Belatacept (Nulojix™)

National Drug Monograph

April 2012

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

Belatacept received FDA-approval in June 2011 for prophylaxis of organ rejection concomitantly with basiliximab, mycophenolate, and corticosteroids in Epstein-Barr virus (EBV) seropositive kidney transplant recipients.

Belatacept is a first-in-class intravenous biologic for primary maintenance of immunosuppression in de novo kidney transplant recipients. It is a selective co-stimulation blocker that binds to a specific site on certain cells of the immune system (i.e., antigen presenting cells) to block the second signal necessary to activate naïve T-cells, which coordinate immune-mediated rejection of transplanted organs.

Belatacept plus mycophenolate mofetil or belatacept plus sirolimus provided primary immunosuppression with acceptable rates of acute rejection, improved renal function compared to a tacrolimus based regimen, and may avoid the need for calcineurin inhibitors and corticosteroids.

Belatacept demonstrates a favorable cardiovascular and metabolic adverse event profile. In comparison to cyclosporine based regimens, belatacept treated patients had statistically significant lower mean blood pressures, lower elevations of non-HDL cholesterol and triglycerides and a lower incidence of new onset diabetes

Common adverse effects with belatacept include anemia, neutropenia, diarrhea, headache and peripheral edema.

Belatacept has been associated with an increased risk for the development of posttransplantation lymphoproliferative disorders (PTLD), occurring most commonly in the first 18 months post transplant. For this reason, belatacept should only be used in patients who are EBV seropositive.

There is a significant increased cost for belatacept containing regimens over current standards of cyclosporine or tacrolimus therapy. Drug acquisition costs are higher and must be added to the monthly cost of an infusion center. Additionally, travel to the transplant center or fee based infusion center would need to be added where applicable.

Introduction

The purposes of this monograph are to 1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating belatacept (Nulojix) for possible addition to the VA National Formulary; 2) define its role in therapy; and 3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Mechanism of action

Belatacept is a human fusion protein combining a modified extracellular portion of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) with the constant-region fragment (Fc) of human IgG1 which acts as a selective T-cell costimulation blocker by binding to the CD80 and CD86 receptors on antigen presenting cells, thereby antagonizing CD28 (12). Activation of CD28, in conjunction with CD3 activation, results in the production of the three-signal transduction pathways: the calcium-calcineurin pathway, the RAS-mitogen-activated protein (MAP) kinase, and nuclear factor–κβ pathway (13). CD28 also promotes prolonged survival of immune cells, prepares cellular pathways for increased metabolic demand related to clonal expansion and substantially increases

cytokine release. Belatacept's antagonistic effect on CD28 results in the inability to produce effector cytokines, such as interleukin (IL)-2, and results in inhibition of T-cell activation.

Pharmacology

Belatacept is a more potent, second-generation molecule of its parent compound, abatacept (Orencia). Abatacept is a biologic that also has antagonistic effects on CD80 and CD86 and has been approved by the FDA for the treatment of moderate to severe rheumatoid arthritis (14). Abatacept lacked potency for solid organ transplantation because of its relatively weak affinity for CD86. This led to the development of belatacept which has shown a 10-fold increase in inhibiting T-cell activation when compared with abatacept in vitro (9).

It was determined that CD80 and CD86 receptors become saturated through a concentration-dependent pathway. The CD80 saturation occurs at a much lower level, 0.1 µg/ml, whereas complete CD86 saturation requires a 10-fold increase in concentration to occur (1.0 µg/ml). Latek et al, suggested that alloresponse would be appropriately inhibited only at the concentrations required to saturate CD86. These results suggest that measurements of CD86 occupancy by the belatacept molecule may be an appropriate measurement of immune inhibition and the pharmacodynamic effect of the drug on a patient-by-patient basis in the future (15).

Pharmacokinetics (PK)[16]

Belatacept is administered intravenously and its absolute bioavailability is 100%. Its pharmacokinetics were determined to be linear, with zero order intravenous infusion and first-order elimination with the standard dose range of 5–10 mg/kg. Exposure is dose proportional with low day-to-day variability. Greater than 80% of kidney transplant recipients who received the low intensity regimen achieved the target C_{min} as predicted in Phase 3 trials, BENEFIT and BENEFIT-EXT (10,11), at all periods post-transplantation. Exposure ($C_{min,}$ the minimum concentration required to saturate CD86) to belatacept was consistently maintained as predicted for up to 5 years post-transplantation with a constant maintenance dose of 5 mg/kg. Belatacept binds CD86 in a predictable, concentration-dependent manner: CD86 receptor occupancy decreased from 94% at Day 5 to 65% at Month 12 as belatacept C_{min} decreased from 35 to 4 µg/mL. In a 5 year follow-up study, trough samples from patients who were receiving 4-week belatacept showed significantly higher saturation of CD86 receptors than samples from patients who were receiving 8-week belatacept (74 versus 56%; $P < 0.05$) supporting the use of the 4 week dosing regimen (17).Population PK analyses show that intrinsic and extrinsic factors, such as gender, race, age, kidney function, serum albumin, diabetic condition, and concomitant dialysis do not affect belatacept exposure and a full dose can be given on the day of transplantation. Because of an increased time to clearance and volume of central compartment as patient weight increases, belatacept is dosed based on total body weight (18). No studies were conducted to evaluate the metabolism and metabolic pathways of belatacept in animals since belatacept consists of amino acids.

Table 1: Pharmacokinetics of Belatacept in Patients with IV Infusions over 30 Minutes[19]

Parameter (Mean±SD [Range])	Healthy Subjects (After 10 mg/kg Single Dose) N = 15	Kidney Transplant Patients (After 10 mg/kg Multiple Doses) N = 10	Kidney Transplant Patients (After 5 mg/kg Multiple Doses) N = 14
C_{max} [µg/mL]	300±77 (190-492)	247±68 (161-340)	139±28 (80-176)
AUC* [µg•h/mL]	26398±5175 (18964-40684)	22252±7868 (13575-42144)	14090±3860 (7906-20510)
$t_{1/2}$ [days]	9.8±2.8 (6.4-15.6)	9.8±3.2 (6.1-15.1)	8.2±2.4 (3.1-11.9)
CL [mL/h/kg]	0.39±0.07 (0.25-0.53)	0.49±0.13 (0.23-0.70)	0.51±0.14 (0.33-0.75)
V_{ss} [L/kg]	0.09±0.02 (0.07-0.15)	0.11±0.03 (0.067-0.17)	0.12±0.03 (0.09-0.17)

* AUC=AUC (INF) after single dose and AUC (TAU) after multiple dose, where TAU=4 weeks.

FDA Approved Indication

Belatacept received FDA-approval in June 2011 for prophylaxis of organ rejection concomitantly with basiliximab, mycophenolate, and corticosteroids in Epstein-Barr virus (EBV) seropositive kidney transplant recipients.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Prophylaxis of organ rejection concomitantly with thymoglobulin, mycophenolate, and corticosteroids in Epstein-Barr virus (EBV) seropositive kidney transplant recipients. Use in other solid organ types than kidney does not have sufficient evidence to recommend use. Additionally, use in liver transplant recipients has demonstrated in clinical trials for liver transplantation, belatacept was associated with a higher rate of graft loss and death compared to the tacrolimus control arms.

Current VA National Formulary Alternatives

Belatacept is first-in-class intravenous biologic for primary maintenance of immunosuppression in de novo kidney transplant recipients. Formulary agents approved for maintenance therapy include tacrolimus, cyclosporine, mycophenolate mofetil, mycophenolate sodium, sirolimus, and azathioprine.

Dosage and Administration

The route of administration for belatacept is distinctive in that it is the first long-term intravenous maintenance therapy for solid organ transplantation.

Table 2: Dosing[a] of Belatacept for Kidney Transplant Recipients[19]

Dosing for Initial Phase	**Dose**
Day 1 (day of transplantation, prior to implantation) Day 5 (approximately 96 hours after Day 1 dose)	10 mg/kg
End of Week 2 and Week 4 after transplantation	10 mg/kg
End of Week 8 and Week 12 after transplantation	10 mg/kg
Dosing for Maintenance Phase	
End of Week 16 after transplantation and every 4 weeks (plus or minus 3 days) thereafter	5 mg/kg

[a]The dose prescribed for the patient must be evenly divisible by 12.5 mg

The total infusion dose should be based on the actual body weight of the patient at the time of transplantation, and should not be modified during the course of therapy, unless there is a change in body weight of greater than 10%. The prescribed dose must be evenly divisible by 12.5 mg in order for the dose to be prepared accurately using the reconstituted solution and the silicone-free disposable syringe provided.

Caution: Belatacept must be reconstituted/prepared using only the silicone-free disposable syringe provided with each vial. If the silicone-free disposable syringe is dropped or becomes contaminated, use a new silicone-free disposable syringe from inventory.

No dose adjustments based on gender, race, age, kidney function, liver function, serum albumin, diabetic condition, and concomitant dialysis.

Preparation for Administration

1) Calculate the number of vials required to provide the total infusion dose. Each vial contains 250 mg of belatacept lyophilized powder.

2) Reconstitute the contents of each vial with 10.5 mL of a suitable diluent using the *silicone-free disposable syringe* provided with each vial and an 18- to 21-gauge needle. Suitable diluents include: sterile water for injection (SWFI), 0.9% sodium chloride (NS), or 5% dextrose in water (D5W).

Note: If the powder is accidentally reconstituted using a different syringe than the one provided, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes.

3) To reconstitute the powder, remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of diluent (10.5 mL of SWFI, NS, or D5W) to the glass wall of the vial.

4) To minimize foam formation, rotate the vial and invert with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. Do not shake.

5) The reconstituted solution contains a belatacept concentration of 25 mg/mL and should be clear to slightly opalescent and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.

6) Calculate the total volume of the reconstituted 25 mg/mL solution required to provide the total infusion dose.

   Volume of 25 mg/mL belatacept solution (in mL) = Prescribed Dose (in mg) ÷ 25 mg/mL

7) Prior to intravenous infusion, the required volume of the reconstituted solution must be further diluted with a suitable infusion fluid (NS or D5W). Should be reconstituted with:
   - SWFI should be further diluted with either NS or D5W
   - NS should be further diluted with NS
   - D5W should be further diluted with D5W

8) From the appropriate size infusion container, withdraw a volume of infusion fluid that is equal to the volume of the reconstituted solution required to provide the prescribed dose. With the same *silicone-free disposable syringe* used for reconstitution, withdraw the required amount of belatacept solution from the vial, inject it into the infusion container, and gently rotate the infusion container to ensure mixing.

   The final belatacept concentration in the infusion container should range from 2 mg/mL to 10 mg/mL. Typically, an infusion volume of 100 mL will be appropriate for most patients and doses, but total infusion volumes ranging from 50 mL to 250 mL may be used. Any unused solution remaining in the vials must be discarded.

9) Prior to administration, the infusion should be inspected visually for particulate matter and discoloration. Discard the infusion if any particulate matter or discoloration is observed.

10) The entire infusion should be administered over a period of 30 minutes and must be administered with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (with a pore size of 0.2-1.2 µm).

    - The reconstituted solution should be transferred from the vial to the infusion bag or bottle immediately. The infusion must be completed within 24 hours of reconstitution of the lyophilized powder. If not used immediately, the infusion solution may be stored under refrigeration conditions: 2º-8ºC (36º-46ºF) and protected from light for up to 24 hours (a maximum of 4 hours of the total 24 hours can be at room temperature: 20°-25°C [68°-77°F] and room light).

    - Infuse in a separate line from other concomitantly infused agents. Should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of belatacept with other agents

REMS Program

Belatacept) was approved with a Risk Evaluation and Mitigation Strategy (REMS). The REMS consists of a medication guide and communication plan. Additionally, the ENLiST registry is designed to provide long term follow up of patients initiated on belatacept and will be used to monitor any safety signals which develop. This registry is not a requirement; patients can be treated without registry participation. Materials concerning the ordering process for belatacept can be found on the National PBM Intranet website. Belatacept Special Handling Instructions.

Efficacy Measures

Many measures are used to demonstrate efficacy in the kidney transplant population. They include but are not limited to:

- Patient survival
- Graft loss
- Delayed graft function (DGF)
- Need for dialysis
- Graft rejection (preferably biopsy proven, though it could be based on clinical and laboratory criteria) which may be defined by subcategories:
    - Acute rejection
    - Chronic rejection
- Reported use of rejection treatment (corticosteroids, anti-thymocyte globulin)
- Kidney impairment such as measured and/or calculated glomerular filtration rate (GFR)

Summary of efficacy and clinical trial findings

Phase III trial, the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) – Year 1, 2 and 3 results[10,20,21]

Vincenti et al. evaluated the efficacy and safety of two belatacept-based maintenance regimens with a cyclosporine-based regimen in a 3-year, randomized, active-controlled, parallel-group, multicenter study.

Table 3: Inclusion and Exclusion Criteria Used in the BENEFIT Trial

Inclusion Criteria	Exclusion Criteria
• Age ≥ 18 years of age • Receiving a living donor or standard criteria deceased donor kidney transplant • Anticipated cold ischemia time of <24h	• Recipients of extended criteria kidneys: ▪ donors ≥60 years old ▪ donors ≥50 years old who had at least two other risk factors (cerebrovascular accident, hypertension and serum creatinine >1.5 mg/dL) ▪ anticipated cold ischemia time of ≥24 h ▪ donation after cardiac death • Prior or concurrent nonrenal solid organ transplants • First-time patients with a panel reactive antibody ≥50% • Retransplants with a panel reactive antibody ≥30%

Patients were randomly assigned to a more intensive (MI) belatacept regimen, a less intensive (LI) belatacept regimen, or a cyclosporine-based regimen in a 1:1:1 ratio. All patients included in the analysis received induction therapy with intravenous basiliximab 20 mg on postoperative days 0 and 4, mycophenolate mofetil 2 g/day, and corticosteroids 500 mg on postoperative day 0, tapered to a minimum of 2.5 mg/day by postoperative day 15. The study was blinded to patients and study personnel with respect to belatacept dose regimen assignment and open-label with respect to allocation to belatacept or cyclosporine, primarily due to the need for therapeutic dose monitoring in cyclosporine-treated patients. T-cell-depleting therapy was permitted in patients treated with cyclosporine who experienced impaired allograft function or were anticipated to experience delayed graft function

after transplantation. Patients with acute rejection ≤Grade IIA (Banff '97 classification) were treated with corticosteroids, while patients with acute rejection ≥Grade IIB could be treated with T-cell-depleting therapy at the investigator's discretion. The protocol recommended antiviral prophylaxis to all patients for at least 3 months post-transplant, and for 3 months upon initiating T-cell-depleting agents, as well as 6 months of prophylaxis against pneumocystis.

