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APPLICATION NUMBER:

125288Orig1s000

SUMMARY REVIEW

BLA 125288, Nulojix (belatacept) intravenous infusion
Proposed indication: prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving kidney transplants

Summary Review #2 for Regulatory Action

Date	See electronic stamp date 6-15-11
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products ¹
Subject	Division Director Summary Review
BLA Number	BLA 125288
Related IND	
Belatacept	IND 9418
Abatacept	IND 9391
Related NDA	BLA 125118, Abatacept (Orencia®)
Applicant Name	Bristol-Myers Squibb (BMS)
Date of Submission	June 30, 2009
Date of Receipt	July 1, 2009
Complete Response Letter	May 1, 2010
Resubmission Date	December 15, 2010
PDUFA Goal Date	June 15, 2011
Proprietary Name / Established (USAN) Name	Nulojix Belatacept
Dosage Forms / Strength	Lyophilized powder for intravenous infusion, 250 mg/vial
Proposed Indication(s)	prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving kidney transplants
Action for NME	<i>Approval (with REMS)</i>

¹ The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

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Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Patrick Archdeacon, Joette Meyer TL
CDTL Review	Bill Taylor/Joette Meyer/Ozlem Belen
Statistical Review	Cheryl Dixon, Karen Higgins TL
Statistics DBVII PTLD Review	Anita Abraham, LaRee Tracy, Aloka Chakravarty
Statistics DBVII PMR Review	John Yap, LaRee Tracy, Aloka Chakravarty
Pharmacology/Toxicology Review	Ying Mu, Janice Lansita, Bill Taylor TL (CDTL)
CMC/OPS/OBP/DTP Review	Jack Ragheb, Susan Kirschner TL, Barry Cherney
Compliance/DMPQ/MAPCB/BMT (DS)	Bo Chi, Patricia Hughes, Michelle Clark-Stuart (DS)
Microbiology/Immunology Review	Aaron Ruhland, Shukal Bala TL
Clinical Pharmacology Review	Seong Jang, Gerlie Gieser, Philip Colangelo TL
Pharmacogenomics Review	Shashi Amur, Li Zhang, Issam Zineh
Pharmacometrics Review	Jiang Liu, Pravin Jadhav
DDMAC	Christine Corser, Michelle Safarik, Sam Skariah
PMHT	Richardae Araojo, Karen Feibus, Lisa Mathis
DSI	Susan Thompson, Tejashri Purohit-Sheth
OSE/DMEPA Proprietary Name	L Shenee Toombs, Irene Z Chan, Denise Toyer, Carol Holquist
OSE/DMEPA Labeling Review	L Shenee Toombs, Irene Z Chan, Carol Holquist
OSE/DPV II (re: abatacept autoimmunity)	Peter Diak, Martin Pollock, Robert Boucher, Karen Townsend (PM)
OSE/DRISK	Tselaine Jones-Smith, Kristina Arwine, Mary Dempsey Sharon Mills, Barbara Fuller, LaShawn Griffiths
OSE/DEPI	Andrew Mosholder, Amariyls Vega, Solomon Iyasu
SEALD	Anne Marie Trentacosti
Interdisciplinary QT Review Team	Suchitra Balakrishnan, Christine Garnett
Advisors and Consultants Staff	Minh Doah, Elaine Ferguson

CDTL=Cross-Discipline Team Leader
 OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 PMHT=Pediatric and Maternal Health Staff
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DDRE= Division of Drug Risk Evaluation
 DRISK=Division of Risk Management
 DMPQ/MAPCB/BMT = Division of Manufacturing and Product Quality/Manufacturing and PreApproval CB/ Biologics Microbiology Team
 OPS/OBP/DTP = Office of Pharmaceutical Sciences/Office of Biologics Products/Division of Therapeutic Proteins
 DB = Division of Biometrics

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1. Summary and Recommendations

Based on the reviews of BLA 125288, each of the individual review disciplines recommended approval of the application from their discipline perspective, therefore, BLA 125288 for Nulojix (belatacept) lyophilized powder for intravenous infusion is recommended for approval for the indication of “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.” The product should be used in patients who are EBV seropositive because the risk of PTLD is higher in EBV seronegative patients (see Section 8). The recommended treatment regimen is the low intensity (LI) regimen consisting of 10 mg/kg infusions on Days 1, 5, 14, 28, then at the end of Week 8 and Week 12, followed by 5 mg/kg given at Week 16 and ever 4 weeks thereafter. Belatacept comes as a lyophilized powder for injection, 250 mg/vial. The product must be prepared using a silicone-free syringe to prevent particle formation, and is infused over 30 minutes through a sterile non-pyrogenic, low-protein-binding filter (pore size 0.2-1.2 µm).

Discussion of labeling (Package Insert, Medguide, Carton and Container), REMS, PMRs and PMCs by staff from OND, OSE, OPS and OC was finalized and documents with final wording were submitted by BMS June 3 and 6, 2011.

The current submission from December 15, 2010 was a resubmission, sent in response to the *Complete Response* letter on May 1, 2010 which listed a number of deficiencies including CMC, Compliance and Clinical deficiencies, and identified the need for a REMS including Medication Guide and Communication Plan to manage the safety signals of PTLD and PML. Following several meetings and agreed-upon pre-submissions in August and September 2010, BMS submitted the final element of their complete response on December 15, 2010.

1.1 Responses to Deficiencies in the Complete Response Letter of May 1, 2010

CMC Deficiencies:

The Product Quality reviewers determined that the deficiencies (provided in red in the figure by Dr Jack Ragheb, below) have been addressed and the application is recommended for approval from CMC perspective; however, one post-marketing requirement (PMRs) and six commitments (PMCs) will be requested.

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(b) (4)

The Product Quality Microbiology reviewers determined that the applicant had addressed the deficiencies, as summarized in the list from Dr Bo Chi below:

1. (b) (4) for (b) (4) was re-adjusted and is now acceptable.
2. Sensitivity of the drug product container closure integrity test was provided and is acceptable.
3. (b) (4) validation was completed.
4. Drug product shipping validation study was completed and adequate.
5. Drug product endotoxin specification was lowered and now provides a safety margin (b) (4)
6. Microbiology data supporting the labeling claim (b) (4)

Dr Chi concluded that the application can be approved from a sterility assurance and product quality microbiology perspective.

Compliance Deficiencies:

The East Syracuse NY facility issues were resolved and issued an NAI and the Manati Puerto Rico facility issues from the initial warning letter were found to have been addressed during the 5-week re-inspection in February - March 2011. However, an eight-item Form 483 (notice of inspectional observations) was issued during the current inspection cycle, and BMS addressed these items, and provided a summary of various personnel and SOP changes at the Manati facility. The Puerto Rico district office updated their initial OAI recommendation to VAI and the TB-EER (therapeutic biologic-establishment evaluation report) issued June 2, 2011 summarizes that inspectional findings are acceptable.

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Clinical Deficiency:

BMS provided the 3-year outcome data as requested, and the information on efficacy and on safety is summarized under Sections 7 and Section 8, below. The data confirmed that belatacept was effective in the prevention of organ rejection in patients with kidney allografts, and the data also indicated that a REMS was needed to assure that the benefit of the product outweighs the risks of the product. Overall, survival of patients using the recommended (LI) regimen was no different (and numerically somewhat higher) at 3-years in the belatacept arm compared to the cyclosporine control arm.

