

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125288Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 31, 2011
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Subject	Cross-Discipline Team Leader Review
NDA/BLA #	125,288
Supplement#	
Applicant	Bristol-Myers Squibb Company
Date of Submission	
PDUFA Goal Date	April 15, 2010 (internal goal date) June 15, 2010
Proprietary Name / Established (USAN) names	Belatacept (Nulojix®)
Dosage forms / Strength	Lyophilized Powder for Intravenous Infusion 250 mg single-use vial
Proposed Indication(s)	NULOJIX™ (belatacept) is indicated for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. NULOJIX has been used in combination with an interleukin-2 (IL-2) receptor antagonist, a mycophenolic acid (MPA), and corticosteroids.
Recommended:	Approval, with revised indication shown below: <i>NULOJIX™ (belatacept) is indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant. NULOJIX is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.</i>

1. Introduction

Belatacept is a selective T-cell costimulation blocker indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant.

The Division of Special Pathogen and Transplant Products (DSPTP) agreed to a rolling resubmission of the BLA. The original BLA was submitted by the applicant, Bristol-Myers Squibb (BMS) on June 30, 2009, received July 1, 2009. A standard review was undertaken.

A Complete Response (CR) letter was issued May 1, 2010 which outlined deficiencies in the product quality, product quality microbiology, and facilities inspections portions of the application. The CR letter also requested additional clinical data and Risk Evaluation and Mitigation Strategy (REMS) information.

A CR to the May 1, 2010 letter was submitted by BMS in “reviewable units” as noted below. The final piece was submitted December 15, 2010, which started the 6-month PDUFA review clock.

August 16, 2010:	Response to the proposed REMS deficiency
September 9, 2010:	Response to the CMC product quality deficiency
September 24, 2010:	Responses to the clinical, product quality microbiology, facility inspections, safety update, labeling, nonclinical study reports, clinic study reports, and Medication Guide deficiencies.
December 15, 2010:	Response to facilities inspection readiness

2. Background

Please refer to CDTL review of the original BLA submission, dated April 30, 2010 for a complete discussion of the BLA. This CDTL review only addresses the deficiencies noted in the CR letter and any additional data that was submitted for review as part of the CR submission.

3. CMC/Device

CMC Quality (Team Leader’s Review)

Susan Kirshner, Ph.D., Associate Laboratory Chief, Laboratory of Immunology, Division of Therapeutic Proteins provided the Quality Team Leader’s review. She recommended approval

of the BLA and included two (2) post-marketing requirements (PMRs) and four (4) post-marketing commitments (PMCs).

The PMRs are (*as summarized by the CDTL*): (1) to qualify the (b) (4) and (2) characterize the micron and submicron particulates in the drug product under real-time and stress stability conditions.

The PMCs are (*as summarized by the CDTL*): (1) to conduct a trend analysis (b) (4) profiles from 30 consecutively released drug substance batches, and reevaluate their acceptance criteria; (2) conduct a trend analysis for (b) (4) content using an extended characterization (b) (4) from 30 consecutively released future drug substance batches and evaluate the need for introducing a validated release method and setting acceptance criteria; (3) place on stability any drug substance lot which is held for the maximum hold time allowed at each (b) (4) and determine its synergistic impact; and (4) study multiple freeze-thaw conditions that are reflective of intended-use conditions to support multiple freeze-thaw conditions. Also provide stability data to support 12 months at 2-8°C following (b) (4) freeze-thaw cycles; and provide stability data supporting stability limits of drug product produced from drug substance (b) (4) following (b) (4) freeze-thaw cycles (b) (4)

Dr. Kirshner notes that the Approval Letter should indicate the following information:

- The names of the approved manufacturing facilities.
- The dating period for Nulojix (belatacept) shall be 30 months from the date of **manufacture when stored at 2 – 8°C** protected from light.
- The dating period for drug substance shall be 30 months (b) (4)
- (b) (4)
- Nulojix is a specified product. Per 21CFR601.2(c)(1) specified products do not need to be on lot release.

Belatacept is produced as a (b) (4) using a Chinese hamster ovary (CHO) cell line. (b) (4)

Product comparability following major manufacturing changes was established throughout product development, and numerous stability assessments were conducted of the drug

substance and/or product, including degradation pathways, photostability, and freeze-thaw assessments.

Dr. Kirshner describes the drug product, the container and container markings, and storage conditions. The product is 250 mg sterile, (b) (4) lyophilized powder for intravenous (IV), single-use administration, packaged in a 20-cc Type I (b) (4) glass tubing vial, stoppered with 20-mm (b) (4) rubber stoppers, sealed with 20-mm aluminum seals with flip-off caps, and co-packaged with a silicone-free syringe. The product includes a (b) (4)

The drug product (b) (4) may be stored for up to 30 months at 2 – 8°C and protected from light.

Additionally, the applicant developed electrochemiluminescence (ECL) based assays to detect binding antibodies to both the CTLA-4 portion of belatacept as well as to the Ig-Fc portion of belatacept. The antigen specificity of samples that screened positive in the binding assay was confirmed. Belatacept specific binding antibodies were assessed for their ability to inhibit the biological effect of belatacept in a cell based potency assay, and all the assays were appropriately validated.

The applicant responded adequately to previous FDA deficiencies concerning manufacturing, specifications, reference standards, stability, clinical infusion rates and (b) (4) and immunogenicity assays.

CMC Sterility Assurance and Product Quality Microbiology

Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT reviewed the applicant's BLA resubmission for CMC sterility assurance and product quality microbiology. Patricia Hughes, Ph.D, Team Leader, provided concurrence with Dr. Chi's conclusions and recommendation.

Dr. Chi's review addresses the Environmental Assessment requirements of 21 CFR 25.31(c), and the six manufacturing deficiencies identified in the OAP May 1, 2010 Complete Response letter.

- Belatacept meets the requirements for a categorical exclusion from having to file an Environmental Assessment, and the product is not expected to significantly affect the quality of the human environment. Therefore, there is no further Environmental Assessment requirement.
- The six technical deficiencies previously identified have all been satisfactorily addressed by the applicant. These deficiencies included a proper setting of (b) (4) (b) (4) qualifying testing methods, (b) (4) (b) (4) justification of the allowed temperature ranges in vehicles used to ship product, endotoxin specifications of drug product, and data to support a label claim for storage conditions for maintaining constituted product.

The CMC sterility assurance and product microbiology team is requesting one post-marketing commitment (PMC) in the May 1, 2010 CR letter:

- *Provide information and summary data on the container closure integrity test developed in support of finished product on stability* (b) (4)

Manufacturing Site Inspections

The manufacturing deficiencies cited in the May 1, 2010 CR letter included those related to sterility assurance and product quality, which were identified during a pre-license inspection of the drug product manufacture site in Manati, Puerto Rico conducted during the week of March 15, 2010. The site was issued an OAI warning letter (Official Action Indicated). In addition, the facility in East Syracuse, New York which makes the drug substance was found to also have microbial control deficiencies when inspected in November 2009. Both sites were considered to have an unacceptable compliance status such that the inspectors recommended withholding approval until the deficiencies were satisfactorily resolved.

The deficiencies at the East Syracuse, NY site have since been resolved. The site in Manati Puerto Rico was reinspected during February 23 to March 28, 2011. During this inspection, the site was issued a Form 483 (used to communicate significant deviations from cGMPs discovered during the inspection). Eight items were identified. The deficiencies cited during the previous inspection and noted in the warning letter were all cleared during this inspection.

At the time of this writing, BMS has submitted a written response on April 18, 2011 to the FDA San Juan District Office addressing each of the eight concerns noted on inspection. The District Office has yet to notify the Office of Compliance of their final decision regarding the **applicant's response**. A **satisfactory response** must be determined by FDA before the application can be considered for approval.

4. Nonclinical Pharmacology/Toxicology

Janice A. Lansita, Ph.D., DABT, reviewed **the applicant's BLA resubmission** for Pharmacology/Toxicology. She recommended approval of the BLA. William H. Taylor, Ph.D., DABT (Pharmacology/Toxicology Supervisor) **concurred with Dr. Lansita's approval** recommendation. There are no Pharmacology/Toxicology recommendations for post-marketing requirements or post-marketing commitments.

Bristol-Meyers Squibb submitted two cynomolgus monkey study reports to the BLA on September 27, 2010. The purpose of the studies was to investigate whether belatacept penetrates into the brain or affects brain permeability when administered alone or with mycophenolate mofetil (MMF), and to better understand the mechanism behind clinical CNS PTLD cases.

In the first study (DS09027), belatacept was administered intravenously to cynomolgus monkeys (4/group) once weekly for 5 weeks at doses of 0 (saline control), 10, and 50 mg/kg/week. Immunofluorescent microscopy was used to identify immune cells, expression of CD80/ CD86 and CD20, and the presence of belatacept.

Low levels of belatacept ($<0.07\%$ of serum concentrations) were identified in the cerebrospinal fluid and brain microvasculature of animals from both belatacept groups, but not in any other (extravascular) brain tissues. The study director indicated the levels of belatacept in CSF were consistent with blood contamination from sample collection. The brain to serum ratios of belatacept levels measured (0.03-0.014%) were consistent with those of IgG (0.03-0.16%) and albumin (0.02-0.03%), which do not normally cross the blood brain barrier. Levels of belatacept in brain microvasculature were consistent with levels of residual red blood cells observed in the brain microvasculature following whole-body saline perfusion. Additionally, the study director stated there were no test article related changes in immune cell populations or CD80/86 expression in the monkey brains.

However, staining for MHC Class II antigens (expressed on macrophages, dendritic cells, granulocytes and B-cells) was increased (non-statistically significantly) in the brain tissue of animals administered both doses of belatacept, compared with controls. Dr. Lansita stated that it is not known whether this change represents an up-regulation of MHC Class II on cells specific to the CNS, since markers for these specific cell types (e.g., microglia, astrocytes, or oligodendrocytes) were not examined. No adverse findings were associated with this observation; therefore the clinical relevance is unknown. This information was included in Section 13.2 (Animal Toxicology and/or Pharmacology) of the package insert (see Section 12 of this review).

In the second study (DS09113), cynomolgus monkeys were administered belatacept intravenously once weekly for 5 weeks (6/group) at 50 mg/kg, with or without daily oral cyclosporine A (CsA) or daily oral MMF. This study was conducted to examine levels of belatacept or mycophenolic acid (MPA) in the brain and CSF when belatacept was administered alone, when belatacept was administered with MMF, and when belatacept was administered with CsA.