Table 4: Dosing Regimen in the BENEFIT Trial

Belatacept MI (n=219)	Belatacept LI (n=226)	Cyclosporine (n=221)
Months 0 – 3 10 mg/kg Days 1, 5 Weeks 2,4,6,8,10,12	Months 0 – 1 10 mg/kg Days 1, 5 Weeks 2, 4	Initial Daily Dose 4 – 10 mg/kg
Months 4 – 6 10 mg/kg Weeks 16,20,24	Months 2 – 3 10 mg/kg Weeks 8, 12	Months 0 – 1 Dose adjusted to 150-300 ng/mL
Months 7 – 36 5 mg/kg Every 4 weeks	Months 4 – 36 5 mg/kg Every 4 weeks	Months 2 – 36 Dose adjusted to 100-250 ng/mL

There were three co-primary outcomes at 12 months: 1) composite patient and graft survival, 2) composite kidney impairment endpoint and 3) incidence of acute rejection. The composite kidney impairment endpoint was defined as the percent of patients exhibiting a measured GFR <60 mL/min/1.73 m^2 at Month 12 or a decrease in measured GFR ≥10 mL/min/1.73 m^2 from Month 3 to Month 12. The endpoint of acute rejection was defined as histologically confirmed rejection as determined by the central pathologist, in which there were protocol-defined reasons for clinical suspicion of rejection (unexplained rise of serum creatinine ≥25% from baseline, unexplained decrease in urine output; fever and graft tenderness or serum creatinine that remains elevated within 14 days post-transplantation) or treatment for acute rejection with other reasons for clinical suspicion. The decision to treat acute rejection was based on the local reading of allograft biopsy.

Secondary outcomes at Month 12 included the mean measured GFR, mean calculated GFR using the modification of diet in renal disease (MDRD) equation, and the prevalence of chronic allograft nephropathy on protocol biopsies at Week 52 (Banff '97 classification). Patients were assessed for delayed graft function by determining whether they had been treated with dialysis within the first week post-transplantation. Cardiovascular and metabolic endpoints at Month 12 included mean systolic and diastolic blood pressure, the incidence of new-onset diabetes after transplant (NODAT), and mean changes in serum lipids.

Table 5: Patient Disposition During BENEFIT Trial

	Belatacept MI (n = 219)	Belatacept LI (n = 226)	Cyclosporine (n = 221)
Not treated	0	0	6
Discontinued	46	45	42
Lack of efficacy	26	24	10
Adverse event	9	12	20
Withdrew consent	5	3	1
Death	4	2	3
Poor/non-compliance	0	0	2
Lost to follow up	0	0	1
Other	2	4	5
Completed 12 Months (%)	n = 173 (79)	n = 181 (80.1)	n = 173 (80.5)
Discontinued	9	5	20

Lack of efficacy	3	1	4
Adverse event	5	3	7
Withdrew consent	0	1	4
Death	0	0	3
Other	1	0	2
Completed 24 Months (%)	164 (75)	176 (78)	153 (71)
Discontinued	6	6	10
Lack of efficacy	0	1	4
Adverse event	2	1	5
Withdrew consent	1	0	1
No longer met criteria	1	0	0
Poor/non-compliance	0	1	0
Death	1	2	0
Other	1	1	0
Completed 36 Months (%)	n = 158 (72)	n = 170 (75)	n = 143 (67)

Results after 1 Year[10]: Of the patients who discontinued the study drug, 29/46 patients in the MI group, 28/45 in the LI group and 22/42 cyclosporine group were switched to tacrolimus. Demographic and baseline characteristics of the recipients and donors in each group were well balanced, including the types of donors (living or deceased), donor age and cold ischemia time. Fifty-eight percent of all transplants were from living donors (42% related; 16% unrelated). The mean age among living donors was 42 years, and was 38 years among deceased donors. The mean cold ischemia time was 1.4 h for living donor transplants and 16.3 h for deceased-donor transplants. The primary _endpoint of noninferiority for both patient and graft survival met the noninferiority margin of 10%. Further analysis showed that with a noninferior margin of 5%, the primary outcome would have been satisfied.

At 12 months, kidney function was superior in patients receiving belatacept versus cyclosporine as demonstrated by the coprimary composite kidney impairment endpoint, mean measured GFR and mean calculated GFR. The rate of proven acute rejection, defined as histologically confirmed clinical suspicion (unexplained rise in serum creatinine concentration ≥ 25% from baseline, unexplained decrease in urine output, fever, and graft tenderness, or serum creatinine concentration that remained elevated for 14 days after transplantation) or treatment of acute rejection, was 22% in the MI group, 17% in the LI group, and 7% in the cyclosporine group. At 12 months, the rate of acute rejection in the LI group was deemed noninferior compared with the cyclosporine group by satisfying a 20% margin for comparison. However, the MI group was found to be statistically significantly inferior to the cyclosporine group for the prevention of acute rejection. A total of 30 patients (7%) receiving belatacept experienced a rejection grade of Banff IIB, 20 (4.5%) of whom were in the MI group compared with only 2 patients (1%) in the entire cyclosporine group. The most common treatment for acute rejection was corticosteroids. By Month 12, 21% of patients in the belatacept MI group, 17% in the LI group and 7% in the cyclosporine group were treated for acute rejection. Initial T-cell-depleting therapy for AR was used in 13, 10 and 2 patients in the MI, LI and cyclosporine groups, respectively. Thirteen patients (6%) in the belatacept MI group and 10 (4%) in the LI group experienced corticosteroid-resistant acute rejection; while no patients in the cyclosporine group experienced corticosteroid-resistant acute rejection. Of the patients with acute rejection by Month 12, 45/48, 36/39 and 15/16 in the belatacept MI, LI and cyclosporine groups survived with a functioning graft. Among patients with acute rejection, 56% in the belatacept MI group, 68% in the LI group and 69% in the cyclosporine group recovered to within 110% of their baseline serum creatinine. Chronic allograft nephropathy at month 12 occurred more often in the cyclosporine group compared with both the MI and LI groups, with a frequency of 32%, 18%, and 24%, respectively, but was not found to be statistically significant. Of note, the mean measured GFR at

Month 12 was higher in belatacept patients with acute rejection than in cyclosporine patients without acute rejection. *[For results pertaining to primary outcomes year 1 through year 3 see Table 1 in Appendix.]*

The percentage of patients with delayed graft function was similar between groups (MI: 16%, LI: 14% and cyclosporine: 18%). Blood pressure was lower in the belatacept group despite the fact that patients in the cyclosporine group were taking antihypertensive therapy more often ($p<0.0273$). Although non–high-density lipoprotein cholesterol (non-HDL) levels increased in all treatment groups, the MI group demonstrated a smaller increase from baseline compared with the cyclosporine group, as well as the LI group. Triglyceride levels decreased in both the MI group and the LI group compared with an increase in the cyclosporine group. [*For results pertaining to secondary outcomes year 1 see Table 2 in Appendix.]*

The most frequent adverse events (25%) were anemia, urinary tract infection, hypertension, constipation, diarrhea, nausea and peripheral edema, which occurred at similar rates in all groups. Belatacept's intravenous administration was noted to cause infusion related reactions in four patients (2%) each in the more intensive and less intensive regimen groups. All infusion-related reactions documented were considered mild and did not result in discontinuation of belatacept therapy. Occurrences of bacterial, viral, and fungal infections were similar in all groups, including the frequency of cytomegalovirus and BK virus infections. Malignancy was diagnosed in five patients (2%) in the MI group, four (2%) in the LI group, and one (1%) in the cyclosporine group. [*For listing of most common adverse reactions year 1 through year 3 see Table 3 and 4 in Appendix.]*

Results after 2 years[20]: Patient and allograft survival continued to be similar in all groups, with rates of 94%, 95%, and 91% in the MI, LI, and cyclosporine groups, respectively. Between months 12 and 24, four more episodes of acute rejection were recorded in both the MI regimen and cyclosporine groups. Most episodes occurred within the first 90 days post-transplant, and few acute rejection episodes occurred after month 12. Acute rejection was the adjudicated cause of graft loss in two patients in each treatment group. The improvement previously seen in measured GFR at the end of the 1-year analysis continued at 24 months, with both belatacept groups sustaining a mean GFR of 15–17 ml/ minute higher than that in the cyclosporine group. Advantages in cardiovascular and metabolic markers, such as lower low-density lipoprotein cholesterol level, were continued in the belatacept groups. Infectious and safety risks were similar among all three groups with 7 (3%), 9 (4%), and 14 (6%) deaths in the MI, LI, and cyclosporine groups, respectively. The most common cause of death was infections (MI, n=3; LI, n=2; and cyclosporine, n=5). The overall incidence of serious adverse events (SAEs) was 55% to 59% in the MI and LI groups, compared with 62% in the cyclosporine group. The frequency of malignancies in BENEFIT was lower in the LI (4%) and CsA (5%) groups compared with MI group (8%).

Outcomes in EBV (+) Patients

The increased risk of posttransplantation lymphoproliferative disorders (PTLD) with belatacept was highest in EBV (-) patients, supporting the EBV (+) population as the recommended patients to be treated with belatacept.

Table 6: Selected Outcomes in Patients Who Were EBV (+) at Baseline

	Belatacept MI (n = 219)	Belatacept LI (n = 226)	Cyclosporine (n = 221)
Patients included in analysis (n)	194	199	184
Patients surviving with functioning graft, n (%)	182 (94)	191 (96)	165 (82)
Acute rejection, n (%)	50 (26)	35 (18)	16 (9)
Patients included in analysis (n) due to data availability	153	162	139
Mean mGFR, mL/min/1.73 m^2 (SD)	70.3 (26.37)	72.3 (29.25)	52.5 (18.9)

An increased risk of PTLD associated with the belatacept-based regimens was previously reported based on 1-year data. The combined data from BENEFIT, BENEFIT-EXT and a phase II study (19) indicated that both EBV (-) and EBV (+) patients were at an increased risk for PTLD with belatacept, specifically CNS PTLD. The highest risk was in patients who were EBV (-) and patients who received the MI regimen

Results after 3 Years[21]:
Between years 1 and 3, cyclosporine trough levels remained stable (mean ~149–170 ng/mL) and within the protocol-specified range of 100–250 ng/mL. Patients in each treatment group who discontinued belatacept or cyclosporine were most commonly switched to tacrolimus. The proportion of patients surviving with a functioning graft by year 3 was 92% (95% CI 88.7–95.8), 92% (88.5– 95.6) and 89% (84.5–92.9) in the MI, LI and cyclosporine groups, respectively. Most deaths or graft losses occurred in the first 12 months, only 6 patients died (n = 2 MI; n = 2 LI; n = 2 cyclosporine) and 9 patients lost their graft (n = 3 MI; n = 4 LI; n = 2 cyclosporine) from year 2 to year 3. The mean cGFR was consistently higher over time in the belatacept groups compared to cyclosporine. The difference between both belatacept groups and cyclosporine in the mean cGFR increased from ~15 mL/min/1.73 m2 at year 1 to 21 mL/min/1.73m2 at year 3. There were no new cases of acute rejection in the belatacept groups from year 2 to year 3. One patient experienced acute rejection in the cyclosporine group after year 2. An analysis of 113 patients who experienced an acute rejection episode by year 3 found that 8 (MI), 10 (LI) and 1 (cyclosporine) died or lost their graft by year 3. Conversely, among patients who did not experience an acute rejection episode by year 3, 9 (MI), 8 (LI) and 23 (cyclosporine) died or lost their graft by year 3.

The most common adverse events occurred with a similar rate across groups, and were similar to those reported at year 2. Sixteen patients (7%) in the MI and LI groups discontinued study therapy due to adverse events, compared to 31 (14%) in the cyclosporine group. No new cases of PTLD were reported between years 2 and 3. The overall rate of infections as an adverse event was similar among treatment groups (MI: 80%; LI: 82%; cyclosporine: 80%). The most common infections included urinary tract infection (30%–36% across groups), upper respiratory tract infection (17%–20% across groups), and influenza (10%–14% across groups). Seven cases of tuberculosis were reported (n = 4 MI; n = 2 LI; n = 1 cyclosporine); 6 of the cases were reported from study sites in India. The rate of serious infections was 28% (MI), 32% (LI) and 33% (cyclosporine). The most common serious infections included urinary tract infection (6%–11% across groups), CMV infection (3%–6% across groups), gastroenteritis (1%–3% across groups) and pyelonephritis (2%–3% across groups).

Conclusions: Belatacept was associated with similar patient and graft survival, superior kidney function, a trend toward less chronic allograft nephropathy and an improved cardiovascular and metabolic profile compared with cyclosporine 1 year post-transplant, despite an increase in acute rejection in the early post-transplant period. Treatment with belatacept was generally safe, although there was a higher incidence of PTLD in belatacept patients with known risk factors, especially EBV (-) at the time of transplantation. There appeared to be no additional efficacy gained using the belatacept MI regimen compared with the LI regimen. The higher incidence of acute rejection between the LI group (17%) and the cyclosporine group (7%), while within the prespecified noninferiority margin, could be clinically meaningful. However, the acute rejection rates in the belatacept groups in BENEFIT are similar to rates observed in other trials of calcineurin inhibitor-based regimens in kidney transplant recipients, which range from 12% to 30% (22). Also, the rate of acute rejection in the cyclosporine arm in BENEFIT is markedly lower than observed with cyclosporine in the above-mentioned studies. Overall, one-year patient and graft survival were similar between all treatment groups, and acute rejection was rarely associated with graft loss.

At 2 years post-transplant, belatacept-based immunosuppressive regimens were associated with a comparable proportion of patients surviving with a functioning graft, better allograft function, and an improved cardiovascular/metabolic risk profile compared with a CsA-based regimen. The kidney function benefit widened over time with belatacept compared with CsA , because of decreasing kidney function over time in the CsA group

and improving kidney function in the belatacept groups. The decreasing kidney function in the CsA group is consistent with reports on the impact of CNI-related nephrotoxicity (23). There were few episodes of acute rejection in any treatment groups after month 12. The lack of association between the acute rejection episodes in the belatacept groups and the development of donor specific antibodies (DSAs) is important, because early rejection that is not associated with development of DSAs is generally less detrimental to long-term graft survival (24,25). The increased PTLD risk in EBV (-) patients confirm EBV seronegativity as a PTLD risk factor.