(b) (4)

Risk Evaluation and Mitigation Strategy (REMS):

Because an increased incidence of PTLD was seen in patients who were not EBV seropositive, and PML was seen in patients who received higher than recommended doses, a REMS to manage these serious risks was developed. It includes a Medication Guide and Communication Plan. The components of the plan are provided under Section 8.1 of this document.

1.2 Post-Marketing Studies:

Post Marketing Requirements (PMR):

Three clinical PMRs to evaluate belatacept use and incidence of PML and PTLD, and one CMC PMR to examine (b) (4), will be included in the approval letter. These are summarized in Section 8.2 of this document.

Post Marketing Commitments (PMC):

Six CMC PMCs will be included in the approval letter and are summarized in Section 8.3 of this document.

1.3 Other Issues

In the liver transplant Phase 2 clinical trial of belatacept, one patient developed PTLD, another developed PML and there was a higher number of patients who died on the belatacept arm compared to the tacrolimus control arm; therefore, a boxed warning advises that “use in liver transplant patients is not recommended due to an increased risk of graft loss and death.” Further details about this trial are included in the primary MO review.

2. Background

The application for Nulojix was submitted on June 30, 2009 for the proposed indications: prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving kidney transplants. Two belatacept regimens were tested. The less intensive (LI) regimen is being recommended for approval in prophylaxis of rejection in kidney transplantation. The preservation of functioning allograft indication is not being granted; the

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higher GFR seen in belatacept-treated patients is likely to be due to the absence of cyclosporine toxicity instead of increased efficacy due to belatacept. A graphical presentation of GFR results over the 3-year course of the study is presented in Section 8 and is being provided in approved labeling.

Belatacept is a fusion protein of human cytotoxic T-lymphocyte antigen-4 (CTLA-4) extracellular domain and modified human IgG₁ Fc domain (hinge CH2-CH3). It binds to B7-1 (CD80) and B7-2 (CD86) of the antigen presenting cells (APC), thereby interferes with the interaction between CD28:CD80/CD86 and blocks the co-stimulatory pathway to T lymphocyte activation via CD28. This is the co-stimulatory signal needed for T-cell activation. Inhibition of this signal blocks T lymphocyte activation interleukin-2 (IL-2), IL-4, TNF- α and INF- γ production, leading to immunosuppression.

Belatacept is related to abatacept (two amino acid difference in CTLA-4 domain) which is marketed as Orencia® for rheumatoid arthritis and JRA; both products have the same mechanism of action but different potencies (see Section 4, Pharmacology/Toxicology section).

The indication of prophylaxis in kidney transplant patients is based on two Phase 3 clinical trials, both of which evaluated a moderate intensity (MI) and low intensity (LI) belatacept regimen and compared these to a control regimen that included cyclosporine (CsA). In all arms, patients received basiliximab (interleukin-2 receptor antagonist) induction, mycophenolate mofetil (MMF), and steroids. The LI regimen is recommended for approval.

2.1 Belatacept Product Development and Submission Milestones

Belatacept (LEA29Y, BMS-224818) was developed under IND 9418, submitted to CBER October 19, 2000. An EOP-2 meeting was held September 21, 2004 to review data from Phase 2 study IM103100 in kidney transplant patients, and the division concurred with endpoints of non-inferiority in graft loss/death and superiority to cyclosporine (CsA) in preserving renal function at 12 months, but cautioned about the expected large amount of missing data using the iohexol-determined GFR, and requested that patients be followed for 24 and 36 months to assess death/graft loss and renal function. There was discussion of analyzing acute rejection and chronic allograft nephropathy (CAN) endpoints. Fast track designation was granted January 26, 2005. An SPA letter for Phase 3 study IM103008 was dated September 22, 2005. A pediatric Type C meeting was held December 18, 2007 and the question asked whether blocking co-stimulation of pre T cells in thymus might allow thymocytes to escape and lead to autoimmunity – the sponsor conducted juvenile rat studies which are summarized below. Belatacept received orphan designation February 20, 2008, meaning that the pediatric study requirements under PREA do not apply to belatacept.

BMS and FDA met on April 7, 2008 for a pre-BLA meeting to discuss the content and format of the application, and for a focused CMC pre-BLA meeting to discuss the submission of the CMC portion of the BLA application on July 28 2008.

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At BMS's request, a second pre-BLA meeting took place on December 15, 2008 to discuss the one-year data from the Phase 3 studies. At the latter meeting, BMS indicated they believed they had demonstrated a favorable effect of belatacept on the renal function and structure as shown by higher mean GFR and lower rate of chronic allograft nephropathy (CAN).² Discussion followed about the potential challenge of interpreting the results given the vasoconstrictive effects of CsA, the role of ACE inhibitors, NSAIDs, and diuretics on renal function, and the toxicity of CsA on the kidney. BMS noted that while the incidence of acute rejection (AR) in these trials was higher on belatacept than CsA, it did not translate to lower GFR in the belatacept arm; the graft function was maintained. The division suggested an exposure response analysis be done, and an analysis of change in GFR in patients who had AR versus those that did not, and requested details regarding the episodes and their management. Finally, there was also discussion of PTLD and one case of PML and need for further review and potential management of these risks.

The third pre-BLA meeting took place May 20, 2009 during which there was further discussion of the content and format of the BLA, additional analyses requested, REMS elements discussed, and BMS was asked to provide a written justification for their (b) (4)

The application for this biologic product was submitted under section 351 of the Public Health Service Act on June 30, 2009 and filed August 30, 2009. (b) (4)

a CDER Product Quality Assessment form was attached to that letter. The 74-day letter issued September 11, 2009 identifying multiple information requests. Between the time of submission and the Complete Response action, multiple facsimiles and email communications requesting additional information and clarification were sent to BMS, most dealing with CMC issues, others requesting toxicology, clinical pharmacology, clinical and statistical information, as well as communication in preparation for the AC meeting.

Nulojix was presented before the Cardiovascular and Renal Drugs Advisory Committee on March 1, 2010 and the application was issued a Complete Response letter on May 1, 2010 due to Manufacturing and Clinical deficiencies. BMS and DSPTP met on several occasions to discuss how the deficiencies could be addressed and the timing of submissions. After several pre-submissions, the final part of the complete response was sent December 15, 2010.

The Division set an internal goal of April 15, 2010 to complete the application review, however, during the inspection at the Manati, Puerto Rico manufacturing facility, the inspectors found that the issues in the initial warning letter had been addressed but they also identified 8 new items that were included on the 483, and the responses to these deficiencies took additional time to resolve.

3. CMC/Product Quality Microbiology

² The new terminology to refer to this entity is chronic allograft injury (CAI) or interstitial fibrosis/tubular atrophy (IF/TA).

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In brief, belatacept is manufactured in a Chinese hamster ovary cell line. The DS process consists of (b) (4)

During the first review cycle, a number of deficiencies were identified and resolved, however at the completion of the review, Drs. Ragheb and Kirschner of DTP/OBP/OPS (Product Quality) concluded there were remaining deficiencies of (b) (4), process controls, stability protocols, release specifications, in use stability, immunogenicity assays, and they could not conclude that manufacture of Nulojix is well controlled and leads to a product that is pure and potent.