There were no test article-related adverse effects or clinical observations in the second study. As in the first study, belatacept, MPA, and CsA levels in the brain and CSF were consistent with low-level blood contamination. These results suggest belatacept did not alter brain permeability in the presence of MMF or CsA. Both belatacept and CsA decreased systemic MPA levels in monkeys when they were separately coadministered with MMF, but the mean AUC of MPA was nearly twice as high in belatacept + MMF treated animals compared with that in CsA + MMF treated animals.

In summarizing these two monkey studies, belatacept was not associated with any meaningful clinical changes. The studies do not rule out the possibility that some belatacept might be getting into the brain. However, the evidence that belatacept penetrated the brain is very weak. The increased presence of MHC Class II antigens in brain tissue of animals administered

belatacept might be important to understanding the mechanism of PTLT in patients. At this time, however, the meaning of these study findings is unknown.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review by Gerlie Gieser, PhD. (dated March 24, 2011) states that the clinical pharmacology information presented in the submission are acceptable to support approval of the belatacept less intense (LI) regimen provided agreement can be reached on language in Sections 7 (Drug Interactions) and 12.2 (Pharmacodynamics) of the package insert.

The reviewer conducted exploratory analyses using concentrations of immune globulins obtained from patients in the clinical trials and evaluated these concentrations in relation to the incidence of certain adverse events, particularly PTLT, CND PTLT and PML.

The following is a summary of these findings, as proposed for inclusion in the package insert in Section 12.2 Pharmacodynamics:

In clinical trials, greater reductions in mean immunoglobulin (IgG, IgM, and IgA) concentrations were observed from baseline to Month 6 and Month 12 post-transplant in belatacept-treated patients compared to cyclosporine-treated patients. In an exploratory subset analysis, a trend of decreasing IgG concentrations with increasing belatacept trough concentrations was observed at Month 6. Also in this exploratory subset analysis, belatacept treated patients with CNS PTLT, CNS infections including PML, other serious infections and malignancies were observed to have a higher incidence of IgG concentrations below the lower limit of the normal range (< 694 mg/dL) at Month 6 than those patients who did not experience these adverse events. However, it is unclear whether any causal relationship between an IgG concentration below the lower level of normal and these adverse events exists, as the analysis may have been confounded by other factors (e.g., age greater than 60 years, receipt of an extended criteria donor kidney, exposure to lymphocyte depleting agents) which were also associated with IgG below the lower level of normal at Month 6 in these trials.

The reviewer also noted that belatacept inhibits the production of cytokines *in vitro*. Cytokines may affect the mRNA expression of CYP450 metabolizing enzymes, which in turn may result in alterations of the systemic concentrations of the co-administered drug that is a CYP450 substrate; therefore, it was recommended that Section 7 Drug Interactions also discusses this risk:



CDTL comment: The Clinical Pharmacology team and BMS agreed to the version of the package insert which is discussed in Section 12 of this review.

6. Clinical Microbiology/Immunology

Aaron M. Ruhland, PhD, reviewed the applicant's BLA resubmission for Clinical Microbiology/Immunology. He recommended approval of the application. Shukal Bala, PhD (Clinical Microbiology/Immunology Team Leader) concurred with Dr. Ruhland's approval recommendation. There are no Clinical Microbiology/Immunology recommendations for post-marketing requirements or post-marketing commitments.

Dr. Ruhland reviewed the first cynomolgus monkey study (DS09027) which Dr. Lansita reviewed (i.e., the study examining belatacept in brains and CSF with immunologic measurements). Drs. Ruhland and Lansita independently made the same observations and reached the same conclusions regarding the first study. (See summary under Section 4 of this review.)

Dr. Ruhland also reviewed supplemental clinical immunologic data (months 12 – 36) from two phase 3 clinical trials (IM103008 and IM103027) submitted with the applicant's resubmission. A summary of his conclusions follow:

- Patients treated with belatacept, particularly those treated with the less intensive regimen (which is proposed for approval), developed fewer *de novo* donor-specific antibodies (DSAs) than patients treated with CsA.
- DSAs present at baseline in patients treated with belatacept were less persistent than those present at baseline in patients treated with CsA.
- Patients treated with belatacept who tested positive for DSAs were not more likely to experience an episode of acute rejection than those who tested negative for DSAs.
- Patients treated with belatacept who tested positive for DSAs were not at more risk of undergoing acute rejection than patients treated with CsA who test positive for DSAs.
- Patients who discontinued belatacept treatment did not develop DSAs at a higher rate than patients who continued treatment with belatacept.

7. Clinical/Statistical- Efficacy

The CR letter of May 10, 2010 contained two Clinical deficiencies, as noted below. Although not noted as deficiencies in the Clinical or CDTL reviews of the original submission, the Division and Office Directors, in their CR memos requested the 36 month data from Studies IM103008 and IM103027 in order to obtain additional information on outcome, such as mortality, graft loss, PTLTD, and renal function (GFR), to further assess the risk and benefit of belatacept. The data submitted by the applicant on September 24, 2010 addresses the first deficiency. (b) (4)

(b) (4)

As a brief overview, the development program of belatacept consisted of two Phase 3 trials in *de novo* renal transplant recipients. Study IM103008 enrolled recipients of organs from living

donors and deceased standard criteria donors. Study IM103027 enrolled recipients of organs from deceased donors with extended criteria. The extended criteria were: donor age ≥ 60 years; or donor age 50 to 59 and ≥ 2 of the following: cerebrovascular accident, hypertension, and serum creatinine > 1.5 mg/dL; or anticipated cold ischemia time ≥ 24 hours; or donor with cardiac death (non-heart beating donor). Both trials were 3 year multi-center, multi-national, randomized, active controlled trials. Patients were randomized to receive treatment with either belatacept M1 (more intensive), belatacept LI (less intensive), or CsA. All patients received induction with basiliximab and maintenance therapy with mycophenolate mofetil (MMF), and corticosteroids. The trials were open label with respect to belatacept and CsA but the two belatacept regimens were blinded through 12 months. Both were designed as 36 month trials.

CLINICAL DEFICIENCIES

1. Regarding the indication of prophylaxis of organ rejection in adult patients receiving renal transplants, you have not provided sufficient long-term data to evaluate the long-term effect of belatacept on the rate of post-transplant lymphoproliferative disorder (PTLD), renal effects, cardiovascular events, graft and patient survival.

To address this deficiency, provide the 36-month data from your Phase 3 studies, particularly data on outcomes such as mortality, graft loss, GFR, PTLD and other serious adverse reactions.

(b) (4)



The Medical Officer (dated March 25, 2011 by Patrick Archdeacon, MD) and Statistical (dated March 11, 2011 by Cheryl Dixon, PhD) reviews of the resubmission refer mainly to the 36 month findings.

Please see the original Clinical Review (dated April 30, 2010) for detailed discussions of the data and science supporting the application, as well as the 12 and 24 month efficacy and safety analyses. The 12 and 24 month efficacy data was also reviewed in the original Statistical Review (dated March 23, 2010).

Patient Population

In Study IM103008, the intent to treat (ITT) population consisted of 666 randomized and transplanted patients (219 belatacept MI, 226 belatacept LI, and 221 CsA). A total of 471 patients completed 36 months of treatment. In IM103027, the intent to treat (ITT) population consisted of 543 randomized and transplanted patients (184 belatacept MI, 175 belatacept LI, and 184 CsA). A total of 330 patients completed 36 months of treatment. In both trials, slightly more subjects had discontinued treatment with CsA than the belatacept regimens by 36 months, as shown in Table 1. The most common reasons for discontinuation were adverse events and lack of efficacy. At 12 months in IM103008, the primary reason for discontinuation from treatment was different for the belatacept and CsA treatment groups. For the belatacept

treatment groups, the most common reason for discontinuation of treatment was due to lack of efficacy. For the CsA treatment group, adverse event(s) was the most common reason for discontinuation of treatment.

Table 1
Patient Randomization and Treatment Discontinuation up to 36 Months
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	Randomized and transplanted (ITT)	219	226	221
	Randomized, transplanted and treated	219	226	215
	Number discontinuing treatment by 36 months	61 (27.9)	56 (24.8)	72 (33.5)
	Adverse event	29 (13.2)	26 (11.5)	32 (14.9)
	Lack of efficacy			18 (8.4)
027	Randomized and transplanted (ITT)	184	175	184
	Randomized, transplanted and treated	183	174	179
	Number discontinuing treatment by 36 months	74 (40.4)	60 (34.5)	79 (44.1)
	Adverse event	19 (10.4)	15 (8.6)	44 (24.6)
	Lack of efficacy			17 (9.5)

Source: Table 1; Statistical Review by Cheryl Dixon of BLA 125,288 resubmission

Efficacy

Studies IM103008 and IM103027 were both designed as 36 month studies. The primary efficacy evaluation of these trials was conducted at 12 months. However, the applicant's secondary objectives included the assessment of the effects of belatacept, relative to cyclosporine (CsA) at 36 months on patient and graft survival, measures of acute rejection, calculated glomerular filtration rate (GFR), new onset diabetes mellitus after transplant (NODAT), measures of hypertension including systolic and diastolic blood pressure, and measures of dyslipidemia including serum total, LDL, and HDL cholesterol and triglycerides.

The results for these endpoints will be presented and discussed primarily in a descriptive fashion.

The following summary is excerpted from the Clinical and Statistical Reviews and supported by data tables from the Statistical Review. Results for all three treatment arms are included; however, the belatacept MI arm is not being considered for approval.

Composite Biopsy Proven Acute Rejection (BPAR) Endpoint

Demonstration of efficacy of belatacept in the original BLA was primarily supported by an assessment of the composite endpoint of biopsy proven acute rejection (BPAR), graft loss, death, or loss to follow-up at 12 months. Cumulative rates of BPAR at 36 months are presented in Table 2. The observed At 36 months, the rates of BPAR, graft loss, death, or loss

to follow-up were similar between the belatacept LI and CsA treatment groups in both trials and support the conclusion of the original Clinical/Statistical Reviews that belatacept LI has efficacy in the context of kidney transplantation.