At 3 years, a high rate of patient and graft survival and improved kidney function was sustained in kidney transplant recipients treated with belatacept versus cyclosporine. Belatacept, which is intravenously administered, appeared to be well tolerated, with more patients on therapy at year 3 compared to cyclosporine. No belatacept-treated patients experienced acute rejection between years 2 and 3, and there were no new safety signals. Kidney function remained stable over time in the belatacept groups, while function declined in the cyclosporine group.

In a report of over 1000 kidney transplant recipients, both kidney function at 1 year and the rate of kidney function decline during the first year were associated with increased risk for late graft loss (26). The preservation of kidney allograft function observed with belatacept may ultimately contribute to fewer late graft losses. Based on a validated prediction model, (27) the improved kidney function observed in belatacept-treated patients versus cyclosporine projects to a median graft survival difference of 1.9 years (95% CI: 1.5 to 2.2), and potentially ~9 graft loss events averted at 10 years post-transplant. These projections suggest that treatment with belatacept may delay a return to dialysis and the need for retransplantation. The resumption of dialysis results in increased morbidity and mortality, increased health care costs, and negative impacts on patients' quality of life (28).

Acute Rejection

There were no cases of acute rejection after year 2 in the belatacept groups. The results show that acute rejection in the belatacept groups tended to occur early and did not typically recur. The presentation of acute rejection was consistent with clinical expectations, and episodes were treated according to existing clinical practice. Acute rejection had an impact on a number of long-term outcomes. For example, acute rejection was associated with reduced kidney function in all treatment groups. At year 3, more deaths and graft losses were observed in acute rejection patients receiving belatacept than in those receiving cyclosporine, although interpretation is limited by the high rate (~50%) of belatacept discontinuation in patients who developed acute rejection. Despite higher rates and grades of acute rejection, the overall proportion of patients surviving with a functioning graft remained comparable between the belatacept groups and cyclosporine by year 3.

PTLD

There were no new cases of PTLD between years 2 and 3. Previous analyses indicated that the greatest risk of PTLD with belatacept was associated with EBV negative serostatus in the recipient. A higher rate of PTLD was also observed in EBV seropositive patients; however, the magnitude of risk was ~10-fold lower than that in EBV(−) patients. The risk of PTLD involving the central nervous system was also highest in EBV(−) patients and in patients treated with the more intensive belatacept regimen (29). The data in the belatacept phase III studies support the general observation that the risk for PTLD appears to be highest within the first 18 months post-transplant (30).

The authors have concluded that the 3-year results from BENEFIT confirm the persistence of the kidney function benefits of belatacept over time. These benefits balance the early risks associated with belatacept in the study population, namely acute rejection and PTLD. The totality of data suggests that belatacept offers an important therapeutic advance in the care of kidney transplant recipients.

A Phase III Study of Belatacept versus Cyclosporine in Kidney Transplants from Extended Criteria Donors (BENEFIT-EXT Study) – Year 1 and 2 [11,20]

Durrbach et al. evaluated the efficacy and safety of two belatacept-based maintenance regimens with a cyclosporine-based regimen in a 3-year, randomized, multicenter study in adult patients who received a kidney transplant from an extended criteria donor.

Table 7: Inclusion and Exclusion Criteria Used in the BENEFIT-EXT Trial

Inclusion Criteria	Exclusion Criteria
• Age ≥ 18 years of age • Recipients of extended criteria kidneys: ▪ donors ≥60 years old ▪ or donors ≥50 years old who had at least two other risk factors (cerebrovascular accident, hypertension and serum creatinine >1.5 mg/dL) ▪ or anticipated cold ischemia time of ≥24 h ▪ or donation after cardiac death	• Donor age < 10 years of age • Subjects receiving a concurrent solid organ or cell transplant • Subjects with a positive T-cell lymphocytotoxic crossmatch • Subjects who are positive for Hepatitis B or C, or HIV • Active TB • History of cancer in the last 5 years • History of substance abuse • Mammography suspicious for cancer • Allergy to iodine

The study interventions were the same as the BENEFIT trial mentioned above. Each patient was treated with basiliximab induction (20 mg i.v. on Day 1 and Day 5), mycophenolate mofetil (2 g/day p.o. in divided doses) and corticosteroids (tapered ≥2.5 mg/day). T-cell depleting therapy was permitted for anticipated delayed graft function (DGF) in cyclosporine patients only, and for the treatment of rejection in both belatacept and cyclosporine patients. Patients with acute rejection ≤Grade IIA (Banff'97 classification) were treated with pulses of methylprednisolone, whereas patients with acute rejection ≥Grade IIB could be treated with T-cell-depleting therapy at the investigator's discretion. Antiviral prophylaxis was recommended to all patients for at least 3 months post-transplant, and for 3 months upon initiating T-cell-depleting agents, as well as 6 months of prophylaxis against pneumocystis.

Table 8: Dosing Regimen in the BENEFIT-EXT Trial

Belatacept MI (n=184)	Belatacept LI (n=175)	Cyclosporine (n=184)
Months 0 – 3 10 mg/kg Days 1, 5 Weeks 2,4,6,8,10,12	Months 0 – 1 10 mg/kg Days 1, 5 Weeks 2, 4	Initial Daily Dose 4 – 10 mg/kg
Months 4 – 6 10 mg/kg Weeks 16,20,24	Months 2 – 3 10 mg/kg Weeks 8, 12	Months 0 – 1 Dose adjusted to 150-300 ng/mL
Months 7 – 36 5 mg/kg Every 4 weeks	Months 4 – 36 5 mg/kg Every 4 weeks	Months 2 – 36 Dose adjusted to 100-250 ng/mL

There were two primary outcomes at 12 months: 1) composite patient and graft survival and 2) composite kidney impairment. The composite kidney impairment endpoint was defined as the percent of patients exhibiting a measured GFR <60 mL/min/1.73 m^2 at Month 12, or a decrease in measured GFR ≥10 mL/min/1.73 m^2 from Month 3 to Month 12.

Secondary outcomes at Month 12 included measured GFR, calculated GFR, prevalence of biopsy-proven chronic allograft nephropathy (Banff '97 classification) and incidence and severity of clinically suspected, biopsy-proven acute rejection at Months 6 and 12. The incidence and severity of acute rejection was utilized as a secondary outcome in BENEFIT-EXT because of concern that the increased incidence of anticipated delayed graft function (DGF) would skew acute rejection rates and confound comparison of belatacept and cyclosporine, because

cyclosporine patients, and not belatacept patients, could receive lymphocyte-depleting therapy for DGF. Clinical suspicion of acute rejection was defined as an unexplained rise of serum creatinine ≥25% from baseline, unexplained decrease in urine output, fever and graft tenderness or serum creatinine that remained elevated within 14 days post-transplantation. Cardiovascular and metabolic endpoints at Month 12 included mean systolic and diastolic blood pressure, the incidence of new-onset diabetes after transplantation (NODAT) and mean changes in serum lipids. Patients were assessed for DGF by determining whether they had been treated with dialysis within the first week post-transplantation.

Table 9: Patient Disposition During BENEFIT-EXT Study

	Belatacept MI (n = 184)	Belatacept LI (n = 175)	Cyclosporine (n = 184)
Not treated	1	1	5
Discontinued	50	45	54
Lack of efficacy	16	15	14
Adverse event	22	27	31
Withdrew consent	1	0	2
Death	5	2	2
Poor/non-compliance	0	0	0
Lost to follow up	0	0	0
Other	6	1	5
Completed 12 Months (%)	n = 133 (73)	n = 129 (74)	n = 125 (70)
Discontinued	17	10	13
Lack of efficacy	3	0	1
Adverse event	9	5	7
Withdrew consent	1	3	1
Death	1	1	1
Other	3	1	3
Completed 24 Months (%)	116 (63)	119 (68)	112 (63)

Results after 1 Year[11]: Of the patients who discontinued the study drug, 20/50 patients in the MI group, 17/45 in the LI group and 17/54 in the cyclosporine group were switched to tacrolimus. Demographic characteristics among recipient treatment groups were balanced at baseline and the mean donor age was 56.2 years. The primary cause of donor mortality was cerebrovascular accident (69.8%) and the mean cold ischemia time was 20 h.

The composite of patient and graft survival was found to be noninferior among all three groups at 1 year with a 10% noninferiority margin. Graft loss as a result of acute rejection or thrombosis was not noted to be significantly different between any of the three groups. The second primary end point, a composite of kidney impairment defined by GFR < 60 ml/minute at month 12 or a decrease of 10 ml/minute or more in GFR from post-operative months 3–12, was determined to be statistically significantly improved in the MI belatacept group compared with cyclosporine (p=0.0083). The LI belatacept group did not reach a statistically significant difference for the kidney impairment composite end point, but GFR was noted to be 4.3 ml/minute higher compared with the cyclosporine group throughout the study.

The occurrence of acute rejection was determined to reach noninferiority with a 20% inferior margin. However, Banff IIB rejection occurred more frequently in the MI group (9%) and the LI group (5%) compared with the cyclosporine regimen (3%). The most common treatment for acute rejection was corticosteroids, whereas initial T-cell-depleting therapy was used in 13, 5 and 4 patients in the belatacept MI, LI and cyclosporine groups, respectively. Twenty-seven (15%) patients in the cyclosporine group were treated with lymphocyte-depleting therapy for anticipated DGF, whereas no patients in the belatacept groups were permitted to receive such treatment. Of the 27 cyclosporine patients treated with lymphocyte-depleting therapy for anticipated

DGF, 2 (7%) had an episode of acute rejection, compared with 15% of those cyclosporine patients who were not treated with lymphocyte depleting therapy for anticipated DGF.

Diagnosis of chronic allograft nephropathy occurred in 45%, 46%, and 52% of patients in the MI, LI, and cyclosporine groups, respectively, at the end of 12 months. Severe CAN (interstitial fibrosis, tubular atrophy, tubular loss) was also similar in all groups. *[For results pertaining to primary outcomes year 1 through year 2 see Table 5 in Appendix.]*

The percentage of patients with DGF was similar between groups (MI: 47%; LI: 47%; cyclosporine: 49%). Non-HDL levels had a smaller increase from baseline in the MI group compared with the cyclosporine group, as well as the LI group. Triglyceride levels decreased in both the MI group and the LI group compared with an increase in the cyclosporine group, respectively. Mean systolic and diastolic blood pressures were considered improved in both belatacept groups. [*For results pertaining to secondary outcomes year 1 see Table 6 in Appendix.]*

The most common (>20%) adverse events included anemia, graft dysfunction, constipation and diarrhea, and occurred with a similar frequency between groups. Malignancy developed in eight patients (2%) in the belatacept groups and in six patients (3%) in the cyclosporine group. Four of the five cases of PTLD in the belatacept groups involved the central nervous system, and two of five (both of the post- Month 12 cases) had cytomegalovirus (CMV) disease. No patients on cyclosporine developed PTLD. Three of the five PTLD patients had negative Epstein-Barr virus (EBV) serology pretransplant. In relation to belatacept's intravenous route of administration, infusion-related reactions occurred in seven patients (4%) and nine patients (5%) in the MI and LI belatacept groups, respectively. One infusion event resulted in prolonged hypotension but was considered non–life threatening. Aside from this hypotensive episode, belatacept maintenance therapy was not interrupted as a result of any infusion-related injury. Rates of bacterial, cytomegalovirus, BK viral and fungal infections were determined to be similar; however, a total of six fungal infections (2%) occurred in the belatacept groups and were declared serious. [*For listing of most common adverse reactions year 1 through year 2 see Table 7 in Appendix.]*

Results after Year 2[20]: Patient and allograft survival continued to be similar in all groups, with rates of 83%, 84%, and 83% in the MI, LI, and cyclosporine groups, respectively. Between months 12 and 24, three more episodes of acute rejection were recorded in both the low intensity and cyclosporine groups. Most episodes occurred within the first 90 days post-transplant, and few acute rejection episodes occurred after month 12. Acute rejection was the adjudicated cause of graft loss in three, three, and six of patients in the MI, LI, and cyclosporine groups, respectively, by month 24. The estimated difference in cGFR (MDRD) between the belatacept and cyclosporine groups was 8 to 10 mL/min, compared with 7 mL/ min at month 12. Advantages in cardiovascular and metabolic markers, such as lower blood pressure and lipid profile were continued with the belatacept groups. Infectious and safety risks were similar among all three groups with 19 (10%), 13 (7%), and 16 (9%) deaths in the MI, LI, and cyclosporine groups, respectively. The most common cause of death was infections (MI, n=5; LI, n=5; and cyclosporine, n=6). There was a one new CNS PTLD case that occurred after month 18. This case occurred in the belatacept LI group in a 62-year-old EBV (+) male with over 4 years exposure to belatacept. The patient died of sepsis with a functioning graft approximately 2 months after the PTLD diagnosis.

Outcomes in EBV (+) Patients

The increased risk of PTLD with belatacept was highest in EBV (-) patients, supporting the EBV (+) population as the recommended patients to be treated with belatacept.

Table 10: Selected Outcomes in Patients Who Were EBV (+) at Baseline

	Belatacept MI (n = 184)	Belatacept LI (n = 175)	Cyclosporine (n = 184)
Patients included in analysis (n)	169	156	168
Patients surviving with functioning graft, n (%)	138 (82)	132 (85)	139 (83)
Acute rejection, n (%)	30 (18)	27 (17)	25 (15)

Patients included in analysis (n) due to data availability	104	112	168
Mean mGFR, mL/min/1.73 m2 (SD)	52.9 (23.49)	49.8 (23.8)	45.9 (29.5)

Conclusions

The BENEFIT-EXT study addresses two key concerns in extended criteria donor kidney recipients: impaired kidney function and adverse cardiovascular risk profile. Belatacept use resulted in better kidney function, similar patient/graft survival, comparable acute rejection and an improved cardiovascular/metabolic profile versus cyclosporine, and an increase in the number of cases of PTLD. The belatacept-based regimens demonstrated superior kidney function soon after transplantation (measured glomerular filtration rate was 4–7 mL/min/1.73 m^2 higher in the belatacept groups compared with cyclosporine at 12 months), whereas DGF was similar in the post-transplant period. The kidney benefit in the belatacept groups was maintained through the 1-year follow-up. The acute rejection rates were similar between the belatacept and cyclosporine groups, despite the use of lymphocyte-depleting agents to treat DGF in the cyclosporine group. Of note, some of the differences in serum lipid concentrations, as well as other cardiovascular/metabolic risk factors, could have been influenced by the greater incidence of diabetes in the cyclosporine group compared to the belatacept groups at baseline. However, the overall differences in cardiovascular risk factors in BENEFIT-EXT are similar to those in BENEFIT, where there was no significant difference in the baseline incidence of diabetes between treatment groups. Primary graft thrombosis as the adjudicated cause of graft loss occurred more frequently in the belatacept groups. Examination of recipient and donor characteristics did not reveal any common cause or suggestion of a hypercoagulable state in subjects treated with belatacept. The overall rate of thrombotic adverse events in BENEFIT-EXT was similar between groups (11–12%).