Drs. Chi and Hughes and colleagues of OC/DMPQ/MAPCB/BMT (Product Quality Microbiology) identified deficiencies regarding the (b) (4) the container closure integrity test, (b) (4) validation, shipping validation, drug product endotoxin specification, and the labeling claim (b) (4) are not adequate.

In the resubmission, the CMC issues were addressed and Drs Ragheb and Chi recommended approval. One CMC-related PMR and six PMCs are being included in the approval letter (see Section 8.2 and 8.3).

Comment: The application is recommended for approval from a CMC perspective. Labeling has been completed.

4. Nonclinical Pharmacology/Toxicology

The reviewers recommend that the application has sufficient pharmacology/toxicology data to support approval. The applicant conducted general toxicity, reproductive and developmental toxicity, carcinogenicity and immunotoxicity in rodents, rabbits and monkeys. The drug is pregnancy category C. In animals, fetal loss was noted but not teratogenicity. The labeling recommends that HCP encourage pregnant patients to register in the National Transplant Pregnancy Registry (NTPR) by calling 1-877-955-6877.

The question of autoimmunity has been raised during the initial review, discussed among staff and with the Maternal Health Staff. Findings of thyroiditis and insulinitis were seen in juvenile and adult rats given abatacept (greater binding in rats than belatacept), but not in monkeys. Juvenile monkey studies were not conducted. Information on potential autoimmunity is included in Section 13.2 Animal Toxicology:

Studies in rats exposed to abatacept have shown immune system abnormalities including a low incidence of infections leading to death (observed in juvenile rats and pregnant rats) as well as autoimmunity of the thyroid and pancreas (observed in rats exposed *in utero*, as juveniles or as adults). Studies of abatacept in adult mice and monkeys, as well as belatacept in adult monkeys, have not demonstrated similar findings.

Administration of abatacept to rats was associated with a significant decrease in T-regulatory cells (up to 90%). Deficiency of T-regulatory cells in humans has been associated with autoimmunity. The

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occurrence of autoimmune events across the core clinical trials was infrequent. However, the possibility that patients administered NULOJIX could develop autoimmunity (or that fetuses exposed to NULOJIX *in utero* could develop autoimmunity) cannot be excluded.

Animal data suggested that pregnant and juvenile animals were more susceptible to infections than non-pregnant adult animals in the toxicology studies; the current application is for use of belatacept in adults, but whether there would be an increased risk in children and pregnant women will be kept in mind based on these findings. The table below is reproduced from the pharmacology/toxicology review, page 80.

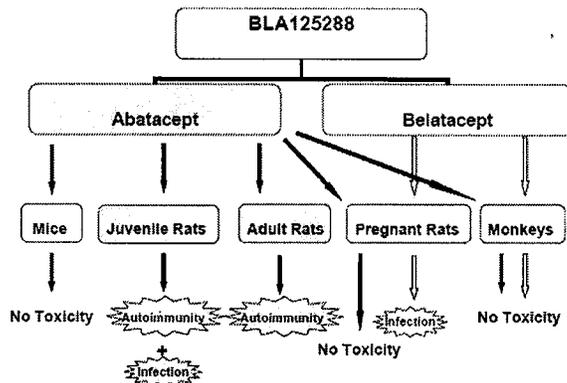


Figure 4: A summary of the significant toxicities observed in each animal study by treatment. The solid black arrows signify the abatacept studies and outcomes. The open-hatched arrows signify the belatacept studies and outcomes.

Regarding the overall findings in pharmacology/toxicology studies, Drs. Mu and Lansita wrote:

“Pharmacology and pharmacokinetic studies with belatacept were conducted in mice, rats, rabbits, and cynomolgus monkeys. The *in vitro* and *in vivo* pharmacology studies showed that belatacept binds to CD80 and CD86, as well as inhibits T-cell activation, proliferation, and the T-cell dependent antibody response *in vivo*. Belatacept did not induce complement mediated cytotoxicity or antibody-dependent cytotoxicity *in vitro*. The PK of belatacept was generally characterized across species by low clearance, low volume of distribution, and a long half-life that increased with dose.

“The major safety signals observed in nonclinical toxicology studies with belatacept or abatacept included a risk of infections, autoimmunity, and carcinogenicity, which are all described in the product label. All findings except autoimmunity are related to the expected pharmacology of belatacept. No effects on reproductive function or teratogenicity were observed.

“In summary, the pharmacology, PK, and toxicology studies support the proposed use of belatacept in the prophylaxis of organ rejection in kidney transplant patients.”

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Comment: The application is recommended for approved from a pharmacology/toxicology standpoint and labeling has been finalized.

Human autoimmunity evaluation in patients and offspring was discussed within the Division and with MHT and OSE; however no feasible pathway such as a trial or registry was identified to study the risk systematically. It was also noted that Orencia (abatacept), a similar product, includes labeling regarding potential autoimmunity, and lists the NTPR registry, but does not have a prospective registry for adult patients. Of note, in clinical trials of Nulojix, the incidence of NODAT was numerically lower than in the control CsA arm, therefore, at least this does not indicate a higher risk of insulinitis for Nulojix. Therefore, adverse events of autoimmunity are likely to be identified during postmarketing adverse event reporting, including reporting from the PMR studies, and through the NTPR registry. Should such signals be identified, further evaluation of autoimmunity may be undertaken.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology program included 21 trials, and the reviewers agree the data support approval and the LI regimen. The pharmacokinetics are linear and plasma exposure increases dose proportionally. Pharmacokinetic parameters in healthy subjects and kidney transplant patients are presented in the table below from the review by the Clinical Pharmacology, Pharmacogenomic and Pharmacometric reviewers. A summary of the pharmacokinetic information that will be included in the approved labeling is provided below.

Table : Pharmacokinetic Parameters (Mean±SD [Range]) of Belatacept in Healthy Subjects and Kidney Transplant Patients After 5 and 10 mg per kg Intravenous Infusions Administered Over 30 Minutes

Pharmacokinetic Parameter	Healthy Subjects (After 10 mg per kg Single Dose) N=15	Kidney Transplant Patients (After 10 mg per kg Multiple Doses) N=10	Kidney Transplant Patients (After 5 mg per kg Multiple Doses) N=14
Peak concentration (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)
Terminal half-life (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)
Systemic clearance (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)
Volume of distribution (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

Based on the clinical pharmacology reviews, the following observations were made: Exposure-response analyses suggest that higher belatacept troughs on day 5 are related to lower acute rejection rates in month 1, but no apparent relationship between troughs and AR was noted after month 1 in Studies IM103008 and IM103027. Exposure-response analysis of trough levels did suggest a relationship between higher troughs and less loss in GFR; higher

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belatacept troughs were also associated with less CAN in study 008 (SCD kidneys) but not in study 027 (ECD kidneys). Although there were very few cases of PTLD and PML, there is a suggestion that these are associated with higher belatacept exposure (rate 0% in lower quartiles, 0.6% in higher two quartiles, p 27). EBV positive patients who were CMV negative may be at increased risk of PTLD (1.91%) versus CMV positive patients (0.34% risk) – based on an analysis of 795 patients of whom about ¾ were CMV positive and ¼ were CMV negative. Serious CNS infections were reported in 7 MI patients and 1 LI patient, again suggesting a relationship to higher levels. There is a suggestion that BK virus infection was more likely with higher troughs but only during months 2 to < 6, not before or after these time points. No association between troughs and lipids, blood pressure, diabetes was noted. The reviewers concluded that the data in the NDA were insufficient to determine whether TDM is warranted, but suggest it be further explored.