Table 2: Biopsy Proven Acute Rejection, Graft Loss, or Death at 36 Months
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	Met Endpoint	70/219 (32.0)	58/226 (25.7)	57/221 (25.8)
	Biopsy Proven Acute Rejection	59	50	31
	Graft Loss	5	4	8
	Death	4	3	13
	Unknown	2	1	5
	Difference from CsA (97.3% CI)	6.2 (-3.8, 16.2)	-0.1 (-9.7, 9.5)	
027	Met Endpoint	70/184 (38.0)	63/175 (36.0)	68/184 (37.0)
	Biopsy Proven Acute Rejection	41	42	42
	Graft Loss	14	14	15
	Death	15	7	8
	Unknown	0	0	3
	Difference from CsA (97.3% CI)	1.0 (-10.7, 12.7)	-1.0 (-12.8, 10.8)	

*First occurrence of biopsy proven acute rejection, graft loss, or death. Refer to patient and graft survival table for total number of graft loss and/or death.

Source: Table 2; Statistical Review by Cheryl Dixon of BLA 125,288 resubmission

Patient and Graft Survival Endpoint

Patient and graft survival at 36 months is presented in Table 3. In IMI03008, there were 8, 12, and 14 fewer belatacept MI, belatacept LI, and CsA patients surviving with a functioning graft at Month 36 compared to Month 12. In IM1 03027, there were 11, 12, and 13 fewer belatacept MI, belatacept LI, and CsA patients surviving with a functioning graft at Month 36 compared to Month 12. The observed rates and confidence intervals support the conclusion of the original Clinical/Statistical Reviews that belatacept LI has efficacy in the context of kidney transplantation.

Table 3: Patient and Graft Survival at 36 Months
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	Surviving with a functioning graft	200/219 (91.3)	206/226 (91.2)	192/221 (86.9)
	Graft Loss	10 (2 died)	9 (1 died)	10 (1 died)
	Death w/ functioning graft	7	9	14
	Unknown status	2	2	5
	Difference from CsA (97.3% CI)	4.4 (-2.6, 11.4)	4.3 (-2.7, 11.3)	
027	Surviving with a functioning graft	147/184 (79.9)	143/175 (81.7)	143/184 (77.7)
	Graft Loss	18 (4 died)	21 (5 died)	23 (4 died)
	Death w/ functioning graft	18	10	13
	Unknown status	1	1	5
	Difference from CsA (97.3% CI)	2.2 (-7.8, 12.2)	4.0 (-5.9, 13.9)	

Source: Table 3; Statistical Review by Cheryl Dixon of BLA 125,288 resubmission

The incidence and severity of BPAR at 36 months is shown in Table 4. The results are consistent with those seen at 12 months: In IMI03008, there are numerically more biopsy proven acute rejections in the belatacept treated patients than in the CsA treated patients and

the severity of the BPAR episodes is greater in the belatacept groups. In IM103027, the incidence and severity of BP AR are more similar across treatment groups.

Table 4: Biopsy Proven Acute Rejection at 36 Months
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	BPAR, N (%)	59 (26.9)	50 (22.1)	31 (14.0)
	Mild Acute (IA), N (%)	7 (3.2)	6 (2.7)	8 (3.6)
	Mild Acute (IB), N (%)	6 (2.7)	10 (4.4)	9 (4.1)
	Moderate Acute (IIA), N (%)	20 (9.1)	19 (8.4)	9 (4.1)
	Moderate Acute (IIB), N (%)	23 (10.5)	14 (6.2)	5 (2.3)
	Severe Acute (III), N (%)	3 (1.4)	1 (0.4)	0
027	BPAR, N (%)	41 (22.3)	42 (24.0)	42 (22.8)
	Mild Acute (IA), N (%)	2 (1.1)	5 (2.9)	2 (1.1)
	Mild Acute (IB), N (%)	6 (3.3)	3 (1.7)	6 (3.3)
	Moderate Acute (IIA), N (%)	14 (7.6)	24 (13.7)	25 (13.6)
	Moderate Acute (IIB), N (%)	18 (9.8)	10 (5.7)	9 (4.9)
	Severe Acute (III), N (%)	1 (0.5)	0	0

Source: Table 4; Statistical Review by Cheryl Dixon of BLA 125,288 resubmission

Glomerular Filtration Rate

Mean calculated GFR at 1, 3, 12, 24, and 36 months is depicted in Figures 1 and 2 for IM103008 and IM103027, respectively. The differences in renal function for the belatacept regimens compared to CsA that were apparent in the first month after transplant and maintained up to 24 months continue to be maintained up to 36 months. Slopes of the calculated GFR curves from Month 3 (the time when post-transplant GFR appeared to stabilize) were calculated and are shown in Table 5. For the belatacept regimens, the 95% confidence intervals about the slopes do not exclude 0 indicating that there is maintenance, but not improvement, of calculated GFR over time.

Due to the vasoconstrictive effects of CsA on the afferent renal artery, it remains unclear whether the superior GFRs observed in belatacept patients reflect a healthier transplant kidney, more favorable renal hemodynamics, or both.

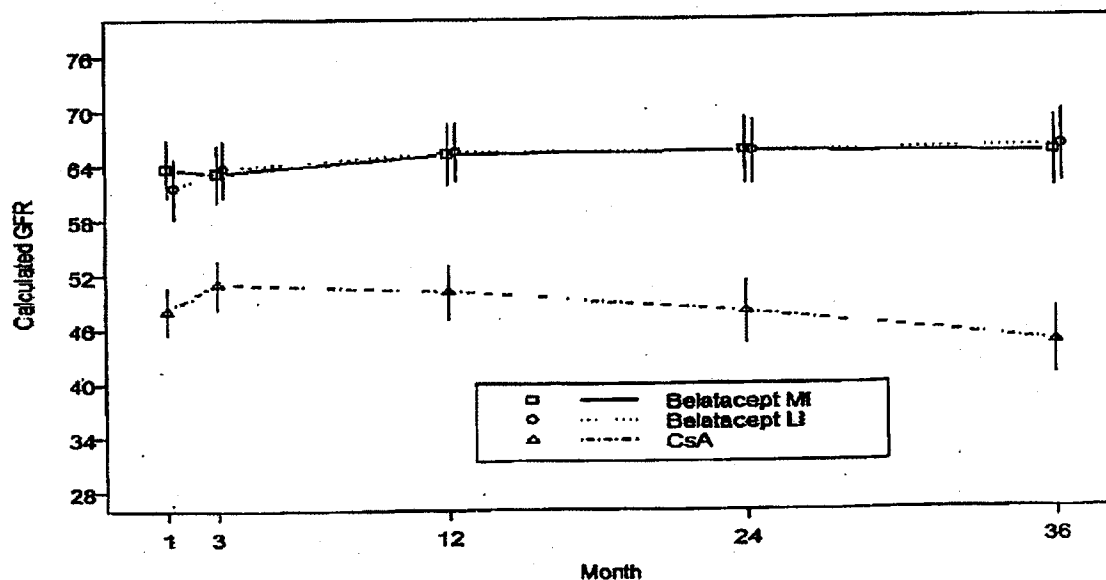
Table 5: Slope for Calculated GFR from Month 3 to 36
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	Slope* (standard error)	0.53 (0.52)	0.77 (0.51)	-2.21 (0.53)
	95% Confidence Interval	(-0.49, 1.54)	(-0.23, 1.77)	(-3.25, -1.17)
027	Slope* (standard error)	-0.92 (0.58)	-0.80 (0.58)	-1.97 (0.58)
	95% Confidence Interval	(-2.05, 0.22)	(-1.93, 0.33)	(-3.11, -0.82)

*mL/min/1.73 m²/year

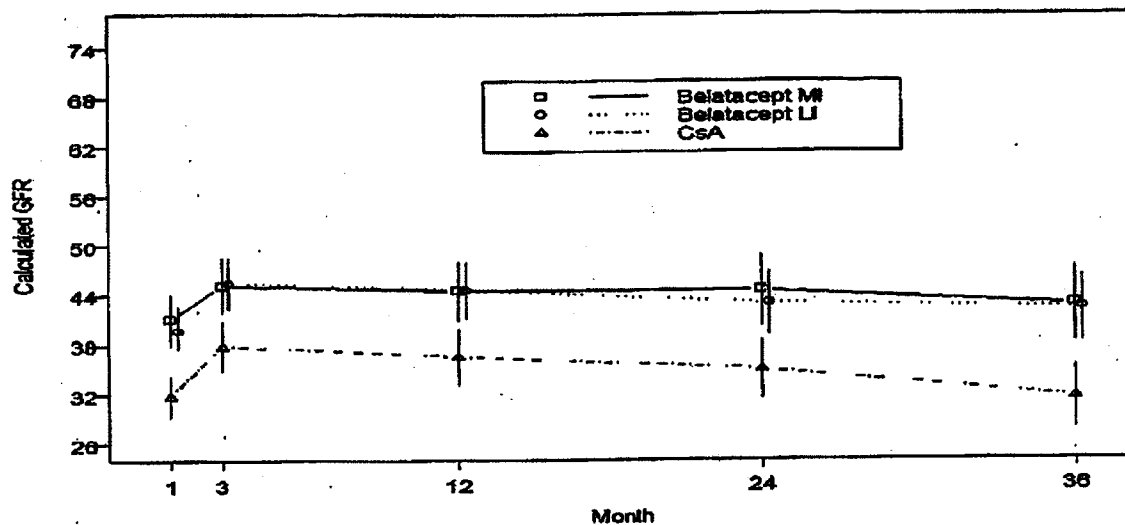
Source: Table 6; Statistical Review by Cheryl Dixon of BLA 125,288 resubmission

Figure 1: Mean Calculated GFR (mL/min) through 36 Months
IM103008



Error bars represent 95% confidence interval of the mean
Source: Figure 1; Statistical Review by Cheryl Dixon of BLA 125,288 resubmission

Figure 2: Mean Calculated GFR (mL/min) through 36 Months
IM103027



Error bars represent 95% confidence interval of the mean
Source: Figure 2; Statistical Review by Cheryl Dixon of BLA 125,288 resubmission

Table 6: Slope for Calculated GFR from Month 3 to 36
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	Slope* (standard error)	0.53 (0.52)	0.77 (0.51)	-2.21 (0.53)
	95% Confidence Interval	(-0.49, 1.54)	(-0.23, 1.77)	(-3.25, -1.17)
027	Slope* (standard error)	-0.92 (0.58)	-0.80 (0.58)	-1.97 (0.58)
	95% Confidence Interval	(-2.05, 0.22)	(-1.93, 0.33)	(-3.11, -0.82)

*mL/min/1.73 m²/year

Source: Table 6; Statistical Review by Cheryl Dixon of BLA 125,288 resubmission

In order to determine the impact of the difference in the number and severity of acute rejection events, analyses of calculated GFR at 36 months by rejection status were conducted, as was done previously for the 12 month analyses. As was seen at 12 months, in patients with acute rejection and in subjects without acute rejection, mean calculated GFR was higher in the belatacept groups than in the CsA group. Mean calculated GFR was lower for patients who experienced an acute rejection compared to those who did not experience an acute rejection. The differences in calculated GFR for those who did and did not experience an acute rejection were greatest for belatacept treated patients compared to CsA patients in IMI03008 but more similar in IMI03027. Interpretation of these analyses should be made with caution because of limitations in the data due to the following reasons: missing GFR at 36 months for some patients; not all patients remained on study therapy for the entire 36 months and those who didn't may have switched to a regimen containing a calcineurin inhibitor; and these subsets of patients are based on an outcome variable that is affected by treatment. Data not shown. See Table 7 in the Statistical Review.

