines (http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm).

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

This is a single-center, randomized, controlled trial to evaluate the efficacy of belatacept to prevent the formation of donor-specific antibody in patients with a failing renal allograft thereby preventing sensitization and facilitating re-transplantation. Based on clinical and statistical judgment, it is anticipated that a sample size of 36 patients per group will provide valuable preliminary data to assess the impact of belatacept on this growing population of patients.

The sample size for each arm will be 36 patients (Phase I 18 patients in each arm, Phase II 18 patients in each arm, total for each phase 36 patients). From previous work it is assumed that the control arm will have about 60% of patients developing antibodies within a 3 year period. (unpublished results, analysis of patients at Emory Hospital) It is proposed that the group treated with belatacept will have a dramatic decrease in allo-antibody production. Assuming a rate of 20% in the treatment group, the power would be calculated at 90%.

8.2 Endpoint Definitions

Primary Endpoint: The rate of donor-specific antibody formation 36 months following randomization.

Secondary Endpoints:

-Rate of change in GFR

-Time to dialysis measured from the time of randomization to initiation of dialysis

- Overall level of alloantibody as indicated by PRA.

- Incidence of infectious complications.

8.3 Analyses

8.3.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics of subjects will be summarized descriptively by means and standard deviations for continuous variables and frequency distribution for categorical variables. Summaries will be performed based on all randomized subjects.

8.3.2 Safety Analyses

All adverse events and serious adverse events will be summarized by treatment group. Serious adverse events will be collected and summarized following the subject's written consent to participate in the study. Non-serious adverse events will be collected and summarized beginning at the time of randomization. Laboratory abnormalities will be descriptively summarized.

8.3.3 Efficacy Analyses

There will be two main methods of analyzing the primary outcome at the study end. One will be a chi-squared test comparing the proportion of patients who developed donor specific antibodies in each study group. The second analysis will be a log-rank test comparing the Kaplan-Meier time to event curves between the two study groups. In both cases we will use a two-sided test with a significance level of 0.05.

The sample size for each arm will be 36 patients. This sample size calculation is based on several assumptions. We assume that the incidence of developing donor-specific antibody among the control group is 60% and among the belatacept-treated group it is 20% or less. We also assume an alpha level of 0.05 and corresponding Z-alpha = 1.96 and a one-to-one ration of exposed to unexposed subjects. Calculations with these estimates yield a power of 90% to detect a three-fold difference in risk of developing donor specific antibodies between the control and belatacept-treated group.

In addition to the aforementioned assumptions, additional assumptions required for the log-rank test include no loss to follow-up in 36 months and that the distribution of the incidence of the primary endpoint follows an exponential distribution. Assuming an incidence of development of anti-donor antibody in the control group is 60% at 36 months then the hazard rate can be calculated as 0.02545. In the treatment arm, if the incidence of the primary endpoint is 30% then the hazard ratio becomes 0.0099 and if the incidence is 20% then the hazard rate is 0.00619.

Analysis of secondary endpoints will be performed at the end of the study period. Differences in the mean level of allo-antibody (ie PRA) by control and belatacept-treated groups will be compared using a t-test statistic. The rate of decline of GFR among the belatacept group will be compared to the rate of decline of the control group using a Rate Ratio and corresponding 95% Confidence Intervals using the Mantel-Haenszel chi-square test statistic for significance. The time from randomization to initiation of dialysis will be compared between groups using Kaplan-Meier analysis and the log-rank test for significance. The small subset of subjects already requiring dialysis at the time of enrollment will be excluded from this analysis. The incidence of overall infectious episodes will be compared among the belatacept vs. control group by calculating a Risk Ratio and corresponding 95% Confidence Intervals and using the Mantel-Haenszel chi-

square test statistic for significance. For all secondary endpoint analyses, two-tailed p <0.05 will be considered statistically significant.

Interim analyses will be performed at 18 months to compare the primary endpoint between the belatacept-treated and control groups, using the log-rank test for significance. A two-sided test with a more stringent significance level of 0.001 will be used to preserve the overall significance level of the trial.