The reviewers further note that because belatacept is an inhibitor of the production of cytokines, it may affect mRNA expression and function of hepatic CYP450 metabolizing enzymes, so drugs metabolized via CYP450 like statins, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, oral hypoglycemic drugs and antifungal triazole or antiviral drugs should be further investigated, but the team is not recommending at PMR at this time. Another recommendation would be to evaluate CMV serostatus as a risk factor for PTLD

This large molecule has not apparent effect on QT.

Dr Gieser conducted a series of exploratory analyses and in addition to confirming that immunoglobulin levels decreased following belatacept treatment (and to a smaller degree, CsA treatment), observed that patients whose IgG levels were below the lower limit of normal (< 694 ng/mL) reported more malignancies and serious infections than patients whose levels were above this limit. Confounding factors included age and use of lymphocyte depletion factors (e.g., thymoglobulin) and therefore the significance or cause/effect of the association is unclear. Clinical Pharmacology provided the following information for labeling:

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 PTLD, 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. This observation was more pronounced with the higher than recommended dose of belatacept. A similar trend was also observed for cyclosporine-treated patients with serious infections and malignancies.

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.

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Comment: The application can be approved from a clinical pharmacology/ pharmacometric/ pharmacogenomic standpoint; the labeling has been finalized. There are no PMRs or PMCs recommended.

6. Clinical Microbiology/Immunology

Belatacept inhibits the activation of T cells, lymphocytes involved in mediating immunologic rejection of allografts. Dr. Ruhland noted that in primate models of kidney transplantation, and in transplanted islet cells, belatacept along with other immunosuppressants prolonged graft survival. He also summarized the findings from animals studies showing there was no effect on autoimmunity with belatacept in monkeys. However, in rats given abatacept (higher binding in rodents) there was up to 70% reduction in regulatory T cells, and autoimmune effects in rats which progressed during the post-treatment follow-up period. The effects of belatacept on spleen and lymph node were reversible with belatacept discontinuation. In the clinical trials, flow cytometry on a few patients samples from Phase 2 and 3 trials showed a transient decrease in regulatory T-cells (CD25⁺, FOXP3⁺) in patients treated with either belatacept+basiliximab or CsA+basiliximab, thus no difference in decreases in T-regulatory cells were seen, and no overt evidence of autoimmunity was reported.

There were fewer patients with donor specific antibodies (DSA) on the belatacept arm, and the number was too small to evaluate correlation with antibody mediated rejection. As noted below, acute cell-mediated rejection was higher in the belatacept arm.

Regarding PTLD and EBV status, Dr Bala writes, "In the 3 clinical trials, the EBV serostatus was determined for 95% (1357 of the 1425) of the patients prior to enrollment in the clinical trials. PTLD developed in 16 patients of which 14 were in the belatacept arm and 2 in the CsA arm. Of the 14 patients treated with belatacept who developed PTLD, 7 were EBV negative (of 96 total EBV negative patients on belatacept) and 6 were EBV positive (of 805 total EBV positive patients on belatacept) and 1 was of unknown status. EBV serostatus prior to transplant was unknown in 2 of the patients that developed PTLD (one in the belatacept arm and 1 in the CsA arm). Of the 14 patients in the belatacept arm, 8 developed CNS PTLD, while none of the 2 patients in the CsA arm developed CNS PTLD." In these trials, there were 108 assays to detect EBV status used, 97 of which were FDA cleared; testing was done at 95 different laboratories.

BMS and reviewers recommend that belatacept only be used in EBV positive patients, and not in EBV negative patients, those with unknown EBV serostatus, and those in whom IgM antibodies are present without also having IgG antibodies against VCA and EBNA.

Comment: The application can be approved from a clinical microbiology/immunology standpoint; labeling has been finalized and includes a recommendation to use only in EBV seropositive patients, and use is contraindicated in patients who are EBV seronegative or unknown status because they are at higher risk of PLTD (a B cell hyperplasia or malignant neoplasm).

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7. Clinical/Statistical-Efficacy

The BLA contains results of three controlled clinical trials, all of which compared two doses of belatacept [called moderate intensity (MI) and low intensity (LI)] to a CsA control arm, and all patients received basiliximab, MMF and steroids. Phase 2 study IM103100 used a regimen that did not include the day 5 dose, and was not included in the efficacy evaluation, and while examined for safety, was also not pooled in the safety analyses. Details of these trials are provided in the statistical review by Dr. Dixon and the clinical review by Dr. Archdeacon. The Phase 3 clinical trials were evaluated for efficacy; all were multicenter, prospective studies of 36 months in duration; the agreement was that the application would be submitted for review when 12 month data were available to support a regulatory decision. Because of the early signals of PTLD and PML seen in some of the patients participating in these trials, as well as more Grade2/3 acute rejections seen in the belatacept treatment arms, the *Complete Response* letter of May 10, 2010 included a request that 3 year clinical data be submitted to evaluate whether the benefit continues to outweigh the risk of belatacept us in kidney transplantation. As summarized on the following pages, the 3 year clinical data continue to support the safety and efficacy of belatacept in kidney transplantation. Details of these clinical trials are included in the primary reviews, the CDTL Review and previous DD Review. A brief summary is provided in this document:

Controlled clinical trials - Belatacept BLA

Trial Number	Trial Design	Dosage Regimen and Concomitant Therapy	No. of Subjects (ITT)
IM103008	Phase 3, randomized, partially-blinded, active-controlled	IV bela (MI ^a and LI ^a) or CsA; basiliximab induction, MMF and corticosteroids	Bela MI: 219 Bela LI: 226 CsA: 221
IM103027	Phase 3, randomized, partially-blinded, active-controlled	IV bela (MI ^a and LI ^a) or CsA; basiliximab induction, MMF and corticosteroids	Bela MI: 184 Bela LI: 175 CsA: 184
IM103100	Phase 2, randomized, partially-blinded, active-controlled	IV bela (MI ^b and LI ^b) or CsA; basiliximab induction, MMF and corticosteroids	Bela MI: 74 Bela LI: 71 CsA: 73

Table from Dr. Archdeacon's review

- Phase 3 study IM103008 enrolled 666 patients with living donor and standard donor criteria kidneys; it was conducted at 104 sites worldwide, including 34 in the USA.
- Phase 3 study IM103027 enrolled 543 patients with extended donor criteria kidneys; it was conducted at 79 sites worldwide, 27 in the USA.