Treatment with belatacept-based regimens was generally safe. Acute infusion-related adverse events were infrequent and mild or moderate in nature. There was no increase in the overall rate of serious adverse events, malignancies, serious infections or opportunistic infections compared with cyclosporine. Although the overall rate of malignancies in the study was low and most types of malignancies occurred in only one patient, PTLD occurred in three patients in the belatacept groups through Month 12, and has occurred in one additional patient each in the MI and LI group after Month 12. Four of the five cases involved the central nervous system. The rates of PTLD reported in the literature for kidney transplant recipients range from 0.4% to 2.3%, and PTLD localized in the central nervous system constitutes 11–22% of all PTLD cases among kidney transplant recipients (28). Although the incidence of central nervous system PTLD was higher in the belatacept arms, it occurred in patients who had known risk factors such as EBV negative status and CMV disease (31).

At 2 years post-transplant, belatacept-based immunosuppressive regimens were associated with a comparable proportion of patients surviving with a functioning graft, better allograft function, and an improved cardiovascular/metabolic risk profile compared with a CsA-based regimen. There were few additional episodes of acute rejection during the second year and no new safety signals were identified. By month 24, the overall kidney function benefit had reached an 8 to 10 mL/min advantage in BENEFIT-EXT. Results from the 3-year BENEFIT-EXT study will continue to be assessed to ascertain whether the favorable benefit/risk profile of belatacept is maintained and whether the results in EBV (+) patients—the recommended treatment population—will continue to demonstrate the utility of belatacept as a basis for immunosuppression in kidney transplant recipients.

Phase II trial, Costimulation Blockade with Belatacept in Renal Transplantation and its 5-year long-term extension[32,17]

Vincenti et al. evaluated the long-term efficacy and safety of two belatacept-based maintenance regimens with a cyclosporine-based regimen. The original study was an open-label, partially blinded, randomized, active-controlled, multi-center study. The subjects in the subsequent 5-year extension were self-selected.

Table 11: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Adult recipients of a renal allograft from a non-HLA-identical living or deceased donor • Higher risk patients could not make up more than 10% of the study population. Higher risk being defined as: ▪ Previously undergone renal transplantation or ▪ History of a panel-reactive antibody titer exceeding 20% or ▪ Deemed at increased risk for acute rejection by an investigator	• Underlying kidney disease in the recipient that could recur in the allograft such as: ▪ Focal and segmental glomerulosclerosis ▪ Type I or II membranoproliferative glomerulonephritis ▪ Hemolytic-uremic syndrome ▪ Thrombotic thrombocytopenic purpura • Active hepatitis B or C or any other infection that would normally preclude transplantation • Human immunodeficiency virus infection • History of or evidence of cancer • Positive T-cell lymphocytotoxic cross match with the use of donor lymphocytes and recipient serum • History of drug or alcohol abuse or psychotic disorders • Previous treatment with basiliximab • Use of any investigational drugs within 30 days before the visit on day 1 • Donor age of more than 60 years or less than 16 years • Donor whose heart was not beating at the time of organ procurement • Cold-ischemia time of more than 36 hours

Patients were randomly assigned to one of three groups: a more intensive belatacept group (MI), a less intensive belatacept group (LI), or a cyclosporine-based regimen in a 1:1:1 fashion. Belatacept patients were randomly assigned again at 3 or 6 months to receive 5 mg/kg belatacept at either 4- or 8-week intervals for the maintenance phase. All patients received basiliximab 20 mg as induction therapy on postoperative days 0 and 4, mycophenolate mofetil 2 g/day, and a corticosteroid regimen that began with intravenous methylprednisolone 500 mg intraoperatively and ended with a prednisone taper to 5–10 mg/day by month 4. Belatacept was administered as a 30-minute intravenous infusion. Because of the requirement for therapeutic monitoring and adjustments in dose, cyclosporine was administered in an unblinded fashion. Episodes of acute rejection of Banff '97 grade IIA or less were treated with bolus corticosteroids. Corticosteroid- resistant episodes or episodes of at least grade IIB were treated with antibody therapy.

Table 12: Dosing Regimen

Belatacept MI (n=74)	Belatacept LI (n=71)	Cyclosporine (n=73)
Months 0 – 3 10 mg/kg Days 1, 5, 15, 29, 43, 57, 71, 85	Months 0 – 1 10 mg/kg Days 1, 15, 29	Initial Daily Dose 4 – 10 mg/kg
Months 4 – 6 10 mg/kg Days 113, 141, 169	Months 2 – 3 10 mg/kg Days 57, 85	Months 0 – 1 Dose adjusted to 150-400 ng/mL
Months 7 – 60 5 mg/kg Every 4 or 8 weeks	Months 4 – 60 5 mg/kg Every 4 or 8 weeks	Months 2 – 60 Dose adjusted to 100-300 ng/mL

The primary objective was to demonstrate that belatacept was not inferior to cyclosporine in its ability to prevent rejection at six months. Acute rejection, defined clinicopathologically, required an increase in the serum creatinine level of at least 0.5 mg/dL over prerejection baseline levels in the absence of other confounding factors and findings on renal biopsy consistent with the presence of acute rejection (as defined by the Banff '97 criteria for classifying renal-transplant biopsy specimens). Patients who had had one episode of rejection by month 6 were considered to have reached the primary end point. Subclinical rejection was defined by findings on renal biopsy consistent with the presence of acute rejection without an increase in the serum creatinine level of at least 0.5 mg/dL.

Primary efficacy analyses were performed according to intention to treat with the use of data from all patients who underwent randomization and transplantation. The primary efficacy variable was summarized within and between treatment groups with the use of point estimates and 95 percent confidence intervals. For the primary efficacy end point, the upper bound of the 95 percent confidence interval around the treatment difference had to be less than 20% for belatacept to be considered noninferior to cyclosporine.

Secondary endpoints were the incidence of acute rejection (biopsy-confirmed or presumed) at 6 months and 1 year; the measured glomerular filtration rate, as determined by iohexol clearance, at 1, 6, and 12 months; the prevalence of hypertension; serum cholesterol and triglyceride levels; and overall safety. Other prespecified analyses included the rate of death or graft loss at one year; the incidence of post-transplantation diabetes mellitus, pharmacokinetics, immunogenicity, and the calculated GFR, as determined by the Modification of Diet in Renal Disease method. A post hoc analysis was conducted of the incidence of chronic allograft nephropathy (CAN) (according to the Banff '97 criteria) and of patients who had treatment for hypertension was performed during the 12 months of follow-up.

Patients who completed 12 months on the original study arms were eligible for the long-term extension at the investigators' and patients' discretion. Treatments were administered in an unblinded manner. Switching from CsA to tacrolimus (Prograf ®; Astellas) was permitted at the discretion of the investigator; switched patients were permitted to continue in the study. Patients who did not tolerate MMF could be switched to sirolimus. Corticosteroid weaning and withdrawal was permitted, although all patients continued on corticosteroids; the mean daily dosage ranged from 5.0 to 8.5 mg/d.

The primary objective of the LTE was to assess the safety and tolerability of long-term belatacept administration in kidney transplant recipients. The secondary objective was to assess the efficacy of belatacept as a long-term maintenance immunosuppressant. PK and PD (CD86 receptor saturation) properties of belatacept and anti-belatacept antibody generation were also investigated. The main exclusion criterion for participation in the LTE was development of a malignancy during the initial 12-month study. Because of the small number of patients who were on CsA and participated in the LTE, only limited conclusions can be drawn from direct comparisons between the two arms; therefore, the report focused primarily on the long-term experience with belatacept. Median follow-up was 5 years after transplantation (range 1 to 7 years).

Table 13: Patient Disposition Throughout 5 Year Follow-up

	Belatacept MI (n = 74)	**Belatacept LI (n = 71)**	**Cyclosporine (n = 73)**
Not treated	0	0	2
Discontinued	16	16	20
Breakdown not reported			
Completed 12 Months (%)	n = 58 (78)	n = 55 (77)	n = 51 (70)
Consented to LTE phase and randomized again	102		26
	4 Week Dosing (n = 56)	**8 Week Dosing (n = 46)**	**Cyclosporine (n = 26)**
Discontinued	14 (25)	10 (22)	10 (39)
Withdrew consent	5 (9)	5 (11)	2 (8)
Adverse event	6 (11)	2 (4)	1 (4)
Noncompliance	0	2 (4)	0
Prohibited medication	0	1 (2)	0
Lost to follow up	0	0	2 (8)
Other	3 (5)	0	5 (19)

Data cut-off, n (median follow-up 5 years)	78	16
Switched to tacrolimus, n		
Year 1	NA	NA
Year 2	5	0
Year 3	1	0
Year 4	0	1
Year 5	1	0

Results after 6 and/or 12 months[32]: Baseline demographics and clinical characteristics were reported as similar among groups during the original study. The primary _endpoint of noninferiority in the prevention of acute rejection at 6 months with an inferiority margin of 20% was met in all three groups. The acute rejection rates were 7%, 6%, and 8% in the MI, LI, and cyclosporine groups, respectively. Acute rejection contributed to two graft losses, one in the MI group and one in the cyclosporine group. The incidence of secondary _endpoints of biopsy-proven or presumed acute rejection at six months was similar among the groups (11% in MI, 8% in LI, and 10% in the cyclosporine group). Measured GFR determined by iohexol clearance at 12 months was considered significantly different when comparing the MI group (66.3 ml/min) with the cyclosporine group (53.5 ml/min, p=0.01) and the LI group (62.1 ml/min) with the cyclosporine group (p=0.04). Chronic allograft nephropathy seen at 1 year on histologic examination was more prevalent in the cyclosporine group (44%) compared with both the MI (29%) and LI (20%) belatacept regimen groups. Among patients with CAN, the calculated GFR was higher in both belatacept groups than in the cyclosporine group. Four patients in the cyclosporine group died, and one patient in the MI group died. Two of the four patients who died in the cyclosporine group died of cardiac causes. Graft loss among the surviving patients was infrequent — occurring in three patients receiving MI belatacept, one receiving LI belatacept, and two receiving cyclosporine — and was most commonly due to technical reasons, such as renal-vein or renal-artery thrombosis. *[For results pertaining to outcomes year 1 through year 5 see Table 8 in Appendix.]*

At 12 months, the mean total cholesterol, high-density lipoprotein, low-density lipoprotein levels were similar among the groups. However, more patients in the cyclosporine group than in either belatacept group were receiving lipid-lowering medications (53 percent, as compared with 36 percent in the intensive-therapy group and 32 percent in the group given less intensive therapy; P=0.03 for the comparison with both belatacept groups). A post hoc analysis of the prevalence of hypertension requiring treatment at12 months was 88 percent in the intensive-belatacept group, 83 percent in the group receiving less intensive belatacept, and 92 percent in the cyclosporine group. Diabetes mellitus was infrequent after transplantation, occurring in 12 percent of patients in the group receiving intensive therapy, 6 percent of those in the group receiving less-intensive therapy, and 12 percent of those in the cyclosporine group.

There were no reported infusion-related adverse events. Adverse events whose frequency was at least 5% higher in the cyclosporine group than in either belatacept group included leukopenia, anemia, edema, hypertension, urinary tract infection, hypokalemia, hypomagnesemia, acidosis, tremor, hypertrichosis, and diabetes mellitus. The frequency of infection was similar among the groups with urinary tract infections and cytomegalovirus infections being the most common. *[For results pertaining to adverse events year 1 through year 5 see Table 9 in Appendix.]*

Malignancy occurred in two patients treated with MI belatacept (one had breast cancer, and one had post-transplantation lymphoproliferative disorder) and in two patients treated with cyclosporine (one had skin cancer, and one had thyroid cancer). However, PTLD developed in two additional patients treated with the MI regimen 2 and 13 months after belatacept had been replaced with convention al immunosuppressive agents (tacrolimus, mycophenolate mofetil, and corticosteroids). Of the three patients in whom PTLD developed, two had primary

Epstein– Barr virus infections. The third had received a 10-day course of muromonab-CD3 for acute rejection, and belatacept had been discontinued just before this therapy was administered; PTLD was diagnosed 13 months later.

Results from LTE[17]: Patients who entered the LTE were a self-selected population who did particularly well during the first phase of the study. The average GFR at LTE entry was higher than in patients who did not enter the LTE: 75.8 versus 69.5 ml/min for belatacept and 74.4 versus 67.4 ml/min for CsA. Renal function was stable in belatacept patients over the 5-year period. Average cGFR was 75.8 ml/min in LTE belatacept recipients at 12 months after transplantation and 77.2 ml/min in patients who reached 60 months after transplantation. No substantive differences in GFR were observed between patients on 4- or 8-week dosing. In the CsA group, GFR decreased from 74.4 ml/min at 12 months after transplantation to 59.3 ml/min at month 60. Three patients (3%) died and one patient (1%) lost the graft in the belatacept group compared with two deaths (8%) in the cyclosporine group. No CsA recipients had graft loss.