9 ADMINISTRATIVE SECTION

9.1 Compliance with the Protocol

The study must be conducted as described in the final IRB/IEC-approved protocol. Documentation of approval, signed by the IRB/IEC chairperson or designee, will be sent to the BMS protocol manager.

All protocol amendments and revisions to the informed consent will be submitted to the BMS protocol manager and to the IRB/IEC. No protocol amendments will be implemented until written approval has been given by the IRB/IEC, except when necessary to eliminate an immediate hazard to study subjects. Administrative letters should also be sent to the BMS protocol manager and IRB/IEC; however, they do not require approval.

If a protocol amendment mandates a revision to the informed consent, the revised consent must be used to obtain consent from subjects currently enrolled in the study if it affects them (eg, if it contains new information regarding safety), and the revised consent must be used to obtain consent from new subjects before enrollment.

9.2 Records Retention

The investigator will retain, in a confidential manner, all data pertinent to the study for all treated subjects as well as those entered as control subjects. The investigator will retain source documents and accurate case histories that record all observations and other data pertinent to the investigation (eg, the medical record) for the maximum period required by applicable regulations and guidelines or following institutional procedures. If the investigator withdraws from the study (eg, relocation or retirement), the records will be transferred to a mutually agreed upon designee, such as another investigator or an IRB. Written documentation of such transfer will be provided to BMS.

The investigator will ensure that a current record of disposition of investigational product is maintained at each study site where the investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number and use date or expiry date
- dates and initials of person responsible for each inventory entry/movement
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted, broken), and
- amount destroyed at study site.

9.3 Destruction of Investigational Product

If the investigational product is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor to be related to the investigational product
Expedited Safety Report	Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure), or that could be associated with the study procedures.
SUSAR	Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC).
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

AE	Adverse Event
APC	Antigen Presenting Cell
AUC	Area Under the Concentration-Time Curve
AUD(0-T)	Area Under the Concentration-Time Curve from time zero to the time of the last quantifiable concentration
AUC(INF)	Area Under the Concentration-Time Curve from time zero extrapolated to infinity
AUC(TAU)	Area Under the Concentration-Time Curve in 1 dosing interval
AZA	Azathioprine (Imuran)
BMS	Bristol-Myers Squibb
BPAR	Biopsy-Proven Acute Rejections
CLT	Total Body Clearance
Cmax	Maximum Plasma Concentration
CTCAE	Common Terminology Criteria for Adverse Events
CsA	Cyclosporine
CSBPAR	Clinically-Suspected and Biopsy-Proven Acute Rejection
D5W	5% Dextrose for Injection
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IST	Investigator-Sponsored Trial
LI	Less Intensive
LTE	Long Term Extension
MI	More Intensive
MMF	Mycophenolate Mofetil (Cellcept)
MPA	Mycophenolic Acid (Myfortic)
NCI	National Cancer Institute
NS	Normal Saline

NSAE	Non-Serious Adverse Event
PK	Pharmacokinetics
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWFI	Sterile Water for Injection
T-HALF	Half-Life
VNS	Vial, Needle, Syringe
VSS	Steady-State Volume of Distribution
WOCBP	Women of Child-Bearing Potential

12 REFERENCES

1 Study No. 98642: BMS-224818: Single-dose intravenous toxicity and toxicokinetics study in monkeys. Bristol Myers Squibb Pharmaceutical Research Institute; 1998. Document Control No. 910069252.

2 Study No. 98699: BMS-224818: One-month intermittent-dose intravenous toxicity and toxicokinetics study in monkeys. Bristol Myers Squibb Pharmaceutical Research Institute; 1999. Document Control No. 910056595.

3 Study No. 99655 Amended Report: BMS-224818: Six month intermittent-dose intravenous toxicity and toxicokinetics study in monkeys. Bristol Myers Squibb Pharmaceutical Research Institute; 2004. Document Control No. 920007203.