EBV Seropositive Subpopulation

As previously discussed, a higher rate of PTLT was observed among recipients of belatacept-based immunosuppression compared to CsA-based immunosuppression in the clinical trials. Since belatacept will be contraindicated in patients who are EBV seronegative or with unknown serostatus, an analysis of the 36 month data supporting the efficacy of belatacept in the EBV seropositive subpopulation was performed, as shown in Tables 7 and 8. The conclusions drawn for the EBV positive patients are similar to those drawn for the overall population.

Table 7: Biopsy Proven Acute Rejection, Graft Loss, Death at 36 Months
EBV Positive Subjects
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	Met Endpoint	67/195 (34.4)	50/202 (24.8)	46/184 (25.0)
	Biopsy Proven AR	56	45	25
	Graft Loss	5	2	6
	Death	4	2	11
	Unknown	2	1	4
	Diff from CsA (97.3% CI)	9.4 (-0.9, 19.7)	-0.2 (-9.9, 9.5)	
027	Met Endpoint	65/170 (38.2)	54/156 (34.6)	61/168 (36.3)
	Biopsy Proven AR	38	37	37
	Graft Loss	14	13	14
	Death	13	4	7
	Unknown	0	0	3
	Diff from CsA (97.3% CI)	1.9 (-9.7, 13.5)	-1.7 (-13.5, 10.0)	

*First occurrence of biopsy proven acute rejection, graft loss or death. Refer to subject and graft survival table for total number of graft loss and/or death.

Source: Table 8; Statistical Review by Cheryl Dixon of BLA 125,288 resubmission

Table 8: Patient and Graft Survival at 36 Months for EBV Positive Subjects
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	Surviving with a functioning graft	179/195 (91.8)	187/202 (92.6)	162/184 (88.0)
	Graft Loss	8 (1 died)	5	7 (1 died)
	Death w/ functioning graft	6	8	11
	Unknown status	2	2	4
	Difference from CsA (97.3% CI)	3.8 (-3.1, 10.7)	4.6 (-2.1, 11.3)	
027	Surviving with a functioning graft	135/170 (79.4)	130/156 (83.3)	130/168 (77.4)
	Graft Loss	18 (5 died)	19 (5 died)	22 (4 died)
	Death w/ functioning graft	16	6	12
	Unknown status	1	1	4
	Difference from CsA (97.3% CI)	2.0 (-7.9, 11.9)	5.9 (-3.8, 15.6)	

Source: Table 9; Statistical Review by Cheryl Dixon of BLA 125,288 resubmission

Other Pre-Specified Endpoints

Although the applicant pre-specified an analysis of NODAT, hypertension, and dyslipidemia as part of their assessment of efficacy, these endpoints are discussed as part of the evaluation of safety in both the Clinical and Statistical Reviews. See summary below in the discussion of safety.

Donor Specific Antibodies

The applicant collected data on the development of donor specific antibodies (DSAs) during the three years of the clinical trials. They submitted analyses of the 36 month data suggesting that the production of DSAs was less frequent among the belatacept-treated patients compared to CsA-treated patients and presented these data as a subgroup analysis of patients with and without a history of acute rejection. However, the Clinical Reviewer felt that development of DSAs after an acute rejection event does not have the same diagnostic significance as the presence of DSAs at the time of an acute rejection event.

See summary of Microbiology/Immunology review findings concerning DSAs in Section 6.

Mention of DSAs in the package insert is limited to a sentence describing the overall prevalence in the clinical trials up to 36 months post-transplant (see Section 12 of this review).

Chronic Allograft Nephropathy (CAN)

The occurrence of CAN, as defined by the Banff '97 classification system, was assessed at 12 months as a secondary endpoint in the clinical trials. Data was not collected past 12 months; therefore, no new data was presented in the BLA resubmission. Due to the fact that CAN is a nonspecific diagnosis and that the clinical relevance remains unclear, the Clinical Reviewer was not in favor of not making clinical inferences from the result. Therefore, the prevalence rates of CAN for the belatacept LI and CsA treatment groups in the clinical trials have been included in Section 14 (Clinical Trials) of the the package insert with the qualifier that the "clinical significance of this finding is unknown." (See Section 12 of this review)

Table 9: Prevalence of Chronic Allograft Nephropathy (CAN) at 12 Months

	Belatacept MI	Belatacept LI	CsA
IM103008	N=219	N=226	N=219
Prevalence (n, %)	40 (18.3)	54 (23.9)	71 (32.4)
Difference of CsA 97.3% CI	-14.2 (-23.2, -5.0)	-8.5 (-17.9, 0.9)	NA
IM103027	N=184	N=175	N=184
Prevalence (n, %)	82 (44.8)	80 (46.0)	95 (51.6)
Difference of CsA 97.3% CI	-6.8 (-18.2, 4.7)	-5.7 (-17.2, 6.0)	NA

Source: Original Statistical Review by Cheryl Dixon of BLA 125,288

The Medical Officer's efficacy conclusions (review dated March 25, 2011) are reproduced below:

My analysis of the complete 36 month clinical data provided in the resubmission of BLA 125,288 leads to similar conclusions as my review of the data provided in the original BLA submission... Substantial evidence of the effectiveness of belatacept was demonstrated in the original review on the basis of an endpoint of efficacy failure based primarily on rates of biopsy-proven acute rejection (BPAR) through Month 12, although those data also suggested that belatacept may have less efficacy for the prevention of BPAR than CsA (CsA). An analysis of the secondary efficacy endpoints using the 36 month data are consistent with the conclusions inferred from the primary efficacy endpoint based on the 12 month data...

The Statistical Reviewer's efficacy conclusions (review dated March 11, 2011) are reproduced below:

The data through 36 months in both of the Phase 3 trials continue to support the conclusions drawn at 12 months regarding the efficacy of belatacept. At 36 months, there are comparable rates of the composite endpoint of biopsy proven acute rejection, graft loss, death, or lost to follow-up between the belatacept groups and CsA. There are also comparable rates of patient and graft survival between the belatacept groups and CsA at 36 months. Mean calculated GFR is higher in belatacept treated patients compared to

CsA treated patients. The difference which was apparent at 1 month post transplant was maintained through 36 months.

8. Safety

The following summary of 36 month safety data was obtained from the Medical Officer's Review (dated March 25, 2011).

Deaths (and Graft Loss)

The observed rates of death in both Phase 3 trials were similar across treatment groups at 36 months. The data from the Phase 3 trials support that kidney transplant patients maintained on either belatacept regimen had similar mortality outcomes at 36 months to the CsA control regimen, even among a patient population which included EBV negative recipients and despite the impact of the imbalance in PTLT presentations across treatment groups (see Table 10).

Table 10: Deaths Occurring in IM103008 and IM103027*

	IM103008			IM103027		
	Belatacept MI (n=219)	Belatacept LI (n=226)	CsA (n=221)	Belatacept MI (n=184)	Belatacept LI (n=175)	CsA (n=184)
Death, N (%)						
Up to Month 12	6 (2.7)	4 (1.8)	7 (3.2)	8 (4.3)	5 (2.9)	9 (4.9)
Up to Month 24	8 (3.7)	8 (3.5)	13 (5.9)	13 (7.1)	13 (7.4)	13 (7.1)
Up to Month 36	9 (4.1)	10 (4.4)	15 (6.9)	22 (12)	15 (8.6)	17 (9.2)

Source: Table 11; Clinical Review by Patrick Archdeacon BLA 125,288 resubmission

*At 36 months, survival status was known for all patients except 2 belatacept MI patients, 1 belatacept LI patient, and 5 CsA patients in IM103008; at 36 months, survival status was known for all patients except 3 CsA patients in IM103027

PTLD

An updated assessment of the events of PTLT in belatacept clinical trials IM103008, IM103027, and IM103100 are shown in Table 11, including the status of these patients.

At the time of the original BLA submission, fourteen PTLT events had presented among belatacept-treated patients and two PTLT events had presented among CsA-treated patients. Since then, no additional PTLT events presented among belatacept-treated patients and one additional PTLT event presented in a CsA-treated patient in these trials.

Of note: An additional case of PTLT (confined to the kidney) was reported 55 months post-transplant on (b) (6) in an EBV negative patient who received the belatacept LI regimen. This patient is not reflected in the table below.

Table 11: Summary of PTLD Cases Observed in Belatacept Trials 008, 027 and 100

Trial	Belatacept MI (N=477)			Belatacept LI* (N=472)			CsA (N=478)		
	EBV+ (n=404)	EBV- (n=45)	EBV Unknown (n=28)	EBV+ (n=401)	EBV- (n=51)	EBV Unknown (n=20)	EBV+ (n=399)	EBV- (n=57)	EBV Unknown (n=22)
IM103100									
CNS PTLD		2 ^{Ω,†}							
Non-CNS PTLD			1 [‡]						1 [‡]
IM103008									
CNS PTLD	1 ^Ω	1 ^Ω							
Non-CNS PTLD		1 ^Ω		2 ^{Ω,Ω}				1 [†]	
IM103027									
CNS PTLD	1 [†]	1 [†]		2 ^{†,‡}	1 [†]				
Non-CNS PTLD					1 [‡]		1 [‡]		
Total	2 (0.5)	5 (11.1)	1 (3.6)	4 (1.0)	2 (3.9)	0	1 (0.3)	1 (1.8)	1 (4.5)

*The belatacept LI regimen studied in IM103100 is non-identical to that studied in IM103008 and IM103027

Ω = Patient alive; † = Patient dead in first 36 months; ‡ = Patient died after first 36 months

Source: Table 19; Clinical Review by Patrick Archdeacon BLA 125,288 resubmission

Progressive Multifocal Leukoencephalopathy (PML)

Two events were discussed as part of the Clinical Review of the original BLA submission. No additional events of PML have since been reported.