Six documented cases of biopsy-proven rejection occurred in the belatacept groups, with 2 in the 4-week group and 4 in the 8-week group, whereas the cyclosporine group had no reported episodes of biopsy-proven rejection. No BPAR events in the belatacept group were associated with graft loss.
Cardiovascular, infectious, and other adverse-event outcomes were similar between the belatacept and cyclosporine groups at the end of 5 years. There was a low occurrence of serious cardiac disorders with belatacept in the LTE (2%), with cardiac failure and cardiopulmonary arrest occurring in one (1%) patient each. A total of three (12%) CsA recipients had serious cardiac disorders, including two events of coronary artery stenosis and one each of coronary artery disease, myocardial infarction, and atrial fibrillation. One (4%) patient in the CsA group developed CMV infection. Two (2%) belatacept recipients and no CsA recipients developed human BK polyomavirus infection. Herpes was reported in 21 (21%) belatacept recipients and in three (12%) CsA recipients. *[For results pertaining to cardiovascular risk factors during the LTE Table 10 in Appendix.]*

Most neoplasms occurred in years 3 to 5 after transplantation. One LTE CsA recipient developed PTLD in year 4 after transplantation, whereas no belatacept recipient developed PTLD during the LTE. In the original study, three cases of PTLD occurred between 3 and 13 months after transplantation in belatacept recipients, all in patients who were receiving the more intensive regimen. Taking into account these patients, the overall incidence of PTLD from time of transplantation were three (2.1%) of 143 in the belatacept arms and one (1.4%) of 73 in the CsA arm. *[For results pertaining to neoplasms during the LTE see Table11 in Appendix.]*

Conclusions
In the original Phase II trial, belatacept demonstrated comparable rates of AR, a trend toward reduced CAN, significantly higher measured GFR, and excellent patient/graft survival by 12 months. However, the authors report that the differences identified between belatacept and cyclosporine should be regarded as suggestive rather than definitive because the noninferiority bounds were relatively broad and because of a substantial amount of missing data on the measured glomerular filtration rate, findings of improved renal function with belatacept should be regarded as preliminary.

In belatacept-treated patients, renal function remained stable; death, graft loss, and AR were infrequent; and there were low rates of serious infections or malignancies during 5 years median follow-up. The LTE study demonstrated high patient persistence with intravenous belatacept therapy over the long term. The low rate of discontinuation during long-term treatment suggests that intravenous administration may not be a challenge to persistence. In the LTE, BP remained stable, and non-HDL cholesterol levels decreased in belatacept recipients over time. The study was not powered to detect a difference in outcomes between the 4- and 8-week dosing groups; therefore, safety and efficacy were primarily analyzed using pooled data from both groups. There were no substantive differences in GFR or death/graft loss between the two dosing groups; however, there was a higher incidence of AR with the 8-week dosing.

The major limitation of this study is that the cohort was a nonrandomized, self-selected group of patients who did particularly well during the first year. LTE enrollees had fewer occurrences of AR in the first year, compared with all patients in the original study. Also, the LTE portion of this Phase II study was underpowered to detect

meaningful differences between the treatment arms, particularly when some patients chose not to continue in the LTE or withdrew during long-term follow-up. This particularly affected the CsA group, resulting in a small comparator arm, and the lengths of follow-up were not identical between the belatacept and CsA groups, limiting meaningful data comparisons. Lastly, the study compared belatacept with CsA even though tacrolimus is now the more widely used CNI for maintenance immunosuppression.

Phase II trial, Immunosuppression with Belatacept-Based, Corticosteroid-Avoiding Regimens in *De Novo* Kidney Transplant Recipients[33]

Ferguson et al. conducted a 1-year, randomized, controlled, open-label, exploratory study to assess two belatacept-based regimens compared to a tacrolimus (TAC)-based, steroid-avoiding regimen.

Table 14: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Age ≥ 18 years of age • Receiving a renal allograft from a nonhuman leukocyte antigen (HLA)-identical living donor or • Receiving a standard criteria deceased donor	• Recipients of extended criteria kidneys: ▪ donors ≥60 years old ▪ donors ≥50 years old who had at least two other risk factors (cerebrovascular accident, hypertension and serum creatinine >1.5 mg/dL) ▪ anticipated cold ischemia time of ≥24 h ▪ donation after cardiac death • Prior or concurrent nonrenal solid organ transplants • First-time patients with a panel reactive antibody ≥50% • Retransplants with a panel reactive antibody ≥30% • Any prior graft loss due to acute rejection • Underlying renal disease that could recur in the allograft • Infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C virus, or latent tuberculosis • History of malignancy in the previous 5 years (other than nonmelanoma skin cancer cured by resection). • Patients seronegative for Epstein Barr virus (EBV) • Patients with a body mass index >35 kg/m2

Eighty-nine patients were randomly assigned in a 1:1:1 ratio to receive one of three therapies: belatacept plus mycophenolate mofetil (33 patients), belatacept plus sirolimus (26 patients), or tacrolimus plus mycophenolate mofetil (30 patients). Thymoglobulin® was administered to all 3 treatment groups as a 1.5-mg/kg IV infusion beginning on the day of transplantation (Day 1) and again on Days 2, 3 and 4. Dosing could be stopped earlier if absolute lymphocyte count was <100/mm2, or reduced or extended if a patient developed neutropenia or thrombocytopenia. However, dosing was not to extend past Day 10 or cumulatively exceed 6 mg/kg. All patients received 500, 250, 125 and 60 mg IV methylprednisolone on Days 1, 2, 3 and 4, respectively. Belatacept was initially administered as a maintenance dose of 10 mg/kg, which was reduced to 5 mg/kg 6 months after transplantation, similar to the more intensive belatacept regimen groups discussed previously (selected due to the absence of steroids in the regimen). SRL was initiated at 5 mg/day orally on Day 1 and adjusted to keep predose trough levels at 7–12 ng/mL from Day 3 through Month 6 and 5–10 ng/mL thereafter. The dosage of MMF was 1 g twice daily, which could be reduced and/or split into 4 divided doses. Acute rejection episodes of Banff '97 grade IIA or lower were treated with methylprednisolone. Steroid-resistant acute rejection episodes and those of Banff grade IIB or higher were recommended to be treated with lymphocyte-depleting therapy.

Table 15: Dosing Regimen for Belatacept and Tacrolimus

Belatacept-MMF (n=33)	Belatacept-SRL (n=26)	TAC-MMF (n=30)
Months 0 – 3 10 mg/kg Days 1, 5 Weeks 2,4,6,8,10,12	Months 0 – 3 10 mg/kg Days 1, 5 Weeks 2,4,6,8,10,12	Initial Daily Dose 0.1 mg/kg in two divided doses initiated when SCr improved to < 4 mg/dL

Months 4 – 6 10 mg/kg Weeks 16,20,24	Months 4 – 6 10 mg/kg Weeks 16,20,24	Months 0 – 1 Dose adjusted to 8-12 ng/mL
Months 7 – 12 5 mg/kg Every 4 weeks	Months 7 – 12 5 mg/kg Every 4 weeks	Months 2 – 12 Dose adjusted to 5-10 ng/mL

The primary efficacy endpoint was the incidence of acute rejection by Month 6. Acute rejection was defined as (1) biopsy-proven and either (2) clinically suspected for protocol-defined reasons or (3) clinically suspected for other reasons and treated. Protocol-defined reasons for obtaining a biopsy for suspected acute rejection included unexplained rise in serum creatinine ≥25% from baseline and one or more of the following: any unexplained decrease in urine output, fever and graft tenderness, or a persistent elevation in serum creatinine in the 14 days after transplantation with clinical suspicion of rejection. The presence of anti-donor HLA antibodies was assessed before transplantation, at months 6 and 12 and after any suspected acute rejection episode.

Secondary endpoints included the incidence and severity of acute rejection; patient survival; graft survival and calculated glomerular filtration rate (cGFR) using the Modification of Diet in Renal Disease (MDRD) formula. Other secondary endpoints included steroid-free status and CNI-free status at Month 12 and cardiovascular and metabolic profiles including blood pressure, serum lipids and new onset diabetes.

All safety and efficacy analyses were conducted according to the intention to treat with the use of data from all patients who underwent randomization and transplantation. No statistical testing was prespecified in the study and only descriptive summaries are provided. The number of patients per group was planned so that the upper bound of a 95% confidence interval (CI) would exclude a clinically unacceptable acute rejection rate of 30%

Baseline demographic and clinical characteristics of transplant recipients were similar across treatment groups . During the 12 months of the study, discontinuation or switching of regimen occurred in 8 (24%), 12 (46%) and 2 (7%) of the patients in the belatacept-MMF, belatacept-SRL and TAC-MMF groups, respectively. None of the patients who discontinued the TAC-MMF regimen discontinued due to adverse events or lack of efficacy. Mean trough levels of TAC and SRL at Week 2 were 10.6 ng/mL and 17.7 ng/mL, respectively, and were 9.6 ng/mL and 9.0 ng/mL, respectively, at Month 12.

Results after 12 months: The primary end point of acute rejection at 6 months occurred in 12%, 4%, and 3% of patients receiving belatacept-MMF, belatacept-SRL, and TAC-MMF, respectively. One episode of rejection occurred between months 6 and 12 in the belatacept-MMF group. The composite end point of patient and graft survival was found to be 91%, 92%, and 100% for the three groups, respectively. One patient receiving belatacept-MMF died during the study. Four others lost grafts including 2 from graft thrombosis (belatacept-MMF and belatacept-SRL on Days 2 and 5, respectively), 1 on Day 185 from BK virus nephropathy (belatacept-SRL) and 1 from a second episode of acute rejection after discontinuation from the study (belatacept-MMF). The mean ± SD calculated GFR for each group was 64 ± 27, 62 ± 31, and 54 ± 15 ml/minute, respectively. Ten patients had delayed graft function (n = 5 belatacept-MMF; n = 3 belatacept-SRL; n = 2 TAC-MMF); only four (n = 2 belatacept-MMF; n = 2 belatacept-SRL) required >1 day of dialysis. Avoidance of a calcineurin inhibitor and remaining corticosteroid free was achieved in 73% of the belatacept-MMF group and 77% of the belatacept-SRL group. *[For results pertaining to efficacy outcome see Table 12 in Appendix.]*

No clinically significant changes in cardiovascular or metabolic risk factors were noted. The most common adverse events by Month 12, which included anemia, pyrexia, leukopenia, diarrhea and constipation, occurred with a similar incidence across groups (data not shown). Five serious adverse events led to treatment discontinuation (belatacept-MMF: increased serum creatinine, graft loss and pyrexia; belatacept-SRL: renal artery thrombosis, proteinuria). Occurrence of infection was similar among all three groups, occurring at a rate of 26%, 20%, and 20%, respectively. BK virus (n = 2; 1 each in belatacept-MMF and TAC-MMF) and CMV infection (n = 4 total; n = 1 each belatacept-MMF and belatacept-SRL, n = 2 TAC-MMF) occurred infrequently across groups. Malignancies were recorded in 2 patients: 1 in the belatacept-SRL group (basal cell carcinoma) and 1 in the TAC-MMF group (squamous cell carcinoma). There were no cases of PTLD or progressive multifocal leukoencephalopathy. *[For results pertaining to cardiovascular endpoints and adverse events see Table 13 and 14 in Appendix.]*

Conclusions

This exploratory, Phase 2, open-label, randomized study is the first to assess the safety and efficacy of belatacept as a component of an immunosuppressive regimen that avoids both CNIs and corticosteroids. In addition, the study provides the first belatacept clinical study experience with Thymoglobulin induction and combination with a mammalian target of rapamycin (mTOR) inhibitor.

The 6-month acute rejection rate was 12% in the belatacept-MMF group, 4% in the belatacept-SRL group and 3% in the TAC-MMF group. The current study also showed evidence of improved renal function with belatacept compared with TAC however that failed to translate into improved patient and graft survival. The overall safety profile of belatacept was generally consistent with the profile reported in the BENFIT trials. There were no cases of PTLD reported with either belatacept regimen or tacrolimus regimen.

Limitations to the study include its relatively small size and lack of statistical power. The number of patients who discontinued or switched part of their regimen limits the conclusions that can be drawn regarding treatment groups. For example, 10 patients in the belatacept-SRL group switched from SRL to MMF, often due to poor tolerability associated with SRL. However, approximately 81% of patients in the belatacept treatment groups remained on belatacept through Month 12, suggesting belatacept itself was well tolerated. Chronic allograft nephropathy (IF/TA) was not assessed in this study, which may have provided more information about allograft health. Larger studies that build on this exploratory study, optimizing the potential advantages of a CNI- and steroid-avoiding regimen, would further define the most favorable steroid-avoiding belatacept regimen.

Phase II trial, Switching from Calcineurin Inhibitor-based Regimens to a Belatacept-based Regimen in Renal Transplant Recipients[34]

Rostaing et al. evaluated the safety and efficacy of switching stable renal transplant patients from maintenance CNI therapy to a belatacept-based regimen in a randomized, open-label, multicenter trial.

Table 16: Inclusion and Exclusion

Inclusion Criteria	Exclusion Criteria
• Age ≥ 18 years of age • Received a living donor or deceased donor at least 6 months but no longer than 36 months before enrollment • Receiving CNI-based maintenance immunosuppression at a stable dose during the month immediately before randomization • And have a cGFR between 35 and 75 ml/min per 1.73 m^2 at enrollment, based on the Modification of Diet in Renal Disease formula	• History of recent, recurrent, or severe AR in the current allograft or • History of graft loss due to acute rejection. ◦ A single acute rejectionepisode was not exclusionary if it occurred >3 months before randomization, was Grade IB (Banff 97 criteria) or milder, did not recur, and had been successfully reversed with corticosteroids. • Positive T or B cell crossmatch • C4d-positive biopsy in the current allograft • Recent >30% serum creatinine (SCr) increase • Underlying renal disease that could adversely affect the current graft • Current infection, and a history of malignancy (other than nonmelanoma skin cancer cured by local resection) in the past 5 years.

Kidney transplant patients receiving a CNI-based regimen (cyclosporine or tacrolimus) were randomly allocated 1:1 to switch to belatacept or remain on their existing therapy. Patients allocated to the comparator group continued receiving cyclosporine or tacrolimus according to local practice and the respective package inserts. Acute rejection episodes were treated with bolus corticosteroids, except for episodes that were Banff Grade IIB or higher and/or corticosteroid- resistant; those episodes were recommended to be treated with lymphocyte-depleting therapy.

Table 17: CNI Switching Dosing Regimen

Belatacept (n=84)	CNI Dose Taper	CNI (n=89)
Months 0 – 3 5 mg/kg Days 1, 15, 29, 43, 57	Day 1: 100% Day 15: 40-60%	Cyclosporine Target 100 – 250 ng/mL
Months 4 – 12 5 mg/kg Every 4 weeks	Day 23: 20-30% Day 29: None	Tacrolimus Target 5 – 10 ng/mL

The primary endpoint was the change in cGFR from baseline to month 12, calculated using the MDRD. Secondary endpoints included the incidence of acute rejection (AR), patient and graft survival, new onset diabetes after transplantation (NODAT), blood pressure, serum lipids, and Kidney Disease Outcomes Quality Initiative chronic kidney disease stage. Patients with signs and symptoms suspicious for AR (defined in the protocol as unexplained rise of SCr ≥25% from baseline, unexplained decreased urine output, or fever and graft tenderness) underwent a renal biopsy.