In the control arm, CsA troughs were 150 to 300 ng/mL in first month, 100 to 250 ng/mL thereafter; about 30-40% of patients exceeded these in the first three months, thereafter about 70 to 80% of patients were within range. MMF doses of 2 g/day were used, but because CsA inhibits enterohepatic recirculation of MPA, lower MPA ensues. Thus C_{max} and AUC were 20% and 40% higher, respectively, when given with belatacept compared to CsA.

The co-primary endpoints specified in the protocols were the composite endpoint of patient and graft survival by 12 months, the composite renal impairment endpoint defined as measured GFR < 60 mL/min/1.73 m² at Month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73 m² from Month 3 to Month 12. The incidence of acute rejection by 12 months

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was a co-primary endpoint in IM103008, and a secondary endpoint in IM103027. Other endpoints included measured and calculated GFR, chronic allograft nephropathy (CAN), and examination of cardiovascular risk factors including hypertension, dyslipidemia, and NODAT. Primary analyses were done on the ITT population. The endpoints are further discussed in the primary reviews.

Although all endpoints were analyzed, the FDA based the decision of efficacy using the endpoint of biopsy confirmed acute rejection (BPAR) in which patients who have graft loss, death or loss to follow up are imputed as failure. When looking at the applicant's analysis and FDA analysis of acute rejections, the numbers are fairly similar and the non-inferiority (NI) margin for the LI regimen is met in all analyses. In addition, Dr. Dixon also looked at the efficacy in EBV positive patients only, given that the indication will be limited to this subset of patients because their risk of PTLD is lower than for EBV negative patients (see Section 8), and showed in her subset analysis that the efficacy results were similar.

At 3 years, overall graft and patient survival on belatacept LI versus CsA was 91.2% versus 86.9% in study 008 and 81.7% versus 77.7% in study 027. While neither of these differences are not statistically significant, it is noted that survival rates are slightly numerically higher (approximately 4%) in the belatacept arms. Thus, despite a higher risk of PTLD (a serious and potentially fatal ADR), belatacept patients do not have an overall lower survival.

The summary of the efficacy results, including the 1 year and 3 year outcomes, is presented below for studies 008 and 027 and included in product labeling. The results for the EBV seropositive subset are comparable and included in product labeling.

Table: Biopsy Proven Acute Rejection Analyses:

Efficacy Outcomes by Years 1 and 3 for Study IM103008 (Study 1): Recipients of Living and Standard Criteria Deceased Donor Kidneys

Parameter	NULOJIX Recommended Regimen N=226 n (%)	Cyclosporine N=221 n (%)	NULOJIX-CSA (97.3% CI)
Efficacy Failure by Year 1	49 (21.7)	37 (16.7)	4.9 (-3.3, 13.2)
Components of Efficacy Failure*			
Biopsy Proven Acute Rejection	45 (19.9)	23 (10.4)	
Graft Loss	5 (2.2)	8 (3.6)	
Death	4 (1.8)	7 (3.2)	
Lost to follow-up	0	1 (0.5)	
Efficacy Failure by Year 3	58 (25.7)	57 (25.8)	-0.1 (-9.3, 9.0)
Components of Efficacy Failure*			
Biopsy Proven Acute Rejection	50 (22.1)	31 (14.0)	
Graft Loss	9 (4.0)	10 (4.5)	
Death	10 (4.4)	15 (6.8)	
Lost to follow-up	2 (0.9)	5 (2.3)	

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Efficacy Outcomes by Years 1 and 3 for Study IM103008 (Study 1): Recipients of Living and Standard Criteria Deceased Donor Kidneys

Parameter	NULOJIX Recommended Regimen N=226 n (%)	Cyclosporine N=221 n (%)	NULOJIX-CSA (97.3% CI)
Patient and graft survival [†]			
Year 1	218 (96.5)	206 (93.2)	3.2 (-1.5, 8.4)
Year 3	206 (91.2)	192 (86.9)	4.3 (-2.2, 10.8)

* Patients may have experienced more than one event.

[†] Patients known to be alive with a functioning graft.

Table: Efficacy Outcomes by Years 1 and 3 for Study IM103027 (Study 2): Recipients of Extended Criteria Donor Kidneys

Parameter	NULOJIX Recommended Regimen N=175 n (%)	Cyclosporine N=184 n (%)	NULOJIX-CSA (97.3% CI)
Efficacy Failure by Year 1	51 (29.1)	52 (28.3)	0.9 (-9.7, 11.5)
Components of Efficacy Failure*			
Biopsy Proven Acute Rejection	37 (21.1)	34 (18.5)	
Graft Loss	16 (9.1)	20 (10.9)	
Death	5 (2.9)	8 (4.3)	
Lost to follow-up	0	2 (1.1)	
Efficacy Failure by Year 3	63 (36.0)	68 (37.0)	-1.0 (-12.1, 10.3)
Components of Efficacy Failure*			
Biopsy Proven Acute Rejection	42 (24.0)	42 (22.8)	
Graft Loss	21 (12.0)	23 (12.5)	
Death	15 (8.6)	17 (9.2)	
Lost to follow-up	1 (0.6)	5 (2.7)	
Patient and graft survival [†]			
Year 1	155 (88.6)	157 (85.3)	3.2 (-4.8, 11.3)
Year 3	143 (81.7)	143 (77.7)	4.0 (-5.4, 13.4)

* Patients may have experienced more than one event.

[†] Patients known to be alive with a functioning graft.

7.2 Noninferiority Margin:

As summarized by Dr. Dixon, the NI margin was justified using information from different studies because there was no study comparing the control to the putative placebo. The three treatment groups of interest are listed below:

Experimental:	belatacept + basiliximab + MMF + corticosteroids (CS)
Control:	CsA + basiliximab + MMF + corticosteroids
Putative Placebo:	basiliximab + MMF + corticosteroids

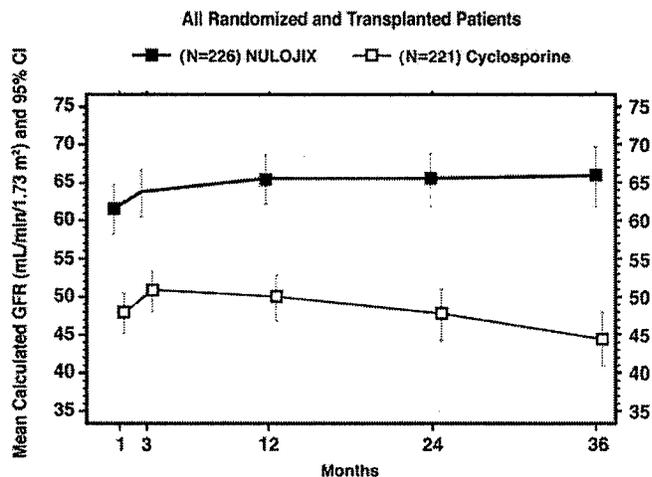
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One trial examined a regimen of daclizumab + MMF + corticosteroids (the putative placebo with a different IL-2 blocker) and showed a 58% BPAR rate, 95% CI (47.9, 68.4). Four studies examined CsA + basiliximab + MMF + corticosteroids regimens similar to the one in the belatacept studies, and the pooled BPAR rate with a 95% CI of (17.0, 26.0). Thus comparing the conservative placebo rate 47.9 and the conservative control rate of 26.0 yields a treatment effect (M1) of 21.9%. This supports a margin of 20%. Furthermore, a mixed effect model (MEM) was also used to estimate the contribution of each drug to the therapy; these analyses also supported the 20% margin. When examining the results from studies 008 and 027, however, the NI margins show that in both trials, a 15% margin could have been met, and about 30-40% of the treatment effect is preserved in LI regimens of the two studies. Results at 3 years show the lower limit of the 97.3% CI to be near 10%.