Infections

Overall rates of infections at 36 months appeared similar across treatment arms of the clinical trials, as shown in Table 12. An imbalance, however, existed with regards to herpes infections: belatacept patients had reported significantly more episodes of herpes infections at 36 months.

Table 12: Patients with Infections as Adverse Events up to 36 Months in IM103008 and IM103027

	IM103008, N (%)			IM103027, N (%)		
	Bela MI (N=219)	Bela LI (N=226)	CsA (N=221)	Bela MI (N=184)	Bela LI (N=175)	CsA (N=184)
Infections reported as SAEs	62 (28.3)	73 (32.3)	73 (33.0)	89 (48.4)	71 (40.6)	84 (45.7)
AEs in SOC of Infections and Infestations	175 (79.9)	185 (81.9)	176 (79.6)	146 (79.3)	144 (82.3)	151 (82.1)
PTs Related to Viral Infections	84 (38.4)	86 (38.1)	81 (36.7)	73 (39.7)	68 (38.9)	70 (38.0)
CMV	22 (10.0)	26 (11.5)	25 (11.3)	32 (17.4)	27 (15.4)	31 (16.8)
Polyoma Virus	18 (8.2)	10 (4.4)	18 (8.1)	12 (6.5)*	7 (4.0)	9 (4.9)
Herpes	29 (13.2)	26 (11.5)	21 (9.5)	32 (17.4)	29 (16.6)	25 (13.6)
PTs Related to Fungal Infections	50 (22.8)	46 (20.4)	45 (20.4)	45 (24.5)	24 (13.7)	43 (23.4)

SOC = System Organ Class

PT = Preferred Term

* Includes one event of PML

Source: Table 34; Clinical Review by Patrick Archdeacon of BLA 125,288 resubmission

CNS Infections

No new CNS infections were reported in the BLA resubmission.

Tuberculosis

As noted in the original reviews, more belatacept-treated patients developed tuberculosis than CsA-treated patients. Between Month 24 and Month 36, two new cases were reported in belatacept MI patients in IM103008, two new cases were reported in belatacept LI patients in IM103008, and one new case of tuberculosis was reported in a belatacept LI patient in IM103027. No new cases were reported between Month 24 and Month 36 among CsA-treated patients in either trial. See Table 13.

Most of the cases of tuberculosis involved extra-pulmonary sites and developed in patients who lived in locations where tuberculosis is endemic.

Table 13: Cases of Tuberculosis in IM103008 and IM103027 by 36 Months

	IM103008			IM103027		
	Belatacept MI (n=219)	Belatacept LI (n=226)	CsA (n=221)	Belatacept MI (n=184)	Belatacept LI (n=175)	CsA (n=184)
Tuberculosis						
All Cases	4	2	1	2	4	0
Extra- pulmonary involvement	3	1	1	1	4	0
Death at time of database lock	1	2	0	0	1	0

Source: Table 36; Clinical Review by Patrick Archdeacon of BLA 125,288 resubmission

NODAT, Hypertension and Dyslipidemia

For a detailed discussion of these pre-specified endpoints of please see the Clinical and Statistical Reviews. The following summary was taken from the Statistical Review. It should be noted that the analyses of NODAT and hypertension were conducted as observed, i.e., no imputation for missing data, which accounted for $\geq 25\%$ of the patients in the trials.

- **NODAT:** In the trials NODAT was defined as the use of an antidiabetic agent for more than 30 days or at least two fasting plasma glucose values greater than or equal to 126 mg/dL in a subjects who was not diabetic at study entry. Across all treatment groups relatively few patients developed NODAT by Month 12. The greater numerical difference (fewer) in belatacept treated patients compared to CsA treated patients who developed NODAT that was seen by 12 months is not as apparent by 36 months. Data not shown. See Table 14 in Statistical Review.
- **Hypertension:** As was seen at Month 12, the mean systolic and diastolic blood pressures were lower for patients in both belatacept groups relative to the CsA group. At 36 months, the differences in mean blood pressures between the belatacept groups and CsA are only significant in IM103008. Data not shown. See Table 12 in the Statistical Review.
- **Dyslipidemia:** Mean total cholesterol and mean triglyceride levels at Month 36 were lower for patients in both belatacept groups relative to the CsA group in both studies (statistically significant for IM103008 only). Mean LDL cholesterol levels at 36 months were significantly lower for patients in both belatacept groups relative to the CsA group in IM103008 but similar across treatment groups in IM103027. Mean HDL levels at 36 months were similar across treatment groups in both studies. Data not shown. See Table 13 in the Statistical Review.

The Medical Officer's safety conclusions (review dated March 25, 2011) are reproduced below:

An analysis of the safety endpoints using the 36 month data is also consistent with the safety findings from the 12 and 24 month data. The two pivotal trials suggest that belatacept and CsA have safety profiles which differ markedly from one another: exposure to CsA appears to decrease the glomerular filtration rate (through acute and chronic toxicities), increase the blood pressure, and adversely affect the metabolic profile of every patient, whereas exposure to belatacept may result in PTLD (predominantly CNS PTLD), progressive multifocal leucoencephalopathy (PML), and other CNS infections a small number of patients. The safety profile of belatacept cannot, therefore, be declared clearly superior to that of CsA, but it may be preferable to some patients and physicians.

The Statistical Reviewer's safety conclusions (review dated March 11, 2011) are reproduced below:

The general safety profile at month 36 remains consistent with that observed at 12 months and no new safety concerns were identified.

The safety and efficacy profile of belatacept are consistent for EBV positive patients only as compared to the overall population.

9. Advisory Committee Meeting

Belatacept was discussed at the Cardiovascular and Renal Drugs Advisory Committee meeting on March 1, 2010 during the previous review cycle. No AC meeting was held to discuss the resubmission.

Transcripts and other supporting information from the March 1, 2010 meeting are available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm192863.htm>

10. Pediatrics

BMS submitted (November 19, 2007) and was granted (February 20, 2008) Orphan designation for belatacept for prophylaxis of organ rejection in renal allograft recipients.

Under FDAAA 2007 and PREA, pediatric studies are not required.

(b) (4)

(b) (4)

11. Other Relevant Regulatory Issues

Manufacturing Facilities Inspections

Before the product can be approved, the Office of Compliance must issue a formal determination on the acceptability of the Manati, Puerto Rico site in response to BMS's written response to the deficiencies cited by the District Office during the February-March 2011 re-inspection. At this time, no formal determination has been made. (See Section 3 of this review).

DSI Inspections

Inspections of the clinical trial sites were not conducted during this review cycle. Eight sites from the Phase 3 trials in France, Mexico, Brazil and USA sites were selected for inspection during the previous review cycle. DSI concluded that the studies were conducted adequately and the data from the sites could be used to support the application.

Risk Evaluation and Mitigation Strategy (REMS) and DRISK Consult

In the original BLA submission for belatacept, BMS included a voluntarily proposed REMS consisting of Medication Guide (MG) and a Communication Plan (CP) (b) (4)

(b) (4) The review team consulted DRISK of OSE for the review of the proposed REMS and worked very closely with the DRISK review team consisted of Kate Heinrich, MS (Health Education reviewer) and Suzanne Berkman Robottom, Pharm.D (Team Leader). DRISK recommended a REMS with a Medication Guide (MG) and Communication Plan (CP) to communicate the serious risks of PTLT and PML.

The CR letter of May 1, 2010 noted that a REMS would be necessary for belatacept, if approved, to ensure that the benefits of the drug outweigh the risks of PTLT and PML. The required REMS would include a MG and a CP as its elements.

The CP was expected to include a Dear Healthcare Provider (DHCP) letter; additional educational materials targeted at prescribers and allied healthcare professionals, in settings where patients receive belatacept infusions; and dissemination of risk information through professional societies. Further, the CR stated that the CP materials must be available on the belatacept website. A meeting was held between the review team and BMS on June 11, 2010 to discuss the elements of the CR letter, including some of the REMS issues.

BMS submitted a REMS proposal on August 16, 2010 that included a proposed MG and CP consisting of the following documents:

- Dear Healthcare Provider (DHCP) Letter
- Healthcare Provider (HCP) Fact Sheet
- Infusion Specialist Letter
- Infusion Specialist Checklist
- Educational slide presentation/Webinar

A website was also proposed by BMS, but a website landing page was not included. Additionally, BMS stated that the Healthcare Provider Fact sheet would serve as the basis for the safety panels at transplant congresses and journal advertisements. BMS did not include a copy of the journal information piece in this submission.

The first set of comments from DRISK regarding the proposed REMS was sent to BMS on September 24, 2010. The DRISK review team found that the general elements of the REMS outlined in the REMS document were acceptable. However, considerable edits to the REMS

document would be needed, including references to the attachments (MG and CP materials). The template for the REMS document and REMS supporting document (SD) were provided to BMS as attachments. General comments regarding the CP materials were also provided.

During the review, DRISK and the review team agreed on the following REMS goals, which were reflected in the second set of interim REMS comments sent to BMS on March 1, 2011:

The goals of the belatacept REMS are:

- To inform healthcare providers of the increased risk of PTLT, predominantly in the CNS, associated with belatacept
- To inform healthcare providers of the increased risk of CNS infections, including PML, associated with belatacept
- To inform patients of the serious risks associated with belatacept

Subsequent discussions were held between BMS, the review team and DRISK. The following final REMS goals were agreed upon on April 8, 2011:

The goals of the NULOJIX REMS are:

1. To inform healthcare providers of the increased risk of post-transplant lymphoproliferative disorder (PTLD), predominantly in the central nervous system (CNS), associated with NULOJIX
2. To inform healthcare providers of the increased risk of progressive multifocal leukoencephalopathy (PML), a CNS infection, associated with NULOJIX
3. To inform patients of the serious risks associated with NULOJIX

CDTL Comment: During the course of the review, and discussions with BMS, the review team decided that the goals of the REMS would be targeted very specifically to PML and PTLD, only. Both processes involve the CNS; however, it was decided that the REMS goals would not mention CNS infections, in general, as this was thought to be a non-specific warning and was not helpful to health-care providers.