The efficacy data were analyzed according to intention to treat, with all randomized patients included whether or not they remained on treatment. Calculated GFR and its change from baseline were summarized descriptively, and an imputed value of 10 used in the event of death or graft loss. The study was not powered to assess the statistical significance of the change from baseline in cGFR between the belatacept and CNI groups.

Results: The two treatment groups had similar demographic and clinical characteristics except that more belatacept patients had end-stage renal disease secondary to glomerulonephritis. Ninety-eight percent of

patients in each group completed 1 year of treatment. The two patients who discontinued belatacept had AR episodes but did not experience graft loss. Improvements in renal function were greater in the belatacept group compared with the CNI group. The primary outcome of average change in MDRD GFR from baseline showed a mean ± SD increase of 7.0 ± 11.99 ml/minute in the belatacept group and 2.1 ± 10.34 ml/minute in the calcineurin inhibitor group. Twelve months after randomization, six patients (7%) who switched to belatacept experienced an episode of AR, none of which resulted in graft loss. No grafts were lost in the first 12 months. One patient in the CNI group died with a functioning graft (because of myocardial infarction) on day 142. *[For results pertaining to primary and secondary endpoints see Table 15 and 16 in Appendix.]*

NODAT occurred in two patients receiving CNIs and one receiving belatacept. Most adverse events reported during the first 12 months of the study were mild and occurred with similar frequency in the two treatment groups. Few serious adverse events were reported. The overall incidence of viral infections over the 12 months was 13% in each group. The most frequently reported viral infection was influenza. Cytomegalovirus infection occurred in two patients in each group, and BK virus infection occurred in three patients in the belatacept group. There were no cases of progressive multifocal leukoencephalopathy. Malignancies were reported in four patients: two in the belatacept group (one with Kaposi's sarcoma and one with basal cell carcinoma) and two in the CNI group (basal cell carcinoma). There were no cases of post-transplant lymphoproliferative disorder. *[For results pertaining to adverse events see Table 17 in Appendix.]*

Conclusions
This exploratory study of belatacept in stable renal transplant patients demonstrated that switching from a CNI-based therapy to a belatacept-based regimen appeared to be feasible with a mild improvement of renal function and no graft loss. This regimen has the potential to serve as an option in those who cannot tolerate CNI-based therapy. A subgroup analysis showed that the improvement in cGFR after switching to belatacept was similar for cyclosporine-treated patients and tacrolimus- treated patients (7.7 and 6.4 ml/min per 1.73 m2, respectively). However, patients treated with tacrolimus who did not switch also had an improvement in GFR. According to the authors, the lack of AR episodes in the comparator arm is not surprising, because these patients did not switch therapy and had been on stable CNI-based therapy for as long as 3 years. In the current study, all of the AR episodes occurred within the first 6 months, all but one had resolved by 12 months, and none led to graft loss. There were no differences between groups in the incidence of malignancies or serious infections. The small number of subjects in the study limits the conclusions that can be made from the subgroup analyses. Results on the relative clinical benefit of belatacept in a switch paradigm, and particularly in different patient categories, should be considered exploratory and require confirmation in future studies.

Adverse Events

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

Deaths and Other Serious Adverse Events

- Serious infections, including JC virus-associated PML and polyoma virus nephropathy
- PTLD, predominantly CNS PTLD, and other malignancies

WARNING: POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER, OTHER MALIGNANCIES, AND SERIOUS INFECTIONS

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

Common Adverse Events
Most common adverse reactions (≥20% on belatacept treatment) are anemia, diarrhea, urinary tract infection, peripheral edema, constipation, hypertension, pyrexia, graft dysfunction, cough, nausea, vomiting, headache, hypokalemia, hyperkalemia, and leukopenia

Other Adverse Events
See Appendix

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

Contraindications

Transplant recipients who are Epstein-Barr virus (EBV) seronegative or with unknown EBV serostatus due to the risk of post-transplant lymphoproliferative disorder (PTLD), predominantly involving the central nervous system (CNS) should not receive the drug.

Warnings and Precautions

- Post-Transplant Lymphoproliferative Disorder (PTLD): increased risk, predominantly involving the CNS; monitor for new or worsening neurological, cognitive, or behavioral signs and symptoms.
- Other malignancies: increased risk with all immunosuppressants; appears related to intensity and duration of use. Avoid prolonged exposure to UV light and sunlight.
- Progressive Multifocal Leukoencephalopathy (PML): increased risk; consider in the differential diagnosis of patients reporting new or worsening neurological, cognitive, or behavioral signs and symptoms. Recommended doses of immunosuppressants should not be exceeded.
- Other serious infections: increased risk of bacterial, viral, fungal, and protozoal infections, including opportunistic infections and tuberculosis. Some infections were fatal.
- Polyoma virus-associated nephropathy can lead to kidney graft loss; consider reduction in immunosuppression.
- Evaluate for tuberculosis and initiate treatment for latent infection prior to belatacept use.
- Cytomegalovirus and pneumocystis prophylaxis are recommended after transplantation.
- Liver transplant: use is not recommended.
- Avoid use of live vaccines during treatment with belatacept, including but not limited to the following: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines
- Pregnancy: Based on animal data, may cause fetal harm
- Nursing Mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother.

Sentinel Events

No data

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. After searching for LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), no medications were found to be confused with belatacept or its trade name Nulojix™.

Drug Interactions

No formal drug interaction studies have been conducted with belatacept. As a therapeutic protein, belatacept is not expected to have significant drug-drug interactions involving cytochrome P450 (CYP450) enzymes. Therapeutic proteins are usually not metabolized by CYP450 and are unlikely to be a direct inhibitor or inducer of CYP450.

There is also a potential change of MPA exposure after crossover from cyclosporine to belatacept or from belatacept to cyclosporine in patients concomitantly receiving MMF.

Conclusions

In clinical trials, belatacept has demonstrated non-inferiority in both patient and allograft survival rates when compared to cyclosporine based regimens. These trials employed various dosing strategies of belatacept versus a standard cyclosporine protocol in recipients of both living- and deceased-donor renal transplants, as well as in patients receiving kidneys transplanted from extended-criteria donors. Belatacept use was associated with a lower incidence of renal dysfunction, hyperlipidemia, hypertension and new onset diabetes. The significance of increased acute rejection in the belatacept groups has yet to be determined. The effects of increased acute rejection on long-term graft function may over time outweigh the early improvements in GFR seen with the use of belatacept. Of concern is the association of belatacept and PTLD with the greatest risk in transplant recipients who are EBV seronegative before transplantation.

Therapy with belatacept will present different challenges from those faced with standard calcineurin immunosuppression. While belatacept therapy does not require drug monitoring to ensure safe and effective therapy, it does require monthly infusions for therapy. Logistics of giving belatacept infusions at facilities outside of the VA system may be difficult. Also, the best way to address missed doses has not been studied as of yet. Belatacept's use should be considered on a center-by-center and case-by-case basis until more definitive evidence on risks associated with malignancy are defined.

References

1. Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004; 4: 378–383.
2. Gaston RS. Chronic calcineurin inhibitor nephrotoxicity: Reflections on an evolving paradigm. Clin J Am Soc Nephrol 2009; 4:2029–2034.
3. Ducloux D, Motte G, Kribs M et al. Hypertension in renal transplantation: Donor and recipient risk factors. Clin Nephrol 2002; 57: 409–413.
4. Roland M, Gatault P, Doute C et al. Immunosuppressive medications, clinical and metabolic parameters in new-onset diabetes mellitus after kidney transplantation. Transpl Int 2008; 21: 523–530.
5. Mathis AS, Dave N, Knipp GT, Friedman GS. Drug-related dyslipidemia after renal transplantation. Am J Health Syst Pharm 2004; 61: 565–585.
6. Ortiz F, Paavonen T, Tornroth T et al. Predictors of renal allograft histologic damage progression. J Am Soc Nephrol 2005; 16: 817–824.
7. Vanrenterghem YF, Claes K, Montagnino G et al. Risk factors for cardiovascular events after successful renal transplantation. Transplantation 2008; 85: 209–216.
8. Opelz G, Dohler B. Influence of immunosuppressive regimens on graft survival and secondary outcomes after kidney transplantation. Transplantation 2009; 87: 795–802.
9. Larsen CP, Pearson TC, Adams AB, et al. Rational development of LEA29Y (belatacept), a high-affinity variant of CTLA4-Ig with potent immunosuppressive properties. Am J Transplant 2005;5:443–53.
10. Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study).AmJ Transplant 2010; 10: 535.
11. Durrbach A, Pestana JM, Pearson T, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant 2010; 10: 547.
12. Vincenti F, Luggen M. T cell costimulation: a rational target in the therapeutic armamentarium for autoimmune diseases and transplantation. Annu Rev Med 2007;58:347–58.
13. Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med 2004;351:2715–29.
14. Martin ST, Tichy EM, Gabardi S. Belatacept: a novel biologic for maintenance immunosuppression after renal transplantation. Pharmacotherapy. 2011 Apr;31(4):394-407.
15. Latek R, Fleener C, Lamian V, et al. Assessment of belatacept-mediated costimulation blockade through evaluation of CD80/86-receptor saturation. Transplantation 2009;87:926–33.

16. Shen J, et al. Poster presented at the 11th Annual American Transplant Congress; May 2011. Poster 1097.
17. Vincenti F, Blancho G, Durrbach A, et al. Five-year safety and efficacy of belatacept in renal transplantation. J AmSoc Nephrol 2010; 21: 1587.
18. Zhou Z, Shen J, Kaul S, Pfister M, Roy A. Belatacept population pharmacokinetics in renal transplant patients [abstract 1505]. Presented at the American transplant congress, San Diego, CA, May 2–5, 2010.
19. Nulojix™ (belatacept) Prescribing Information. June 2011. Bristol-Myers Squibb Co. Princeton, NJ 08543.
20. Larsen CP, Grinyo J, Medina-Pestana J, et al. Belatacept-based regimens versus a cyclosporine a-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFITEXT studies. Transplantation 2010; 90: 1528–1535.
21. Vincenti F, Larsen CP, Alberu J, et al. Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. Am J Transplant 2011 Oct 12. doi: 10.1111/j.1600-6143.2011.03785.x.
22. Vincenti F, Schena FP, Paraskevas S, Hauser IA,Walker RG, Grinyo J. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. Am J Transplant 2008; 8: 307–316.
23. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol 2009; 4: 481.
24. He X, Johnston A. Early acute rejection does not affect chronic allograft nephropathy and death censored graft failure. Transplant Proc 2004; 36:2993.
25. Sijpkens YW, Doxiadis II, Mallat MJ, et al. Early versus late acute rejection episodes in renal transplantation. Transplantation 2003; 75: 204.
26. Wu J, Li H, Huang H, et al. Slope of changes in renal function in the first year posttransplantation and one-yr estimated glomerular filtration rate together predict long-term renal allograft survival. Clin Transplant 2010; 24: 862–868.
27. Schnitzler MA, Kalsekar A, You M, L'Italien G. Expected median graft survival prediction for belatacept phase III trial outcomes in kidney transplantation. Am J Transplant 2011; 11(S2): 353–354.
28. Rao PS, Schaubel DE, Jia X, Li S, Port FK, Saran R. Survival on dialysis post-kidney transplant failure: Results from the Scientific Registry of Transplant Recipients. Am J Kidney Dis 2007; 49:294–300.
29. Grinyo J, Charpentier B, Pestana JM, et al. An integrated safety profile analysis of belatacept in kidney transplant recipients. Transplantation 2010; 90: 1521–1527.
30. Faull RJ, Hollett P, McDonald SP. Lymphoproliferative disease after renal transplantation in Australia and New Zealand. Transplantation 2005; 80: 193–197.
31. Manez R, Breinig MC, Linden P et al. Posttransplant lymphoproliferative disease in primary Epstein-Barr virus infection after liver transplantation: The role of cytomegalovirus disease. J Infect Dis 1997; 176: 1462–1467.
32. Vincenti F, Larsen C, Durrbach A, et al. Costimulation blockade with belatacept in renal transplantation. N Engl J Med 2005;353:770–81.
33. Ferguson R, Grinyó J, Vincenti F, Kaufman DB, Woodle ES, Marder BA, Citterio F, Marks WH, Agarwal M, Wu D, Dong Y, Garg P. Immunosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. Am J Transplant. 2011 Jan;11(1):66-76. doi: 10.1111/j.1600-6143.2010.03338.x. Epub 2010 Nov 29.
34. Rostaing L, Massari P, Garcia VD, Mancilla-Urrea E, Nainan G, del Carmen Rial M, Steinberg S, Vincenti F, Shi R, Di Russo G, Thomas D, Grinyó J. Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study. Clin J Am Soc Nephrol. 2011 Feb;6(2):430-9.