7.3 Glomerular Filtration Rate

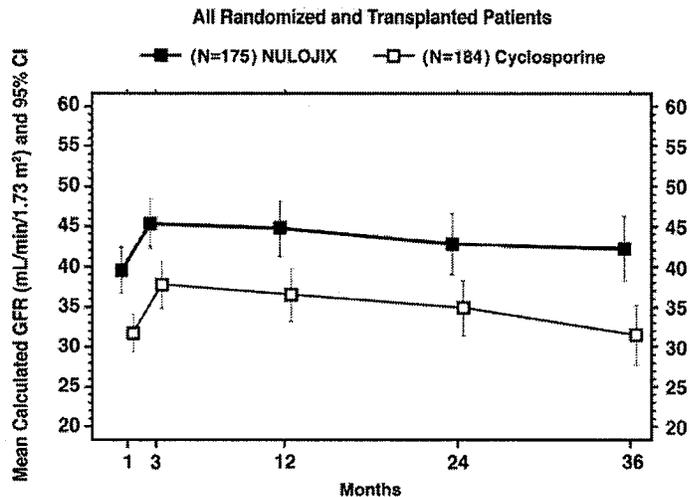
GFR was measured by the iothalamate method in the first 2 years, and also calculated using the Modification of Diet and Renal Disease (MDRD) formula. The GFR over the 3 year period was approximately 15-20 mL/min higher in 008 (SCD kidney) and 8-10 mL/min higher in 027 (ECD kidney) in the belatacept arm compared to the CsA arm, as shown in the figures for studies 008 and 027 below.

Study IM103008: Calculated (MDRD) GFR through Month 36; Study 1: Recipients of Living and Standard Criteria Deceased Donor Kidneys



Study IM103027: Calculated (MDRD) GFR through Month 36; Study 2: Recipients of Extended Criteria Donor Kidneys

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The lines of GFR are separate and run in parallel essentially from the first time point measured, which is probably a reflection of the vasoconstrictive properties of CsA.

An analysis of change of calculated mean GFR in study 008 between three and 36 months demonstrated an increase of 0.8 mL/min/year (95% CI [-0.2, 1.8]) for NULOJIX LI-treated patients and a decrease of 2.2 mL/min/year (95% CI [-3.2, -1.2]) for cyclosporine-treated patients.

An analysis of change of calculated mean GFR in study 027 between Month 3 and Month 36 demonstrated a decrease of 0.8 mL/min/year (95% CI [-1.9, 0.3]) for NULOJIX-treated patients and a decrease of 2.0 mL/min/year (95% CI [-3.1, -0.8]) for cyclosporine-treated patients.

Therefore, in both studies, the GFR is stable to slightly higher in the belatacept arm and is declining by about 2 mL/min/year in the CsA arm, consistent with the recognized nephrotoxic effect of CNIs.

7.4 Chronic Allograft Nephropathy (CAN)

CAN was a prespecified endpoint in the trials. In Study 008, the prevalence of CAN at one year, as defined by the Banff '97 classification system, was 24% (54/226) in patients treated with the NULOJIX recommended regimen and in 32% (71/219) of patients treated with the cyclosporine control regimen. In Study 027, the prevalence of CAN was 46% (80/174) in patients treated with the NULOJIX recommended regimen and 52% (95/184) of patients treated with the cyclosporine control regimen. CAN was not evaluated after the first year following transplantation. The clinical significance of this finding is unknown; the studies were not designed to evaluate whether CAN correlated with a long term survival advantage.

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8. Safety

Safety data were available from over 900 patients treated with belatacept as shown in the table below. During the first review cycle, the data up through 1 year, and for some parameters data through 2 years of follow up were obtained. Due to concerns about the signal of PTLD and 2 cases of PML, the 3 year data were requested in the Complete Response letter of May 10, 2010 and submitted September 24, 2010.

Safety Population from Pooled Studies

Study Number	Belatacept MI	Belatacept LI	CsA
IM103008	219	226	221
IM103027	184	175	184
IM103100	74	71	71
TOTAL	477	472	476

Table from Dr. Archdeacon's review

A detailed discussion of safety can be found in Dr. Archdeacon's review, but the major safety signals were PLTD and PML in the belatacept arm, with the signal somewhat smaller in the LI regimen compared to the MI regimen. Specifically, PTLD was seen at a higher rate in the belatacept LI arm than the CsA arm. Therefore this safety issue was placed in a boxed warning. PML was seen in kidney patient who received the MI regimen and a liver transplant patient also given a higher than LI dose, therefore this information is included in the WARNINGS but not boxed.

There were fewer events related to cardiovascular and metabolic adverse events in the belatacept arm. Overall discontinuations were similar in study 008, yet discontinuation of drug was more commonly due to adverse events in the CsA arm and lack of efficacy in the belatacept arm. In 027 there were somewhat more discontinuations in CsA arm due to toxicity, no apparent difference in efficacy.

Adverse events were reported by the majority of patients in all arms, as shown below:

IM103008 and IM103027: Overall Adverse Events

	IM103008			IM103027		
	Belatacept MI (n=219)	Belatacept LI (n=226)	CsA (n=221)	Belatacept MI (n=184)	Belatacept LI (n=175)	CsA (n=184)
Any AE	218 (99.5)	225 (99.6)	219 (99.1)	182 (98.9)	174 (99.4)	184 (100.0)
Serious AE	112 (51.1)	100 (44.2)	126 (57.0)	129 (70.1)	113 (64.6)	130 (70.7)

AE= adverse event (Table from Dr. Dixon's review)

Acute rejections were more common on belatacept than CsA, including some high grade rejections, most AR events were within the first 6 months of transplant. Mortality and graft loss was similar in the different treatment arms (were not increased in the belatacept arm).

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The main safety signal was the finding of **Post-Transplant Lymphoproliferative Disease (PTLD)**, which was looked at across the Phase 2 and Phase 3 studies. Based on the 3 year follow up, there were 8 cases (1.7%) of PTLT in the belatacept MI group, 5 cases (1.3%) in the belatacept LI group, and 2 cases reported (0.4%) in the CsA group in kidney transplant studies. Eight of the 15 cases presented with CNS involvement (6 belatacept MI, 2 belatacept LI and 0 CSA). The distribution of PTLT cases across the trials is shown in the table below:

Table : Summary of PTLT Reported in Studies 1, 2, and 3 Through Three Years of Treatment

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

* Regimen with higher cumulative dose and more frequent dosing than the recommended NULOJIX regimen.