4 Dodge R and Abraham R. Review of historical in vitro potency and binding data for BMS-224818 (LEA29Y) in murine cells and to murine B7 molecules. Bristol-Myers Squibb Pharmaceutical Research Institute; 2004. Document Control No. 930023829.

5 Study No. DS02008: BMS-188667: One-year intermittent-dose intravenous toxicity and toxicokinetic study in monkeys, Bristol Myers Squibb Pharmaceutical Research Institute; 2004. Document Control No. 930002781.

6 Study Nos. 092804klh, 102704klh, and 020805klh: Efficacy comparison of abatacept and belatacept in murine primary immune response model. Bristol-Myers Squibb Pharmaceutical Research Institute; Document Control No. 930019020.

7 Study No. DS04256: Belatacept and abatacept: Two-week intermittent-dose intravenous exploratory study in rats. Bristol Myers Squibb Pharmaceutical Research Institute; 2005. Document Control No. 930009642.

8 Study DS04284: Belatacept (BMS-224818) and abatacept (BMS 188667): Two week intermittent-dose intravenous exploratory bioactivity and pharmacokinetics study in rats. Bristol-Myers Squibb Pharmaceutical Research Institute; 2005. Document Control No. 930013223.

[9] Study No. DS05055: Belatacept (BMS-224818) and BMS 188667 (abatacept): Two-week intermittent dose intravenous exploratory bioactivity and pharmacokinetics study in rats. Bristol-Myers Squibb Pharmaceutical Research Institute; 2006. Document Control No. 930015077.

[10] Study No. DS04252: BMS-224818 and abatacept: Two week intermittent-dose intravenous exploratory study in female rabbits. Bristol-Myers Squibb Pharmaceutical Research Institute; 2005. Document Control No. 930009600.

[11] Study No. DS04287: Belatacept and abatacept: Two week intermittent-dose intravenous exploratory bioactivity and pharmacokinetics study in female rabbits. Bristol-Myers Squibb Pharmaceutical Research Institute; 2006. Document Control No. 930013910.

[12] Study No. 96633 Amended Report: BMS-188667: Six month intermittent-dose (qw x 26) subcutaneous toxicity study in mice. Bristol Myers Squibb Pharmaceutical Research Institute; 2004. Document Control No. 910066124.

[13] Study No. DS02008: BMS-188667: One-year intermittent-dose intravenous toxicity and toxicokinetic study in monkeys, Bristol Myers Squibb Pharmaceutical Research Institute; 2004. Document Control No. 930002781.

[14] Study IM103001: A phase I, randomized, double blind, placebo controlled study to assess the safety, pharmacokinetics, and immunogenicity of escalating doses of BMS 224818 given as a single intravenous infusion to healthy subjects. Clinical study report. Bristol Myers Squibb Pharmaceutical Research Institute; 2006. Document Control No. 930017678.

[15] Study IM103029: A study to assess the pharmacokinetics, safety, and immunogenicity of single doses of belatacept (BMS-224818) administered subcutaneously to healthy subjects. Executive summary. Bristol Myers Squibb Pharmaceutical Research Institute; 2006. Document Control No. 930018069.

[16] Study IM103002: A pilot, multi center, randomized, double-blind, placebo controlled study to evaluate the safety, preliminary clinical activity and immunogenicity of multiple doses of BMS 188667 and BMS 224818 administered intravenously to subjects with rheumatoid arthritis. Clinical study report. Bristol Myers Squibb Pharmaceutical Research Institute; 2004. Document Control No. 930001816.

[17] Study IM103024: Study to compare the pharmacokinetics of phase III process C belatacept (BMS 224818) to phase II process B belatacept in healthy subjects. Clinical study report. Bristol Myers Squibb Pharmaceutical Research Institute; 2006. Document Control No. 930018756.

[18] Study IM103100: Open-label randomized, controlled, multiple dose study of efficacy and safety of BMS 224818 as part of a quadruple drug regimen in renal transplant recipients. Clinical study report (12-month analysis). Bristol Myers Squibb Pharmaceutical Research Institute; 2006. Document Control No. 930016865.