Prepared: December 2011 by Amanda Wellens, Pharm.D. Candidate 2012 and Katie Derry, Pharm.D., BCPS

Contact Person: Kathryn Tortorice Pharm D, BCPS

Appendix: Clinical Trial Data

Table 1: BENEFIT Outcomes: Patient/graft survival, kidney function and structure and acute rejection

Month 12 Endpoints	Belatacept MI (n = 219)	Belatacept LI (n = 226)	Cyclosporine (n = 221)
Patient/graft survival, n (%)			
Patients surviving with functioning graft	209 (95)	218 (97)	206 (93)
Graft loss or death	10 (5)	8 (4)	15 (7)
Graft loss	4 (2)	5 (2)	8 (4)
Death	6 (3)	4 (2)	7 (3)
Death with functioning graft	6 (3)	3 (1)	6 (3)
Kidney function and structure			
Delayed graft function	(16)	(14)	(18)
mGFR <60 mL/min/1.73 m^2 or decrease Month 3-12 ≥ 10 mL/min/1.73 m^2, n (%)	115 (55)	116 (54)	166 (78)
p-Value	<0.0001	<0.0001	-
Mean mGFR, mL/min/1.73 m^2 (SD)	65.0 (30.0)	63.4 (27.7)	50.4 (18.7)
p-Value	<0.0001	<0.0001	-
CAN, n (% [95%CI])	40 (18 [13.1-23.4])	54 (24 [18.3-29.5])	71 (32 [26.2-38.6])
Mild CAN (stage I)	21 (10)	29 (13)	41 (19)
Moderate CAN (stage II)	5 (2)	6 (3)	9 (4)
Severe CAN (stage III)	4 (2)	6 (3)	6 (3)
Acute rejection			
Acute rejection, n (%)	49 (22)	39 (17)	16 (7)
Banff grade			
Mild acute (IA)	7 (3)	4 (2)	3 (1)
Mild acute (IB)	3 (1)	8 (4)	5 (2)
Moderate acute (IIA)	17 (8)	16 (7)	6 (3)
Moderate acute (IIB)	20 (9)	10 (4)	2 (1)
Severe acute (III)	2 (1)	1 (<1)	0
Selected Endpoints Through Month 24			
Patients included in analysis (n)	219	226	221
Patients surviving with functioning graft, n (%)	206 (94)	214 (95)	200 (91)
Graft loss	7 (3)	5 (2)	8 (4)
Death	7 (3)	8 (4)	13 (6)
Acute rejection	53 (24)	39 (17)	20 (9)
Patients included in analysis (n) due to data availability	192	199	185
Mean mGFR, mL/min/1.73 m^2 (SD)	65 (27.21)	67.9 (29.9)	50.5 (20.52)
Patients included in analysis (n) due to data availability	180	190	164
Mean cGFR, mL/min/1.73 m^2 (SD)	70 (18.8)	70 (19.7)	53 (17.1)
Selected Endpoints Through Month 36			
Patients included in analysis (n)	219	226	221
Patients surviving with functioning graft (%)	(92)	(92)	(89)
Death-censored graft loss, n (%)	10 (5)	9 (4)	10 (5)
Death	9 (4)	10 (4)	15 (7)
Acute rejection	53 (24)	39 (17)	21 (10)
Composite endpoint (graft loss, death, lost-to follow-up or biopsy-proven acute rejection) (%)	32	26	26
Patients included in analysis (%) due to data availability	85	84	77
Mean cGFR, mL/min/1.73 m^2 (SD)	65.2 (26.3)	65.8 (27)	44.4 (23.6)
Mean cGFR, mL/min/1.73 m^2 (SD) On treatment analysis	72.7 (17.49)	74.5 (16.98)	52.4 (16.44)

Table 2: BENEFIT: cardiovascular/metabolic endpoints

Month 12 endpoints	Belatacept MI (n = 219)	Belatacept LI (n = 226)	Cyclosporine (n = 221)
Incidence of NODAT, n (%)	11 (7)	7 (4)	16 (10)
p-Value	0.4825	0.0687	-
Serum lipids			
Non-HDL			
Mean change from baseline, mg/dL (SD)	8.1 (2.8)	8.0 (2.8)	18.3 (2.8)
p-Value	0.0115	0.0104	-
Triglycerides			
Mean change from baseline, mg/dL (SD)	-17.0 (7.0)	-21.2 (6.9)	6.6 (6.9)
p-Value	0.0165	0.0047	-
Blood pressure, mmHg (SD)			
Mean systolic	133 (SD)	131 (16.5)	139 (20.1)
p-Value	0.001	<0.0001	-
Mean diastolic	79 (11.6)	79 (10.9)	82 (11.2)
p-Value	0.0273	0.005	-

Table 3: BENEFIT: Most common serious adverse events, malignancies and infections

Endpoints Through Month 12	Belatacept MI (n = 219)	Belatacept LI (n = 226)	Cyclosporine (n = 221)
Serious adverse events, n (%)	112 (51)	100 (44)	126 (57)
Urinary tract infection	10 (5)	9 (4)	15 (7)
Pyrexia	10 (5)	7 (3)	9 (4)
CMV infection	9 (4)	10 (4)	6 (3)
Serum creatinine increased	4 (2)	9 (4)	10 (5)
Graft dysfunction	4 (2)	6 (3)	10 (5)
Acute kidney failure	2 (1)	2 (1)	7 (3)
Kidney impairment	4 (2)	6 (3)	1 (1)
Pneumonia	2 (1)	3 (1)	5 (2)
Diarrhea	1 (1)	3 (1)	5 (2)
Lymphocele	2 (1)	2 (1)	5 (2)
Malignancies, n (%) (excluding nonmelanoma skin cancer)	5 (2)	4 (2)	1 (1)
PTLD	1 (1)	1 (<1)	0
Bone neoplasm	1 (1)	0	0
Breast cancer	1 (1)	0	0
Breast neoplasm	1 (1)	0	0
Chronic myeloid leukemia	0	0	1 (1)
Leukemia	0	0	1 (1)
Malignant lung neoplasm	1 (1)	0	0
Lymphoma	0	1 (<1)	0
Renal cell carcinoma	0	1 (<1)	0
Sarcoma	1 (1)	0	0
Thyroid neoplasm	0	1 (<1)	0
Infectious adverse events, n (%)	152 (69)	158 (70)	157 (71)
Urinary tract infection	54 (25)	63 (28)	50 (23)
Upper respiratory tract infection	24 (11)	22 (10)	26 (12)
CMV infection	13 (6)	17 (8)	19 (9)
Nasopharyngitis	15 (7)	10 (4)	20 (9)
Influenza	15 (7)	17 (8)	10 (5)
Oral candidiasis	12 (6)	6 (3)	13 (6)
BK virus infection	10 (5)	3 (1)	9 (4)
Bronchitis	9 (4)	7 (3)	5 (2)
Gastroenteritis	9 (4)	4 (2)	7 (3)
Serious infectious adverse events, n (%)	44 (20)	42 (19)	47 (21)
Urinary tract infection	10 (5)	9 (4)	15 (7)
CMV infection	9 (4)	10 (4)	6 (3)
Pneumonia	2 (1)	3 (1)	5 (2)
Sepsis	2 (1)	1 (<1)	4 (2)
Selected endpoints through month 24			
Most common serious adverse events, n (%)			
Urinary tract infection	13 (6)	13 (6)	23 (10)
CMV infection	12 (6)	12 (5)	7 (3)
Pyrexia	11 (5)	9 (4)	11 (5)
Kidney failure acute	4 (2)	3 (1)	8 (4)
Blood creatinine increased	4 (2)	10 (4)	11 (5)
Pneumonia	3 (1)	6 (3)	9 (4)
Diarrhea	3 (1)	6 (3)	8 (4)
Lymphocele	2 (1)	2 (1)	8 (4)
Malignances	8%	4%	5%
Basal cell carcinoma, n	4	1	4
Squamous cell carcinoma, n	3	0	3

Table 4: BENEFIT: Rate of malignancies and infections through year 3

n (%)	Belatacept MI (n = 219)	Belatacept LI (n = 226)	Cyclosporine (n = 221)
All malignancies	18 (8)	10 (4)	12 (5)
PTLD	3 (1)	2 (1)	1 (<1)
Most common malignancies			
Basal cell carcinoma	5 (2)	3 (1)	4 (2)
Squamous cell carcinoma of skin	4 (2)	1 (<1)	0
EBV-associated PTLD	2 (1)	1 (<1)	1 (1)
Breast cancer	2 (1)	0	0
Bowen's disease	1 (1)	0	2 (1)
Thyroid cancer	0	0	2 (1)
Renal cell carcinoma	0	2 (1)	0
All infections	175 (80)	185 (82)	176 (80)
CMV infections	22 (10)	26 (12)	25 (11)
BK polyoma virus	18 (8)	10 (4)	18 (8)
BK virus infection	13 (6)	8 (4)	12 (5)
Polyoma test positive	6 (3)	5 (2)	4 (2)
Human polyoma virus infection	1 (1)	1 (<1)	1 (1)
Polyomavirus-associated nephropathy	1 (1)	1 (<1)	4 (2)
Herpes virus	29 (13)	26 (12)	21 (10)
Oral herpes	13 (6)	15 (7)	7 (3)
Herpes zoster	10 (5)	8 (4)	11 (5)
Herpes simplex	5 (2)	1 (<1)	2 (1)
Fungal infections	50 (23)	46 (20)	45 (20)
Oral candidiasis	17 (8)	9 (4)	14 (6)
Onchomycosis	9 (4)	10 (4)	6 (3)
Candidiasis	7 (3)	7 (3)	2 (1)
Body tinea	6 (3)	2 (1)	1 (1)
Tuberculosis	4 (2)	2 (1)	1 (1)
Rate of serious infections (%)	28	32	33

Table 5: BENEFIT-EXT: Patient/graft survival, kidney function and structure and acute rejection

Month 12 Endpoints		Belatacept MI (n = 184)	Belatacept LI (n = 175)	Cyclosporine (n = 184)
Patient/graft survival, n (%)				
Patients surviving with functioning graft		159 (86)	155 (89)	156 (85)
Graft loss or death		25 (14)	20 (11)	28 (15)
Graft loss		17 (9)	16 (9)	20 (11)
Death		8 (4)	4 (2)	8 (4)
Death with functioning graft		6 (3)	3 (2)	5 (3)
Imputed as graft loss or death		2 (1)	1 (1)	3 (2)
Kidney function and structure				
Delayed graft function		(47)	(47)	(49)
mGFR <60 mL/min/1.73 m^2 or decrease 3-12 ≥ 10 mL/min/1.73 m^2, n (%)	Month	124 (70.5)	130 (76.5)	151 (84.8)
p-Value		0.0018	0.0656	-
Mean mGFR, mL/min/1.73 m^2 (SD)		52.1 (21.9)	49.5 (25.4)	45.2 (21.1)
p-Value		0.0083	0.1039	-
CAN, n (% [95%CI])		82 (45 [37.6-52.0])	80 (46 [38.6-53.4])	95 (52 [44.4-58.9])
Mild CAN (stage I)		45 (25)	40 (23)	49 (27)
Moderate CAN (stage II)		10 (6)	14 (8)	13 (7)
Severe CAN (stage III)		8 (4)	7 (4)	12 (7)
Acute rejection				
Acute rejection, n (%)		33 (17.9)	31 (17.7)	26 (14.1)
Banff grade				
Mild acute (IA)		-	4 (2)	2 (1)
Mild acute (IB)		7 (4)	2 (1)	2 (1)
Moderate acute (IIA)		10 (5)	17 (10)	17 (9)
Moderate acute (IIB)		16 (9)	8 (5)	5 (3)
Severe acute (III)		-	-	-
Selected Endpoints Through Month 24				
Patients included in analysis (n)		184	175	184
Patients surviving with functioning graft, n (%)		152 (83)	147 (84)	152 (83)
Graft loss		18 (10)	20 (11)	22 (12)
Death		13 (7)	11 (6)	12 (7)
Acute rejection		32 (17)	32 (18)	28 (15)
Patients included in analysis (n) due to data availability		136	139	136
Mean mGFR, mL/min/1.73 m^2 (SD)		51.5 (22.19)	49.7 (23.67)	45 (27.18)
Patients included in analysis (n) due to data availability		126	133	127
Mean cGFR, mL/min/1.73 m^2 (SD)		44 (26.7)	43 (24.1)	35 (21.6)

Table 6: BENEFIT-EXT: cardiovascular/metabolic endpoints

Month 12 endpoints	Belatacept MI (n = 184)	Belatacept LI (n = 175)	Cyclosporine (n = 184)
Incidence of NODAT, n (%)	3 (2)	7 (5)	11 (9)
p-Value	0.0308	0.2946	-
Serum lipids			
Non-HDL			
Mean change from baseline, mg/dL (SD)	12.6 (3.6)	11.2 (3.6)	29.3 (3.8)
p-Value	0.0016	0.0006	-
Triglycerides			
Mean change from baseline, mg/dL (SD)	-1.0 (9.5)	-18.2 (9.2)	34.5 (10.0)
p-Value	0.0106	0.0001	-
Blood pressure, mmHg (SD)			
Mean systolic	141	141	150
Mean diastolic	78	78	82

Table 7: BENEFIT-EXT: Most common (>20%) adverse events, serious adverse events (≥3%) and most common (≥4%) infections

Endpoints Through Month 12	Belatacept MI (n = 184)	Belatacept LI (n = 175)	Cyclosporine (n = 184)
Adverse events, n (%)			
Anemia	87 (47)	85 (49)	92 (50)
Graft dysfunction	70 (38)	67 (38)	89 (48)
Constipation	52 (28)	57 (33)	73 (40)
Diarrhea	54 (29)	58 (33)	47 (26)
Hypertension	41 (22)	40 (23)	61 (33)
Nausea	42 (23)	37 (21)	41 (22)
Leukopenia	44 (24)	30 (17)	49 (27)
Pyrexia	41 (22)	42 (24)	39 (21)
Hyperkalemia	38 (21)	42 (24)	35 (19)
Serious adverse events, n (%)			
Urinary tract infection	13 (7)	15 (9)	11 (6)
CMV infection	12 (7)	14 (8)	12 (7)
Serum creatinine increased	7 (4)	8 (5)	14 (8)
Graft dysfunction	8 (4)	6 (3)	10 (5)
Pyrexia	10 (5)	7 (4)	7 (4)
Lymphocele	2 (1)	5 (3)	10 (5)
Infectious adverse events, n (%)			
Urinary tract infection	55 (30)	57 (33)	62 (34)
CMV infection	21 (11)	24 (14)	24 (13)
Nasopharyngitis	21 (11)	12 (7)	13 (7)
Bronchitis	14 (8)	13 (7)	11 (6)
Upper respiratory tract infection	11 (6)	11 (6)	14 (8)
Oral candidiasis	7 (4)	5 (3)	12 (7)
Escherichia urinary tract infection	7 (4)	4 (2)	12 (7)
Gastroenteritis	3 (2)	8 (5)	10 (5)
Pneumonia	8 (4)	7 (4)	5 (3)
Selected endpoints through month 24			
Most common serious adverse events, n (%)			
Urinary tract infection	18 (10)	20 (11)	17 (9)
CMV infection	17 (9)	16 (9)	12 (7)
Diarrhea	11 (6)	7 (4)	4 (2)
Pyrexia	11 (6)	10 (6)	11 (6)
Pneumonia	9 (5)	5 (3)	6 (3)
Pyelonephritis	9 (5)	1 (1)	8 (4)
Graft dysfunction	8 (4)	6 (3)	11 (6)
Leukopenia	8 (4)	2 (1)	5 (3)
Blood creatinine increased	8 (4)	11 (6)	16 (9)
Lymphocele	2 (1)	5 (3)	10 (5)
Malignances	8%	7%	9%
Basal cell carcinoma, n	3	2	3
Squamous cell carcinoma, n	4	1	3

Table 8: Efficacy end points, renal function and survival

End Point	Belatacept MI (n = 74)	Belatacept LI (n = 71)	Cyclosporine (n = 73)