Additional comments regarding the CP documents were sent to BMS from DRISK and the review team on March 1, 2011 regarding revisions to the DHCP Letter, HCP Fact Sheet, Infusion Letter and (b) (4) (renamed Pre-Infusion Checklist):

- Given that the DHCP letter will be disseminated with the Fact Sheet, the revisions to the DHCP Letter were provided with this in mind. Also, it was recommended that a copy of the Pre-Infusion Checklist accompany the Infusion Specialist Letter.
- It was recommended the electronic version of the checklist be in a format that allows it to be incorporated into existing electronic medical records/systems.

- BMS was asked to provide a copy of their proposed journal information piece, the proposed website landing page, and further clarifications regarding the Webinar.
- Specific revisions to the slide set (for the Webinar) were not provided. BMS was asked to revise the slide/Webinar based on the comments pertaining to the other materials and resubmit.
- BMS was asked to revise the REMS SD to be consistent with the changes made to the REMS document.

BMS revised the REMS document and the attached materials and submitted for review on March 18, 2011.

In preparation for a face-to-face meeting with BMS on April 11, 2011, the review team and DRISK sent BMS revisions to the CP documents. During the meeting, the review team, DRISK and BMS finalized the content of these documents. A final version of all CP documents was submitted by BMS on April 29, 2011.

Following the face-to-face meeting, the revised and agreed upon REMS document was sent to BMS on April 22, 2011. This document will be publicly available and will be appended to the action letter and was sent for clearance through Safety Requirements Team (SRT) and SWAT (version submitted by BMS on April 29, 2011). The REMS document was cleared on May 27, 2011 with minor edits, specifically to the Medication Guide section that the (b) (4) (b) (4) One of the CP materials, however, provides more specific information on the distribution requirements, i.e., Pre-Infusion Checklist states that the MG is to be distributed with each infusion. The final, cleared version of the REMS document was sent to BMS on May 31, 2011.

The review team, DRISK review team and Office of Compliance (reviewer Kendra Biddick) worked on the REMS document and the REMS assessment plan.

The REMS assessment plan will be as follows:

1. The number of live webinars conducted and their dates.
2. The total number of unique participants at live webinars for the reporting period.
3. The date(s) of distribution of the Dear HCP Letter that occurred during the period
 - a. The source(s) of the list of health care provider addresses
 - b. The number of recipients at each distribution date
 - c. The number of returned items
 - d. A list of the documents included in each distribution
4. Journal information pieces published, including date and journal name, volume, and issue.

5. For each infusion center ordering Nulojix (belatacept) for the first time during the reporting period, the date of initial order, and the date of distribution of tear pads of pre-infusion checklists.
6. **A survey of healthcare providers' and patients' understanding** of the serious risks of Nulojix (belatacept).
7. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
8. A report on failures to adhere to distribution and dispensing of the Medication Guide, and corrective actions taken to address noncompliance.
9. A summary of all reported cases of PTLD and PML during the preceding reporting period.
10. **An analysis of prescribers' compliance** with the labeled contraindication regarding the use of Nulojix (belatacept) in EBV negative patients and patients in whom EBV-status is unknown.
11. A plan to monitor sales data to evaluate:
 - a. A number of patients treated, reported by transplant organ received
 - b. Number of units shipped, reported by year and type of healthcare setting (e.g., transplant center, infusion center, hospital)
12. Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the list above, the initial assessment should also include the following:

1. Launch date of Nulojix
2. The date the links to the full prescribing information, medication guide, and all approved REMS materials became available on the Nulojix REMS landing page.
3. Number of transplant centers visited within 90 days of launch and within 150 days of launch, and percentage of transplant volume covered by each transplant center visited.
4. The date(s) of distribution of the Dear Infusion Specialist Letter
 - a. The source(s) of the list of infusion specialists
 - b. The number of recipients
 - c. The number of returned items

d. A list of the documents included in the mailing

REMS assessments for belatacept will be required annually from the date of the initial approval of the REMS for the first 5 years and again 7 years from the initial date of approval of the REMS. The first assessment should contain all of the above information with the **exception of the evaluations of patients' and prescribers' understanding of the serious risks of Nulojix (belatacept).** These evaluations should be included in each assessment for years 2 through 5 and in the 7 year assessment.

12. Labeling

Proprietary Name

In the original review cycle, the Division of Medication Errors and Prevention Analysis (DMEPA) found the proposed proprietary name **"Nulojix" conditionally acceptable** on October 5, 2009; however the product was not approved in this review cycle. DMEPA was re-consulted in the current review cycle and **found the name "Nulojix" to be acceptable** on February 28, 2011. In the consult, DMEPA stated they would re-review the proposed proprietary name 90 days before approval of the BLA. However, in an email dated May 27, 2011, Irene Chan, in DMEPA noted that a re-review will not be necessary due to the proximity of the action date and the 90 day time frame.

Package Insert

The PI submitted by the applicant has been revised by the review team and our consultants to address the important findings from the development program, as well as to align with various CDER labeling Guidances and the comments from our consultants:

SEALD – PI reviewed informally by Anne Marie Trentacosti, MD; comments conveyed through email and teleconference

DDMAC – comments from Christine Corser, PharmD were all adequately addressed (email dated March 23, 2011)

DMEPA – comments on Section 2: Dosage and Administration regarding concerns with the **silicone-free dosing syringe packaged with the product.** (consult by L. Shenee' Toombs dated March 23, 2011)

The issue is discussed further in the review:

On March 8, 2011, a joint meeting between DMEPA, CMC, and DSPTP was held to inform DSPTP of concerns related to the silicone-free dosing syringe packaged with Nulojix. Our concerns center around the dosing syringe

(b) (4)

(b) (4)

After discussion with the Division, a decision was made to (b) (4) include language for prescribers to round final calculated doses to the nearest 12.5 mg. This will allow for measurable reconstituted volumes with the dosing syringe proposed by the Applicant.

The following is a summary and rationale for information included in the close to final package insert (see **Appendix 1**), sent to BMS on May 25, 2011:

Boxed Warning

- In addition to a discussion of the general risk of serious infections and malignancies associated with immunosuppressants, there is also a discussion of the risk of PTLT, predominantly CNS PTLT and that the product is to be used in EBV seropositive patients only.
- Based on data not included in the BLA, but which became available during the review cycle from Study IM103045, additional item was added to the box noting that belatacept should not be used in liver transplant patients due to an increased risk of graft loss and death.

Indications and Usage

- The recommended indication for approval is “prophylaxis of organ rejection in adult patients receiving a kidney transplant. NULOJIX is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.”
- (b) (4)
- Limitations of use include EBV seropositive patients only and that use in transplanted organs other than kidney has not been established (due to risk of graft loss in death in liver transplant patients, as noted in the Boxed Warning)

Dosage and Administration

- The section starts with a warning about the belatacept MI regimen with the statement: “Due to an increased risk of post transplant lymphoproliferative disorder (PTLD), predominantly involving the CNS, progressive multifocal leukoencephalopathy (PML), and serious CMS infections, administration of higher than the recommended doses or more frequent dosing of NULOJIX is not recommended.”
- Dosing instructions for the prescriber in order for the dose to be prepared accurately using the reconstituted solution and the silicone-free syringe are included (see DMEPA comments above)
- Dosing guidelines are provided for the belatacept LI regimen (the “recommended regimen”).
- The section on preparation and administration instructions was reviewed and edited by Kimberly Rains (OBP) and DMEPA.

Warnings and Precautions

- The subsection “Post-Transplant Lymphoproliferative Disorder” discusses the risk and states that “higher than the recommended doses or more frequent dosing of NULOJIX and higher than recommended doses of concomitant immunosuppressive agents are not

- recommended.” Other risk factors, including EBV serostatus, CMV infection and T-cell depleting therapies are also discussed.**
- The risk of progressive multifocal Leukoencephalopathy (PML) is also discussed as a **separate subsection. It is noted that “two cases of PML were reported in patients receiving NULOJIX at higher cumulative doses and more frequently than the recommended regimen, along with mycophenolate mofetil (MMF) and corticosteroids; one case occurred in a kidney transplant recipient and the second case occurred in a liver transplant recipient.”**
 - A subsection on **“Liver Transplant”** was added to discuss the higher rate of graft loss and death seen in the belatacept arms of IM103045 compared to the tacrolimus control arms. It also discusses the two events of PTLT and the event of PML seen among those belatacept patients.
 - Other subsections include class labeling on management of immunosuppression, other malignancies, other serious infections (including tuberculosis and polyoma virus nephropathy), and immunizations (avoid live vaccines).

Adverse Reactions

- Discusses first the most serious adverse reactions of **“PTLT, predominantly CNS PTLT, and other malignancies” and “serious infections, including JC virus-associated PML and polyoma virus nephropathy”**
- The clinical studies subsection was organized to summarize the database consisting of 36 month data from Studies IM103008 (Study 1) and IM103027 (Study 2).
- The risks associated with the belatacept MI regimen are noted: **“CNS PTLT, PML, and other CNS infections were more frequently observed in association with a NULOJIX regimen of higher cumulative dose and more frequent dosing compared to the recommended regimen; therefore, administration of higher than the recommended doses and/or more frequent dosing of NULOJIX is not recommended.”**
- The demographics of patients of Studies 1 and 2 are pooled and presented together, followed by the most commonly reported adverse reactions in both studies ($\geq 20\%$) and the number of patients who discontinued treatment due to adverse reactions.
- The following serious reactions are discussed in detail:
 - **PTLT – using data from Studies 1 and 2 and Study 3 (Phase 2 Study IM103100)** for both the MI and LI regimens (Study 3 used a similar, but non-identical regimen to that in Studies 1 and 2) compared to cyclosporine control; Table 1 presents risk in EBV seronegative versus EBV negative or EBV unknown patients by study and by location (CNS vs non-CNS).
 - Malignancies, excluding PTLT (similar in presentation to data in other immunosuppressant labels) in Studies 1 and 2 separately for belatacept LI compared to cyclosporine
 - PML- using data from Studies 1, 2 and 3, along with a liver transplant trial (IM103045)
 - Bacterial, mycobacterial, viral and fungal infections – in Studies 1 and 2; special note is made of the higher rate of tuberculosis with belatacept LI compared to cyclosporine and the higher rate of CNS infections with the belatacept MI regimen
 - **Infusion reactions – similar to placebo in Studies 1 and 2**

- **Proteinuria** – early differences between belatacept and cyclosporine in Studies 1 and 2 are noted, although the clinical significance is unknown
- **Immunogenicity** – discusses development of antibodies against belatacept in Studies 1 and 2 with the belatacept LI regimen. Due to the relatively low numbers, the clinical impact could not be determined
- **New Onset Diabetes After Transplantation, Hypertension, and Dyslipidemia** – these were pre-specified endpoints in Studies 1 and 2. However, the team decided not to discuss them in Clinical Studies (Section 14), as recommended by labeling Guidance, but rather address them as separate subsections in Adverse Reactions due to the fact that the results were not striking and clinical impact was felt to be of minimal significance (especially for the findings of lower triglycerides).
- Common adverse reactions of $\geq 10\%$ in Studies 1 and 2 for belatacept LI compared to cyclosporine are included in Table 4. Certain terms that were felt to be nonspecific (e.g., Incisional site pain) and were removed from the table for both groups. Selected adverse reactions $< 10\%$ in Studies 1 and 2 for belatacept LI were determined by the Clinical team as being biologically plausible and are presented as a listing following Table 4.