† In Studies 1 and 2 the NULOJIX regimen is identical to the recommended regimen, but is slightly different in Study 3. Table from Dr. Archdeacon and Dr. Dixon

Because EBV seronegative status (or unknown status) was associated with higher risk of PTLT, the labeling includes a boxed warning, “Do not use NULOJIX in transplant recipients who are EBV seronegative or with unknown serostatus.” In addition, this information is

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included in the WARNINGS AND PRECAUTIONS section, in the patient Medication Guide and in the REMS program.

Whether CMV status also influences PTLD has been discussed (Dr. Shashi's review), and there is a suggestion that CMV negative status may have increased risk of PTLD in EBV positive patients.

There were two cases of **Progressive Multifocal Leukoencephalopathy (PML)** in the database; one in an MI treated kidney transplant patient and one in a liver transplant patient from a Phase 2 study that has since been stopped by the DSMB. Although no cases of PML were reported in kidney transplant patients receiving the LI regimen, the potential risk of PML in patients will be communicated in labeling and REMS.

Hypertension, dyslipidemias, and new onset diabetes after transplantation (NODAT) are class effects of calcineurin inhibitors (e.g. CsA); mean systolic and diastolic blood pressures were significantly lower on belatacept groups relative to the CsA group in both studies, 6-8 mmHg and 2-4 mmHg, respectively. In the belatacept arm, triglyceride levels were lower but LDL cholesterol levels were comparable to CsA patients. NODAT was seen in 4.6% belatacept and 9.6% CsA patients.

Although adverse events associated with increased cardiovascular and metabolic risk were lower in the belatacept arm, the incidence of cardiovascular mortality as reported during the AC meeting (slide 61 below) was 10/23 (43%) deaths or 10/472 (2%) patients in belatacept compared to 12/35 (34%) or 12/476 (3%) who died of cardiovascular causes. Therefore, the 36 month data will be requested to examine mortality, graft loss, as well as any additional reports of PTLD or PML.

Immunogenicity:

As summarized in labeling,

“Antibodies directed against the belatacept molecule were assessed in 398 patients treated with the NULOJIX recommended regimen in Studies 1 and 2 (212 of these patients were treated for at least 2 years). Of the 372 patients with immunogenicity assessment at baseline (prior to receiving belatacept treatment), 29 patients tested positive for anti-belatacept antibodies; 13 of these patients had antibodies to the modified cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Anti-belatacept antibody titers did not increase during treatment in these 29 patients. “

Eight (2%) patients developed antibodies during treatment with the NULOJIX recommended regimen. In the patients who developed antibodies during treatment, the median titer (by dilution method) was 8, with a range of 5 to 80. Of 56 patients who tested negative for antibodies during treatment and reassessed approximately 7 half-lives after discontinuation of NULOJIX, 1 tested antibody positive. Anti-belatacept antibody development was not associated with altered clearance of belatacept.”

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However, the limitations of these findings, including methodology, small number of patients testing positive, led to the disclaimer that the clinical significance of these findings could not be determined.

8.1 Risk Evaluation and Mitigation Strategy (REMS)

Based on the concerns regarding PTLD and PML, and based on input from the Advisory Committee as well as consultants in OSE Divisions, belatacept will be approved with a REMS including Medication Guide and Communication Plan as detailed in the OSE and CDTL reviews. Briefly, the goals of the REMS are to inform HCP about risk of PTLD (predominantly CNS-PTLD) and PMS, and also inform patients about the risks with Nulojix. The communication plan will include a webpage, www.NULOJIX.com/REMS.aspx, and multiple documents available on that webpage including webinar slides, DHCP letter, HCP fact sheet, Infusion Specialist letter, and Infusion Checklist. (b) (4)

REMS assessments will be submitted annually for the first 5 years and finally at 7 years.

8.2 Post Marketing Requirements (PMRs)

There are three clinical PMRs intended to collect information on belatacept use within the first year post-transplant and information on PTLD and PML as summarized below. The study design and protocol summaries for these studies have been reviewed and detailed recommendations for revisions have been provided by OSE/DEPI and DBVII. In addition CMC is requesting a PMR to assess (b) (4)

CLINICAL

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 PTLD, including Epstein-BarrVirus (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)

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

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 (PTLD) 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 PTLD, and outcome (survival or mortality). Incidence rates of PTLD in belatacept-exposed patients will be quantified beginning when 500 belatacept-exposed patients have at least 1 year of follow-up. Relative risks of PTLD 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)

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

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Final Report Submission: 04/2020

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 (PTLD), PTLN in the central nervous system (CNS PTLN), 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 PTLN, and outcome (survival or mortality). (Protocol Number IM103076)

Final Protocol Submission: 04/2012

Study Completion: 04/2019

Final Report Submission: 04/2020

MANUFACTURING

4. Conduct a study to quantify at the end of the proposed (b) (4) (b) (4) Provide a worst case risk assessment for those (b) (4) including potential toxicity to humans, in your final report.

Final Report Submission: 12/2012

8.3 Post Marketing Commitments (PMC)

The CMC staff further requested that BMS conduct and submit results of further testing, as provided below.

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 a PMC final report that includes the revised specifications together with a justification that includes supporting data and your experience with lots used in the clinical trials.

Final Report Submission: 12/2013

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.

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) (b) (4)

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.

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Final Report Submission: 12/2012

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.

Interim Report Submission: 12/2011

Final Report Submission: 12/2013

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.

Final Report Submission: 12/2012

8.4 Safety Meeting with OSE

The safety meeting was held as part of the wrap-up meeting on March 22, 2011 and the key safety issues of PTLD and PML were discussed, along with a brief summary of the planned REMS and PMRs.

9. Advisory Committee Meeting

The application was discussed before the Cardiovascular and Renal Drugs Advisory Committee on March 10, 2010; presentations were made by BMS and FDA, and the committee was asked to consider results of Studies IM103008, IM103027, and IM103100, and comment on the efficacy, safety, and approvability of the application. The following summary is provided by Minh Doan of the Advisors and Consultants Staff, who was the designated federal official for the meeting.

Efficacy - *While several Committee members expressed that efficacy was demonstrated, others felt that more data were necessary. There was evidence that non-inferiority was met based on a 20% margin, but the size of the margin was debated. The Committee strongly agreed that longer term studies are essential to evaluate the clinical benefits of the drug. Suggestions for additional information needed from additional studies included histological evidence of rejection, protocol biopsies take at 36-48 months, graft and survival data, actual versus estimated GFR measurements (using iothalamate), the use of biomarkers for renal dysfunction such as NGAL and KIM-1, and systematic measurements of proteinuria. The Committee was split on whether these additional studies should be requested prior to approval or if post-marketing studies were sufficient. Committee members also commented on the need for an alternative class of agents to the calcineurin inhibitors.*

Safety - *Although several members agreed that safety was demonstrated, the majority of the Committee felt concern regarding the increased risk of PTLD with cerebral involvement and PML. A registry was recommended to monitor the incidence of PTLD, as well as REMS and*

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observational studies. More long-term data was also suggested by Committee members, particularly by those who did not think that safety had been demonstrated. The Committee also mentioned that the studies involving other populations of patients would be warranted.