Primary efficacy end point			
Clinically suspected and biopsy-proven acute rejection at 6 months	5 (7)	4 (6)	6 (8)
Secondary efficacy end point			
Banff grade			
Mild acute (IA)	2 (3)	0	1 (1)
Mild acute (IB)	0	0	1 (1)
Moderate acute (IIA)	2 (3)	3 (4)	2 (3)
Moderate acute (IIB)	1 (1)	1 (1)	2 (3)
Subclinical rejection	7 (9)	14 (20)	8 (11)
Treated episodes of subclinical rejection	6 (8)	11 (15)	5 (7)
Patient/graft survival, n (%)			
Graft loss or death at 12 months	4 (5)	1 (1)	6 (8)
Graft loss	3 (4)	1(1)	2 (3)
Renal-vein or renal-artery thrombosis	1 (1)	1 (1)	2 (3)
Infarction	1 (1)	0	0
Treatment of PTLD	1 (1)	0	0
Death	1 (1)	0	4 (5)
Cardiac causes	0	0	2 (3)
Infection or sepsis	1 (1)	0	0
Pulmonary embolism	0	0	1 (1)
Other or unknown	0	0	1 (1)
Renal function and structure			
mGFR, n (patients included)	32	37	27
Mean mGFR, mL/min/1.73 m^2 (SD)	66.3 (20.7)	62.1 (15.9)	53.5 (16.4)
CAN, n (patients included)	52	54	45
CAN at 12 months, n (% [95%CI])	15 (29 [16.5 to 41.2])	11 (20 [9.6 to 31.1])	20 (44 [29.0 to 59.0])
Mild CAN (stage I)	11 (21)	6 (11)	16 (36)
Moderate CAN (stage II)	4 (8)	1 (2)	3 (7)
Severe CAN (stage III)	0	4 (7)	1 (2)
cGFR, n (patients included)	60	59	50
Mean cGFR, mL/min/1.73 m2 (SD)	72.4 (22.5)	73.2 (19.8)	68 (28.1)
Number of patients without CAN	49	50	37
Mean cGFR, mL/min/1.73 m2 (SD)	75.9 (21.3)	73.2 (19.8)	76.6 (24.4)
Number of patients with CAN	11	9	13
Mean cGFR, mL/min/1.73 m2 (SD)	56.9 (22.2)	73.1 (35.9)	43.6 (23.5)

Results at 60 months	**Belatacept (n = 102)**	**Cyclosporine (n = 26)**
Mean cGFR, mL/min/1.73 m^2 (SD)	77.2 (22.7)	59.3 (15.3)
Death	3 (3)	2 (8)
With functioning graft	2(2)	2 (8)
Graft loss only	1 (1)	0
Biopsy-proven acute rejection	6 (6)	0
Banff grade		
Mild acute (IA)	0	0
Mild acute (IB)	1 (1)	0
Moderate acute (IIA)	5 (5)	0
Moderate acute (IIB)	0	0

Table 9: Adverse Events During Original Study and LTE

After 12 Months	Belatacept MI (n = 74)	Belatacept LI (n = 71)	Cyclosporine (n = 73)
Incidence of adverse events that occurred ≥5% more in the cyclosporine group, %			
Leukopenia	19	17	30
Anemia	18	17	30
Edema	8	10	16
HTN	22	24	31
Urinary tract infection	23	24	31
Hypokalemia	7	7	13
Hypomagnesemia	3	4	10
Acidosis	4	1	10
Tremor	11	14	20
Hypertrichosis	0	0	6
Hyperlipidemia	12	11	8

During LTE	Belatacept (n = 102)	Cyclosporine (n = 26)
Incidence of adverse events that occurred in ≥10% of patients in any group, %		
Nasopharyngitis	30	27
Urinary tract infection	30	31
Diarrhea	30	35
Upper respiratory tract infection	29	31
Arthralgia	21	15
Peripheral edema	18	15
Cough	17	12
Pyrexia	16	8
Nausea	15	15
Pain in extremity	14	15
Headache	14	12
Bronchitis	14	8
HTN	12	23
Influenza	12	4
Back pain	11	15
Vomiting	11	12
Hyperlipidemia	11	4
Osteopenia	7	12
Hypotension	6	12
Anemia	3	23
Influenza-like illness	3	12
Atrial fibrillation	0	12

Table 10: Cardiovascular Risk Factors

Parameter	24 Months	36 Months	48 Months	60 Months
Non-HDL cholesterol (mg/dl; mean [SD])				
Belatacept	150 (35.7)	144 (37.5)	138 (38.8)	128 (37.3)
CsA	140 (44.9)	130 (31.7)	131 (38.6)	119 (29.5)
NODAT (n [%])a				
Belatacept	7 (7)	8 (90	8 (9)	9 (10)
CsA	2 (9)	2 (9)	2 (9)	2 (9)
Systolic BP (mmHg; mean [SD])				
Belatacept	129 (15.3)	129 (13.4)	126 (15.6)	125 (13.9)
CsA	132 (20.2)	129 (8.9)	140 (21)	138 (18.9)
Diastolic BP (mmHg; mean [SD])				
Belatacept	76 (10.5)	76 (9.5)	76 (9.9)	76 (10.1)
CsA	78 (9.3)	76 (7.5)	77 (11.9)	83 (8.9)

Table 11: Neoplasms in the LTE

Neoplasm (n [%])	Belatacept (n = 102)	Cyclosporine (n = 26)
Nonmelanoma skin cancers	9 (9)	2 (8)
Kaposi sarcoma	1 (1)	0
Breast cancer	2 (2)	0
Prostate cancer	1 (1)	0
Malignant melanoma	1 (1)	0
PTLD	0	1 (4)

Table 12: Efficacy Outcomes at Month 12

	Belatacept-MMF (n = 33)	Belatacept-SRL (n = 26)	TAC-MMF (n = 30)
Acute rejection			
Acute Rejection at Month 6, n (%)	4 (12)	1 (4)	1 (3)
Banff grade			
Mild acute (IA or IB)	0	0	0
Moderate acute (IIA)	2 (6)	0	1 (3)
Moderate acute (IIB)	2 (6)	1 (4)	0
Severe acute (III)	0	0	0
Acute rejection at Month 12, n (%)	5 (15)	1 (4)	1 (3)
Patient/graft survival, n (%)			
Subject and graft survival at Month 12, n (%)	30 (91)	24 (92)	30 (100)
Graft loss	2 (6)	2 (8)	0
Death	1 (3)1	0	0
Death with functioning graft	1 (3)1	0	0
Renal function and structure at Month 12			
Mean mGFR, mL/min/1.73 m^2 (SD)	63.6 (27.27)	61.8 (30.66)	54.0 (14.95)
CAN	Not addressed during this study		
Proportion steroid-free, n (%)	24 (73)	20 (77)	28 (93)
Proportion steroid-free and CNI-free	24 (73)	18 (69)	1 (3)

Steroid-free = not receiving steroids for >7 consecutive days during Days 337 through 392.
CNI-free = not receiving a CNI during Days 337 through 392.

Table 13: Cardiovascular/Metabolic Endpoints

Month 12 Endpoints	Belatacept-MMF (n = 33)	Belatacept-SRL (n = 26)	TAC-MMF (n = 30)
Mean blood pressure (SD), mmHg			
Baseline systolic blood pressure	133.1 (26.43)	126.9 (18.72)	141.8 (23.79)
Month 12 systolic blood pressure	129.3 (19.24)	131.0 (19.88)	138.3 (19.50)
Baseline diastolic blood pressure	78.6 (12.50)	72.3 (11.27)	75.3 (15.08)
Month 12 diastolic blood pressure	73.3 (11.96)	75.1 (10.71)	77.6 (10.51)
Antihypertensive medications taken			
1–2	17 (51.5)	13 (50.0)	17 (56.7)
≥ 3	8 (24.2)	7 (26.9)	3 (10.0)
Use of ≥1 antihyperlipidemic medications	12 (36.4)	10 (38.5)	12 (40.0)
Mean change in lipid values from baseline to Month 12 (SD), mg/dL			
HDL cholesterol	1.5 (12.7)	−3.7 (12.9)	−0.5 (12.2)
LDL cholesterol	23.9 (38.2)	25.0 (37.2)	34.0 (30.2)
Total cholesterol	17.5 (40.7)	12.5 (49.0)	20.0 (45.8)
Triglycerides	−11.4 (63.3)	−1.1 (88.9)	−14.2 (94.8)
Patients without pretransplant diabetes	21	21	17
Incidence of NODAT, n (%)	0	2 (9.5)	1 (5.9)

Table 14: Most common serious adverse events (≥2%) and other events by Month 12

Events, n (%)	Belatacept-MMF (n = 33)	Belatacept-SRL (n = 26)	TAC-MMF (n = 30)
Any serious adverse event	19 (58)	16 (62)	16 (53)
Most common serious adverse events			
Hydronephrosis	1 (3)	2 (8)	1 (3)
Pyrexia	2 (6)	1 (4)	1 (3)
Dehydration	0	1 (4)	2 (7)
Pyelonephritis acute	2 (6)	1 (4)	0
Graft dysfunction	0	1 (4)	2 (7)
Diarrhea	0	2 (8)	1 (3)
Blood creatinine increased	2 (6)	0	1 (3)
Renal tubular necrosis	1 (3)	0	1 (3)
Urinary fistula	0	1 (4)	1 (3)
Graft loss	1 (3)	1 (4)	0
Post procedural hemorrhage	1 (3)	1 (4)	0
Nausea	1 (3)	0	1 (3)
Hyponatremia	0	1 (4)	1 (3)
Deep vein thrombosis	1 (3)	0	1 (3)
Lymphocele	1 (3)	1 (4)	0
Neutropenia	2 (6)	0	0
Pulmonary embolism	1 (3)	0	1 (3)
Events of clinical interest			
Any infection	26 (79)	20 (77)	20 (67)
Any serious infection	7 (21)	4 (15)	5 (17)
Fungal infection	5 (15)	1 (4)	2 (7)
Viral infection	4 (12)	2 (8)	6 (20)
Any malignancy	0	1 (4)	1 (3)

Table 15: Mean cGFR at month 12 and mean change in cGFR from baseline to month 12

	Belatacept (n = 84)			CNI (n = 89)		
Parameter	Baseline	Month 12	Mean Change from Baseline	Baseline	Month 12	Mean Change from Baseline
Mean mGFR, mL/min/1.73 m^2 (SD)	53.5 (11)	60.5 (16.19)	7 (11.99)	54.5 (10.26)	56.5 (14.42)	2.1 (10.34)
Baseline cGFR						
<45 (n = 40)	40.2 (3.87)	43.9 (10.56)	3.7 (11)	41.1 (3.35)	43.9 (7.43)	2.8 (8.17)
45 to 60 (n = 70)	51.7 (3.98)	61.7 (13.88)	10 (13.41)	51.4 (3.67)	53.2 (12.84)	1.9 (11.72)
>60 (n = 59)	66.2 (4.98)	71.8 (11.38)	5.7 (10.17)	65.8 (4.2)	67.8 (10.81)	2 (10.13)
Baseline CNI						
CsA (n = 74)	51.9 (10.11)	59.2 (18.17)	7.7 (14.51)	53.1 (11.66)	53.1 (16.18)	0 (10.86)
TAC (n = 95)	54.8 (11.61)	61.5 (14.59)	6.4 (9.7)	55.6 (8.98)	59.2 (12.41)	3.7 (9.73)
Time from transplantation to randomization						
6 to 12 months (n = 48)	54.2 (10.31)	59.6 (16.24)	5.4 (12.56)	54.5 (8.43)	56.1 (14.23)	1.6 (11.80)
12 to 18 months (n = 25)	49.7 (10.27)	53.8 (19.28)	4.1 (13.57)	53.3 (12.1)	51.8 (16.05)	-1.5 (11.41)
>18 months (n = 85)	53.8 (11.66)	61.4 (15.02)	7.6 (10.68)	54.5 (10.93)	57.1 (14.03)	2.8 (9.49)
Diabetes status						
Diabetic (n = 45)	53.5 (13.27)	55.5 (16.73)	2.7 (11.17)	54.6 (10.61)	54.6 (15.86)	-0.1 (12.64)
Nondiabetic (n = 24)	53.5 (10)	62.5 (15.66)	8.8 (11.95)	54.5 (10.22)	57.1 (13.35)	2.8 (9.51)
Type of transplant						
Living donor (n = 83)	54.9 (10.66)	60.5 (14.07)	5.9 (11.34)	56.1 (10.43)	57.5 (15.86)	1.6 (11.58)
Deceased donor (n = 86)	52.2 (11.29)	60.5 (18.16)	8.0 (12.62)	52.9 (9.94)	55.5 (12.97)	2.6 (9.09)

Table 16: Secondary Outcomes at Month 12

Month 12 Endpoints	Belatacept (n = 84)	CNI (n = 89)
Acute rejection, n (%)	6 (7)	0
Banff grade		
Mild acute (IA)	1 (1)	0
Mild acute (IB)	1 (1)	0
Moderate acute (IIA)	3 (4)	0
Moderate acute (IIB)	1 (1)	0
Severe acute (III)	0	0
Patient/graft survival, n (%)	84 (100)	88 (99)
Graft loss or death	0	1 (1)
Graft loss	0	0
Death	0	1 (1)
Death with functioning graft	0	1 (1)

Table 17: Most Common Serious Adverse Events, Malignancies and Infections

Event, n (%)	Belatacept (n = 84)	CNI (n = 89)
Total patients with serious adverse events, n (%)	20 (24)	17 (19)
Pyrexia	3 (4)	0
Pyelonephritis	2 (2)	1 (1)
Urinary tract infection	2 (2)	0
Basal cell carcinoma	1 (1)	2 (2)
CMV infection	0	2 (2)
Total patients with malignancies, n (%)	2 (2)	2 (2)
Basal cell carcinoma	1 (1)	2 (2)
Kaposi's sarcoma	1 (1)	0
Total patients with viral infections, n (%)	11 (13)	12 (14)
Herpes infections	4 (5)	3 (3)
Varicella	0	1 (1)
BK virus	3 (4)	0
BK - associated nephropathy	1 (1)	0
CMV infection	2 (2)	2 (2)
Total patients with fungal infections, n (%)	11 (13)	3 (3)
Tinea versicolor	5 (6)	0
Fungal infection	1 (1)	1 (1)
Fungal skin infection	1 (1)	1 (1)
Onchomycosis	1 (1)	1 (1)
Body tinea	1 (1)	0
Skin candida	1 (1)	0
Tinea cruris	0	1 (1)
Vulvovaginal mycotic infection	1 (1)	0