Drug Interactions

- A discussion of the potential effect of belatacept on CYP450 enzymes by cytokine inhibition was included; no formal drug interaction studies have been conducted to confirm or refute this effect
- The modest increase in plasma concentrations of mycophenolic acid in the presence of belatacept (20% increase in C_{max} and 40% increase in AUC) was determined in a subset of patients in Studies 1 and 2 and is reported.

Pregnancy

- The effect of belatacept in animals based on the mg/kg administered dose and in relation to the maximum recommended human dose (MRHD) is discussed for belatacept. The fact that a related product, abatacept (Orencia®) is more active in rodents is also noted.
- **The risk of potential autoimmunity is mentioned to humans:** “Autoimmunity was observed in one rat offspring exposed to abatacept *in utero* and/or during lactation and in juvenile rats after treatment with abatacept. However, the clinical relevance of autoimmunity in rats to patients or a fetus exposed *in utero* is unknown.”
- **The availability of a pregnancy registry to monitor outcomes is also mentioned:** “To monitor maternal-fetal outcomes of pregnant women who have received NULOJIX or whose partners have received NULOJIX, healthcare providers are strongly encouraged to register pregnant patients in the National Transplant Pregnancy Registry (NTPR) by calling 1 877-955-6877.”

Pediatric/Geriatric Use

- The potential risk of autoimmunity in offspring exposed to belatacept in utero is mentioned with a cross reference to the non-clinical data (discussed above).
- Belatacept did not appear to behave differently in older subjects compared to younger subjects, but the patient numbers were small.

Clinical Pharmacology

- The **“Mechanism of Action”** (Section 12.1) of belatacept is described as a selective T-cell costimulation blocker, which is consistent with the agreed upon pharmacologic class of the product. The review team discussed the classification with the rheumatology team in the Division of Pulmonary, Allergy and Rheumatology (DPARP) to allow for consistency between belatacept and abatacept (Orencia®). In addition, a statement was added regarding DSAs in monkey models of transplantation: **“In non-human primate models of renal transplantation, belatacept monotherapy prolonged graft survival and decreased the production of anti-donor antibodies, compared to vehicle.”**
- The **“Pharmacodynamics”** subsection (Section 12.2) is based upon the exploratory, subset IgG analyses of Gerlie Gieser, Clinical Pharmacology Reviewer (see Section 5 of this review) and was agreed to by BMS.
- The **“Pharmacokinetics”** subsection (Section 12.3) includes a discussion of the pharmacokinetic parameters of belatacept in healthy adult subjects and kidney transplant patients

Nonclinical Toxicology

- The subsection on **“Carcinogenesis, Mutagenesis, Impairment of Fertility”** (Section 13.1) notes with regard to an increase in the incidence of malignant lymphomas in mice that **“Although the precise relevance of these findings to the clinical use of NULOJIX is unknown, cases of PTLD (a premalignant or malignant proliferation of B lymphocytes) were reported in clinical trials.”**
- In the subsection on **“Animal Toxicology and/or Pharmacology”** (Section 13.2), the results with abatacept are discussed (since the product is considered to be more active than belatacept in rodents). In addition, the results from a CNS study of belatacept in monkeys are discussed. While belatacept was not detected in brain tissue and there were no other histological changes in the brain **“The number of cells expressing major histocompatibility complex (MHC) class-II antigens (potential marker of immune cell activation) in the brain were increased in monkeys administered belatacept compared to vehicle control.”** This finding was felt important to mention, given the fact that belatacept increases the risk of PTLD, although the section does not mention this link and concludes with the statement **“The clinical relevance of the findings is unknown.”**

Clinical Studies

- The clinical results of Studies 1 and 2 are discussed in Section 14.1 (**“Prevention of Organ Rejection in Kidney Transplant Recipients”**). Initially, the study design of the studies is discussed (including treatment arms and inclusion/exclusion criteria), followed by a discussion about the higher rate of efficacy failures with the belatacept MI regimen: **“The NULOJIX regimen with higher cumulative doses and more frequent dosing was associated with more efficacy failures. Higher doses and/or more frequent dosing of NULOJIX are not recommended.”**
- The results of Studies 1 and 2 (belatacept LI compared to cyclosporine control regimens) are presented sequentially and follow the same format:
 - Demographics

- Premature discontinuation rates and reasons for discontinuation
- Efficacy failure rate at one year (primary efficacy endpoint, as per FDA analyses) and three years; along with rates of patient and graft survival
- Discussion of the higher rates of BPAR with belatacept compared to cyclosporine and GFR in patients who experienced BPAR compared to those who did not. The rates of DSAs are also included:
 - **Study 1: “The overall prevalence of donor-specific antibodies was 5% and 11% for the NULOJIX recommended regimen and cyclosporine, respectively, up to 36 months post-transplant.”**
 - **Study 2: “The overall prevalence of donor-specific antibodies was 6% and 15% for the NULOJIX recommended regimen and cyclosporine, respectively, up to 36 months post-transplant.”**
- Efficacy in the EBV seropositive subpopulation (since the product is Contraindicated in EBV seronegative or unknown patients)
- GFR rates out to 3 years
- Rate of CAN at the end of the first year, followed by the statement: “The clinical significance of this finding is unknown.”

Patient Counseling Information

- The following risk information was felt to be important to convey to the patient:
 - PTLD
 - Other Malignancies
 - PML
 - Other Serious Infections
 - Immunizations (avoid live vaccines)
 - Pregnant Women and Nursing Mothers (discuss risks with HCP)

Medication Guide

The review team consulted DRISK patient labeling team on September 24, 2010 to review the Medication Guide (MG). The final DRISK consult review by Sharon Mills, RN (Acting Team Leaders Barbara Fuller and LaShawn Griffiths) was dated March 2, 1011.

DRISK recommended changes to the MG to enhance patient comprehension and clarified concepts where possible, ensured the MG was consistent with the prescribing information, removed redundant information and ensured that the MG met the regulations specified in 21 CFR 208.20. In addition, they ensured that the materials were written at a 6th and 8th grade reading level.

CDTL Comment: BMS inquired whether the MG would be part of the REMS as the draft Guidance on Medication Guides became public on February 25, 2011. This Guidance addressed two topics that should be considered in the development of MGs for drug and biological products: distribution requirements and inclusion in REMS.

Following discussions with DRISK it was decided that belatacept MG will be approved as a part of REMS, as it needs to be distributed with each infusion as stated in the Pre-Infusion Checklist.

A copy of the revised MG, agreed upon by the review team and DRISK, can be found in **Appendix 1**.

Carton and Immediate Container Labels

Joint comments provided by Kimberly Rains (OBP) and L. Shenee' Toombs (DMEPA) in an email dated April 1, 2011. Comments sent to the applicant on April 5, 2011. Revised carton and container labels were received from the sponsor on May 3, 2011 (unofficial submission). Kimberly Rains did not note any objections the revised versions of the labels in an email dated May 4, 2011. Irene Chan from DMEPA concurred with the versions in an email dated May 27, 2011.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

All disciplines support approval of the belatacept LI regimen for the indication of prophylaxis of organ rejection in adult patients receiving a kidney transplant in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.

However, before the product can be approved the Office of Compliance must issue a formal determination on the acceptability of the Manati, **Puerto Rico site, in response to BMS's** written response to the cited deficiencies. At this time, no formal determination has been made.

Should the manufacturing site receive a favorable determination, the dosing regimen to be approved consists of the following:

(b) (4)

Limitations of use include the following:

- Belatacept should be limited to those patients who are EBV seropositive
- Belatacept should not be used for the prophylaxis of organ rejection in transplanted organs other than kidney (i.e., liver).

The Medical Officer's recommendations (review dated March 25, 2011) are reproduced below:

My analysis of the complete 36 month clinical data provided in the resubmission of BLA 125,288 leads to similar conclusions as my review of the data provided in the original BLA submission:

- The belatacept LI regimen studied in the Phase 3 kidney transplant trials should receive approval for the indication of prophylaxis of organ rejection in adult kidney patients receiving a kidney transplant in combination with basiliximab induction and mycophenolate mofetil and corticosteroid maintenance immunosuppression.
- The belatacept MI regimen studied in those trials should not receive approval
- Belatacept should be contraindicated among kidney transplant recipients whose EBV serostatus is negative or unknown at the time of transplantation due to the increased risk of post-transplant lymphoproliferative disorder (PTLD) in this population.
- A Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure the safe use of belatacept in the indicated population (as discussed in Section 1.3).

(b) (4)

Risk Benefit Assessment

The relative risks and benefits identified during the review of the BLA resubmission by the Clinical and Statistical Reviewers are similar to those identified in the original BLA submission. The identified risks of using a belatacept-based regimen rather than a CsA-based regimen included 1) higher rates and grades of BPAR, 2) higher rates of PTLD (predominantly CNS PTLD), and 3) higher rates of CNS infections (including PML). The identified benefits of using belatacept rather than CsA appear to derive from avoiding known toxicities of CsA and include 1) substantially higher glomerular filtration rates (GFR) and 2) improved cardiovascular risk profiles. The observed rates of BPAR, PTLD, and CNS infections (including PML) were numerically higher in recipients of the belatacept MI regimen than recipients of the belatacept LI regimen. Therefore the benefit only weighs the risk for the belatacept LI regimen.