Appendix 1: DSMB Charter

Belatacept Therapy for the Failing Renal Allograft (Protocol IM103-133)

Dr. Idelberto R. Badell, M.D., Principal Investigator
Emory University

The Data Safety Monitoring Board (DSMB) will act in an advisory capacity to monitor patient safety and evaluate the efficacy of the intervention. Dr. Idelberto R. Badell, Emory University, Atlanta, GA is conducting a clinical trial entitled, Belatacept Therapy for the Failing Renal Allograft (Protocol IM103-133).

At periodic intervals as described in the study protocol, the DSMB responsibilities are to:

- review the research protocol, informed consent documents and plans for data safety and monitoring;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, 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 clinical center performance, make recommendations and assist in the resolution of problems reported by the PI;
- protect the safety of the study participants;
- report on the safety and progress of the trial;
- make recommendations to the the PI, and, if required, to the FDA concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- if appropriate, conduct interim analysis of efficacy;
- ensure the confidentiality of the trial data and the results of monitoring

MEMBERSHIP

The Data Safety Monitoring Board will consist of 3 members. Two members will constitute a quorum. Membership consists of persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. The DSMB includes experts in or representatives of the fields of:

- Transplant Surgery,
- Transplant Nephrology
- General nephrology
- Department of Pathology and Laboratory Medicine

Dr. Avinash Agarwal, University of Virginia has been selected to serve as the chairperson. He is responsible for overseeing the meetings, developing the agenda in consultation with the PI. The chair is the contact person for the DSMB.

Board Process

The first review of data by the DMC will occur either after 10 subjects have been enrolled and randomized or approximately 6 months after the first subject is enrolled, whichever comes first. The second review of the data by the DMC will occur either after 30 subjects have been enrolled or 6 months after the first patient is enrolled, whichever comes first. Subsequent reviews of data by the DMC will occur every 3 months during the remainder of the first year and approximately every 6 months thereafter.

Meetings will be conducted via teleconference and scheduled/coordinated by the site study team. Meetings will be attended by the principal investigator and members of his/her staff. An emergency meeting of the DSMB may be called at any time at the request of the PI or the DMC Chairperson should questions of patient safety arise.

REPORTS

Interim Reports. Interim reports will be prepared by the study team and distributed to the DSMB at least 3 business days prior to a scheduled meeting. Additions and modifications to the content of the reports may be directed by the DSMB. Interim data reports generally consist of two parts. Part 1 provides information on study aspects such as accrual, baseline characteristics, and other general information on study status. Part 2 may contain data on study outcomes, including safety data and depending on the study, perhaps efficacy data. Reports are considered confidential. Data files to be used for interim

analyses should have undergone established editing procedures to the extent possible. Interim analyses of efficacy data are performed only if they are specified and approved in advance and criteria for possible stopping is clearly defined.

Reports from the DSMB. A formal report from the Chair will be sent to the full DSMB within 3 weeks of the meeting. Once approved by the DSMB, the Chair will forward the approved minutes to the PI within 6 weeks of each meeting.

Each report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. The Chair should transmit such a recommendation to the PI as rapidly as possible, by immediate telephone if sufficiently urgent. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. The report should not include unblinded data, discussion of the unblinded data, etc.

Mailings to the DSMB: On a scheduled basis (as agreed upon by the DSMB) blinded safety data should be communicated to all DSMB members. Any concerns noted should be brought to the attention of the Chair who will take appropriate action.

Access to Interim Data: Access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to interim data to the DSMB members relieves the investigator of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry and/or evaluation.

CONFIDENTIALITY

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

DSMB Membership

Chair:

Avinash Agarwal, MD
Assistant Professor of Surgery
University of Virginia

Membership:

Colleen S. Kraft, MD, MSc
Associate Professor, Department of Pathology and Laboratory Medicine
Associate Professor, Division of Infectious Diseases
Emory University Hospital

Wasim A. Dar, MD, PhD
Assistant Professor of Surgery
McGovern Medical School University of Texas Houston