Approval – *the vote by the committee was 13 “yes” and 5 “no” in response to whether the overall benefits outweigh the risks and the application should be approved.*

A majority of the Committee members felt that belatacept should be approved for the indication of prophylaxis of acute rejection in de novo renal transplant recipients. The Agency confirmed that the EBV(+) population of patients and the less intensive regimen were parameters to be considered in the question. Members expressed that a tight registry should be maintained to monitor the risks involved with the drug. Members who did not think that the drug should be approved noted the large margin and lack of long-term data as reasons behind their decision. Collection of long-term data was strongly encouraged by all the members.

10. Pediatrics

BMS was granted orphan status for belatacept on February 20, 2008; therefore the application is exempt from PREA requirements. Despite this, the Division could consider whether pediatric studies should be requested under BPCA. However, given that the product will be contraindicated for use in patients who are EBV negative, and significantly more pediatric patients than adult patients are EBV negative, use in pediatrics would likely be low. Although the issue of whether to write a pediatric written request can be revisited, this discussion can be deferred until after the product is marketed and more clinical data are available from post-marketing and the implementation of REMS.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection

As reported in the Therapeutic Biologic – Establishment Evaluation Report (TB-EER), all manufacturing site inspections are considered acceptable.

11.2 DSI Audits

The Phase 3 studies were multinational, therefore the Division asked DSI to inspect 8 sites in France, Mexico, Brazil and USA. Dr. Thompson concluded that the studies were conducted adequately and the data from the sites may be used to support the application.

11.3 Debarment certification

BMS certified that they had not used services of any debarred individual [as required under FD&C Act Section 306(k)(a)].

11.4 Orphan Status

BMS requested orphan drug designation on November 19, 2006, and pursuant to section 526 of FD&C Act, belatacept was granted orphan status on February 28, 2008 for “prophylaxis of organ rejection in renal allograft recipients.” Therefore, the application is exempt from user fees and from PREA requirements. The orphan designation also states that if the drug receives

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marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc) of FD&C Act.

11.5 Other Regulatory Issues

As noted above, there are a number of PMRs and PMCs included in the approval letter.

12. Labeling

The package insert, Medication Guide, and carton and container labeling were reviewed as applicable by the Division, DDMAC on March 10, 2011, OSE/DMEPA on March 23, 2011, OSE/DRISK on March 2, 2011, SEALD, MHT.³ The Division has also determined that belatacept would need a REMS including Medication Guide and Communication plan and worked with DRISK to address this part of the application. The Division staff held extensive and frequent labeling discussions among review staff, with the various consulting groups and with BMS. The final labeling includes the agreed-upon wording having taken into consideration all the various recommendations and is written in the PLR format consistent with available labeling guidances.

- **Package insert (PI):** The PI is written in PLR format and has been reviewed by all groups, and includes the recommendations made by these groups.
- **Medication Guide (MG):** The MG reflects recommendations from all applicable review groups.
- **Carton and Container Labels:** The labels include revisions as recommended by CMC and DMEPA. (b) (4)
- **REMS:** The REMS was developed in collaboration with OSE/DRISK and has gone through applicable clearances.
- **Proprietary Name:** The proposed proprietary name Nulojix has been reviewed by DMEPA and a letter stating that the name is acceptable was issued by Dr. Holquist of DMEPA on October 6, 2009. The name was re-reviewed and found acceptable on February 28, 2011 and DMEPA/Irene Chan stated that since the PDUFA goal date is close enough to the 90 day time frame, a re-review is not necessary.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

³ DMEPA reviews PI, Medguide and Proprietary name; DRISK reviews PI, Medguide and REMS; DDMAC reviews PI, Medguide, carton and container; CMC reviews carton and container.

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The deficiencies identified in the *Complete Response* letter issued May 1, 2010 have been addressed, the inspectional findings at the Manati, Puerto Rico manufacturing facility have been classified as VAI, and the TB-EER found to be acceptable, therefore BLA 125288 for Nulojix is recommended for approval. A summary of the deficiencies and their resolution is summarized in Section 1, and is presented in detail in the respective primary reviews and CDTL review.

13.2 Risk Benefit Assessment

In transplantation, immunosuppressants that show efficacy in preventing acute rejection, graft loss and death are associated with adverse events in the majority of patients (nearly 99% in the control arm of the belatacept studies), ranging from mild to serious. Management of transplant patients involves the use of several immunosuppressive agents and optimization of a regimen that maximizes efficacy and minimizes toxicity. Belatacept was developed as an alternative to currently available products, mainly cyclosporine a calcineurin inhibitor, with the goal of minimizing the toxicity seen with CNIs such as nephrotoxicity, hypertension and dyslipidemia, NODAT, and in the NULOJIX Phase 3 clinical trials, the rates of these events were no different or were lower than in the CNI control arm. A number of products, including cyclosporine, need to be used with therapeutic drug monitoring (TDM) to minimize toxicity which the NULOJIX regimen is weight-based and does not involve TDM. Although clinical pharmacology suggests that TDM be evaluated for belatacept, such evaluation does not need to be done before approval.

As noted by Dr. Archdeacon, while there is a concern regarding the consequences of a potential loss of efficacy, from a clinical point-of-view, the potential loss of efficacy is an important consideration, but not necessarily a contraindication to approval. Dr Archdeacon notes: “immunosuppressive regimens in solid organ transplantation always represent a balance of efficacy and toxicity. A regimen which may have less efficacy in the prevention of AR episodes may still be preferable if it has also been shown to potentially have less toxicity.” In the case of belatacept, the increased number of BPAR cases did not correlate to an increase in graft loss/mortality, and although there was an increased risk of PTLD (including CNS involvement) there were also fewer adverse events that are considered to increase risk of cardiovascular events. Of note, GFR which is considered a measure of renal function was higher in the belatacept arms, but again did not correlate with significantly higher patient or graft survival compared to CsA. The higher measured and calculated GFR in the belatacept patients over the 3 year follow up is likely due to the absence of CNI toxicity; GFR at 3 years was lower in the CNI containing control arm in both Phase 3 clinical trials. Dr. Archdeacon’s review includes a detailed and quantitative discussion of the individual safety and efficacy analyses and notes that the main factors relevant to the benefit risk determination include:

- Evidence of efficacy based on BPAR, graft loss, death, loss to follow up, made pre-specified margin of 20%
- No significant difference in mortality and graft loss
- Higher mean GFR (which may be evidence of absence of toxicity)
- Less toxicity related to lipids, hypertension, and NODAT

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- Increased risk of acute rejection, including high grade rejection managed with steroids and other modalities
- PLTD, including CNS cases (plan to limit population to EBV positive patients, which represent about 80% of transplant patients, as well as 80% of patients in belatacept trials)
- Risk of PML at higher than recommended doses
- IV administration (approximately weekly, then monthly)

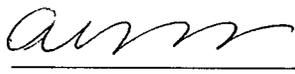
Overall, the primary efficacy endpoint has been met, the overall patients and graft survival is not significantly different (and numerically higher in both Phase 3 trials), the risk of PTLT and PML is relative higher but overall infrequent and to-be-managed under the REMS. Finally, other adverse events associated with CNIs were observed at no higher or even lower rates in the belatacept arm.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

See primary reviews and summary in Section 8.1.

13.4 Recommendation for other Postmarketing Requirements and Commitments

See summary in Section 8.2 and 8.3

 6/10/11

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 6/15/11

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