In addition, the overall rate of PLTD in patients treated with either the belatacept MI or LI regimens was 10-fold higher in those who were EBV seronegative or EBV serostatus unknown compared to those who were EBV seropositive. Therefore the benefit is thought to outweigh the risk for the belatacept LI regimen only in patients who are EBV seropositive

Postmarketing Risk Evaluation and Management Strategy (REMS)

The REMS contains the elements of a Medication Guide and Communication Plan.

REMS Goals

1. The goals of the NULOJIX REMS are:

2. To inform healthcare providers of the increased risk of post-transplant lymphoproliferative disorder (PTLD), predominantly in the central nervous system (CNS), associated with NULOJIX
3. To inform healthcare providers of the increased risk of progressive multifocal leukoencephalopathy (PML), a CNS infection, associated with NULOJIX
4. To inform patients of the serious risks associated with NULOJIX

Medication Guide

See **Appendix 1**.

Communication Plan

A summary of components for the CP is as follows:

1. REMS-specific landing page (www.NULOJIX.com/REMS.aspx).

(b) (4)

2. Webinar.

(b) (4)

3. Dear healthcare Professional (HCP) Letter.

(b) (4)

(b) (4)

(b) (4)

4. HCP Fact Sheet.

(b) (4)

5. Dear Infusion Specialist Letter.

(b) (4)

6. Pre-infusion Checklist.

(b) (4)

7. Journal Information Piece.

(b) (4)

The REMS document will be publicly available and it is attached in **Appendix 2**.

Postmarketing Requirements and Commitments
Clinical PMRs

1. Conduct a prospective, observational study utilizing data from the United Network for Organ Sharing (UNOS) on the pattern of belatacept use in US adult kidney-only transplant recipients at transplant and one year post-transplant. Specifically, the

study will assess the prevalence of belatacept use and the characteristics of belatacept users, as related to the risk of PTLT, including Epstein-Barr Virus (EBV) and cytomegalovirus (CMV) serostatus. In addition, the study will collect information on adult kidney-only transplant recipients who switch to or from belatacept within one year post-transplant. (Protocol Number IM103074)

This study will be conducted according to the following schedule:

Final Protocol Submission:	04/2012
Study Completion:	04/2019
Final Report Submission:	04/2020

Rationale: Clinical trial experience suggested an increased incidence of post-transplant lymphoproliferative disorder PTLT, particularly PTLT in the central nervous system (CNS PTLT) in patients exposed to belatacept compared to cyclosporine. Therefore, it is necessary to define the profile of belatacept users post-approval, particularly Epstein-Barr Virus (EBV) and cytomegalovirus (CMV) serostatus as these variables are considered risk factors for PTLT post-transplant. The United Network for Organ Sharing (UNOS) already collects data among kidney transplant recipients. The Boxed Warning/Contraindication in the package insert (PI) states not to use belatacept in transplant recipients who are EBV seronegative or with unknown serostatus; therefore, this study will evaluate how well prescribers are following the approved PI. Additionally, belatacept was studied in *de novo* patients during registrational trials; this observational study will also identify switch use (i.e. patients converted to belatacept after initial transplant period) and its implications.

2. Conduct a prospective observational study utilizing data from the United Network for Organ Sharing (UNOS) on the incidence rates of post-transplant lymphoproliferative disorder (PTLT) in US adult kidney-only transplant recipients who are treated with belatacept compared to recipients treated with calcineurin inhibitor (CNI)-based regimens. Recipient characteristics will be collected, including EBV and CMV serostatus, location of the PTLT, and outcome (survival or mortality). Incidence rates of PTLT in belatacept-exposed patients will be quantified beginning when 500 belatacept-exposed patients have at least 1 year of follow-up. Relative risks of PTLT for belatacept compared to CNI-based regimens will be estimated after 1,000 person years have been accumulated in transplant recipients initiated on belatacept at transplantation. (Protocol Number IM103075)

This study will be conducted according to the following schedule:

Final Protocol Submission:	04/2012
Interim Analysis Report:	06/2014
Study Completion:	04/2019
Final Report Submission:	04/2020

Rationale: An increased incidence of PTLT and CNS PTLT with belatacept compared to cyclosporine was identified during registrational trials for belatacept, especially in EBV seronegative patients. Therefore, it is important to define the profile of belatacept users post-approval, particularly Epstein-Barr Virus (EBV) and cytomegalovirus (CMV) serostatus as these variables are considered risk factors for PTLT post-transplant. In addition, information regarding the nature of PTLT (location) and its outcome (survival or mortality) will be collected in order to better define this serious risk as opposed patients exposed to calcineurin inhibitor (CNI)-based regimens. Incidence rates of PTLT will be quantified among belatacept- vs. CNI-exposed renal transplant recipients.

3. Conduct a prospective registry of belatacept use in US adult kidney-only transplant recipients to determine the incidence rates of post-transplant lymphoproliferative disorder PTLT, PTLT in the central nervous system (CNS PTLT), and progressive multifocal leukoencephalopathy (PML) in US adult EBV seropositive kidney transplant recipients treated with belatacept in clinical practice. All US adult kidney transplant centers dispensing belatacept will be asked to participate in the study (i.e., if a center does not respond or declines to participate, the reason(s) for nonparticipation will be identified and documented). Recipient characteristics will be collected, including EBV and CMV serostatus, timing of initiation of belatacept in relation to the transplant, location of the PTLT, and outcome (survival or mortality). (Protocol Number IM103076)

This study will be conducted according to the following schedule:

Final Protocol Submission:	04/2012
Study Completion:	04/2019
Final Report Submission:	04/2020

Rationale: Clinical trial experience suggested an increased incidence of PTLT, particularly CNS PTLT and PML in patients treated with belatacept compared to cyclosporine. The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met in March 2010 (during previous review cycle) to discuss the belatacept application. Although several members agreed that safety was demonstrated, the majority of the Committee felt concern regarding the increased risk of PTLT with CNS involvement and PML. A registry was recommended to more precisely estimate the incidence of PTLT and PML.

All US adult kidney transplant centers dispensing belatacept will be asked to participate in the study (i.e., if a center does not respond or declines to participate, the reason(s) for nonparticipation will be identified and documented). This registry is meant to collect near complete post marketing data on renal transplant patients exposed to belatacept to better define the incidence of PML and PTLT and associated risk factors for PTLT such as EBV and CMV serostatus in a prospective manner.

Manufacturing PMRs

4. Conduct a study to quantify at the end of the proposed

(b) (4)

(b) (4)

(b) (4)

Provide a worst case risk assessment for those (b) (4) including potential toxicity to humans, in your final report.

This study will be conducted according to the following schedule:

Final Report Submission: 12/2012

Rationale: Certain (b) (4) represent a direct toxicological risk to human health and can also impact product quality. BMS reported that the levels of these (b) (4) were safe at 24 hours, but did not provide the data in the BLA, nor did they provide any information for these (b) (4) at the limit of the proposed (b) (4). Based on the data provided at 24 hours of storage, it is believed that the levels observed at (b) (4) will pose a low risk, or no risk, of human toxicity.

Postmarketing Commitments (PMCs) Chemistry

5. Conduct a trend analysis of (b) (4) profiles based on the results from 30 consecutively released future drug substance batches. Re-evaluate the acceptance criteria for these product attributes and, if appropriate, submit the final report with the revised specifications together with data justification that includes supporting data and reflective of your experience with lots used in the clinical trials.

This study will be conducted according to the following schedule:

Final Report Submission: 12/2013

Rationale: Recent data indicates there may be emerging change in the trend of this

(b) (4)

6. Conduct a trend analysis for (b) (4) content using an extended characterization (b) (4) to generate informational data and based on the results

from 30 consecutively released future drug substance batches, evaluate the need for introducing a validated release method and setting acceptance criteria for this product attribute, or provide justification for not requiring a (b) (4) content release method.

This study will be conducted according to the following schedule:

Final Report Submission: 12/2013



7. Provide a protocol describing the conditions and criteria which will be applied for assessing the stability of any drug substance lot held for the maximum hold time allowed at each (b) (4)

This study will be conducted according to the following schedule:

Final Report Submission: 12/2011



8. Provide information and summary data on the product specific dye-ingress container closure, integrity test method and provide an updated post-marketing stability protocol replacing the sterility test with CCIT.

This study will be conducted according to the following schedule:

Final Report Submission: 12/2012

Rationale: BMS will need to conduct laboratory studies to develop a dye ingress test to replace the sterility test on the stability program. This is appropriate as a PMC because the test will provide an improved assessment of the maintenance of sterility of lots on stability.

9. Perform a study to support multiple freezing-thawing of drug substance (DS) that incorporates conditions reflective of the intended use (multiple freeze-thaws, including shipping). Also, provide DS stability data confirming a cumulative stability limit of greater than 12 months at 2-8°C before and after multiple freeze-thaw cycles. In addition, provide stability data for drug product produced from DS that has undergone multiple freeze-thaw cycles.

This study will be conducted according to the following schedule:

Interim Report Submission: 12/2011

Final Report Submission: 12/2013

Rationale: The sponsor has purposed up to (b) (4) freeze-thaw cycles for DS and intends to ship (b) (4) but has only provided DS data to support one freeze-thaw cycle. Freeze-thawing is a condition that can cause changes in product quality and thus poses at least a theoretical risk to this DS. The length of the study needed to support the proposed storage conditions precludes performing the study preapproval. The goal of this study is to demonstrate the stability of the DS under the proposed storage conditions and of DP produced from DS subjected to these storage conditions.

10. Develop characterization methodology for micron and submicron subvisible particulates using stressed and/or accelerated drug product samples to assess whether a correlation may exist between subvisible particulates in the micron and submicron ranges and propose an appropriate control strategy for drug product stored under the approved conditions.

This study will be conducted according to the following schedule:

Final Report Submission: 12/2012

Rationale: Subvisible particulates (b) (4) in size are currently not monitored or controlled for this drug product. Subvisible particulates of biological drug products consist of large protein aggregates composed of thousand to millions of molecules. In general, these particulates appear to increase over time. Aggregated proteins are associated with the development of anti-drug antibodies (ADA); however, these characteristics appear to be product specific. The assessment of subvisible

particulates in the (b) (4) range presents some technological challenges but is feasible. Since this is an emerging area of technology and the particulates are of theoretical concern this should be a PMC.

Based on the study results, BMS will propose an appropriate control strategy for drug product subvisible particulates (b) (4)

Appendix 1 – Package Insert

50 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page