CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125288Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125,288
Priority or Standard	Complete Response
Complete Response Submit Date	December 15, 2010
Clinical Data Received Date	September 24, 2010
PDUFA Goal Date	June 15, 2011
Division / Office	DSPTP/OAP/OND
Reviewer Name(s)	Patrick Archdeacon, M.D. 3/25/11
Review Completion Date	March 23, 2011
Established Name	Belatacept
(Proposed) Trade Name	Nulojix
Therapeutic Class	Immunosuppressant
Applicant	Bristol-Myers Squibb Company
Formulation(s)	Lyophilized powder for IV infusion
Dosing Regimen	10 mg/kg on Day 1, 5, 14, 28,56, and 84; then 5 mg/kg every 4 weeks thereafter
Indication(s)	Prophylaxis of organ rejection
Intended Population(s)	Adult kidney transplant recipients

Joette Meyer 3/25/11

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 7

1.1 Recommendation on Regulatory Action 7
1.2 Risk Benefit Assessment 9
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies 12
1.4 Recommendations for Postmarket Requirements and Commitments 13

2 INTRODUCTION AND REGULATORY BACKGROUND 16

2.1 Product Information 16
2.2 Tables of Currently Available Treatments for Proposed Indications 16
2.3 Availability of Proposed Active Ingredient in the United States 16
2.4 Summary of Presubmission Regulatory Activity Related to Submission 16

3 ETHICS AND GOOD CLINICAL PRACTICES 17

3.1 Submission Quality and Integrity 17
3.2 Compliance with Good Clinical Practices 17
3.3 Financial Disclosures 18

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 18

4.1 Chemistry Manufacturing and Controls 18
4.2 Clinical Microbiology/Immunology 18
4.3 Preclinical Pharmacology/Toxicology 18
4.4 Clinical Pharmacology 19

5 SOURCES OF CLINICAL DATA 21

5.1 Studies/Clinical Trials in the Belatacept Developmental Program 21
5.2 Discussion of Individual Studies/Clinical Trials 23

6 REVIEW OF EFFICACY 26

Efficacy Summary 26
6.1 Indication 28
6.1.1 Methods 28
6.1.2 Demographics 29
6.1.3 Subject Disposition 29
6.1.4 Analysis of Efficacy Endpoint(s) 30
6.1.6 Other Efficacy Endpoints 32
6.1.7 Subpopulations 32

7 REVIEW OF SAFETY 34

Safety Summary 34
7.1 Methods 35

7.1.1 Studies/Clinical Trials Used to Evaluate Safety 35
7.1.2 Categorization of Adverse Events 35
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 35
7.2 Adequacy of Safety Assessments 36
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 36
7.2.4 Routine Clinical Testing 36
7.3 Major Safety Results 37
7.3.1 Deaths (and Graft Loss) 37
7.3.2 Serious Adverse Events 42
7.3.3 Dropouts and/or Discontinuations 46
7.3.4 Significant Adverse Events 48
7.4 Supportive Safety Results 63
7.4.1 Common Adverse Events 63
7.4.2 Laboratory Findings 64
7.6 Additional Safety Evaluations 65
7.6.1 Human Carcinogenicity 65
7.6.2 Human Reproduction and Pregnancy Data 65
7.6.3 Pediatrics and Assessment of Effects on Growth 65

8 POSTMARKET EXPERIENCE 65

9 APPENDICES 66

9.1 Literature Review/References 66
9.2 Labeling Recommendations 66
9.3 Advisory Committee Meeting 70

Table of Tables

Table 1: Maintenance Immunosuppressants in Kidney Transplantation 16
Table 2: Core clinical trials supporting the Belatacept BLA 22
Table 3: Demographics in the Phase 3 Kidney Transplant Trials 29
Table 4: Reasons for Treatment Discontinuations at 36 Months in IM103008 30
Table 5: Reasons for Treatment Discontinuations at 36 Months in IM103027 30
Table 6: Patient and Graft Survival at 36 months 31
Table 7: Biopsy Proven Acute Rejection, Graft Loss, or Death at 36 Months 32
Table 8: Patient and Graft Survival at 36 months among EBV Positive Subjects 33
Table 9: BPAR, Graft Loss, Death at 36 months among EBV Positive Subjects 33
Table 10: Safety Population at 36 Months for IM103008 and IM103027 36
Table 11: Deaths Occurring in IM103008 and IM103027* 37
Table 12: Narratives of Deaths among CsA Patients in IM103008 at 36 Months 38
Table 13: Narratives of Deaths among Belatacept LI Patients in IM103008 at 36 Months 38
Table 14: Narratives of Deaths among Belatacept MI Patients in IM103008 at 36 Months 39
Table 15: Narratives of Deaths among CsA Patients in IM103027 at 36 Months 39
Table 16: Narratives of Deaths among Belatacept LI Patients in IM103027 at 36 Months 40
Table 17: Narratives of Deaths among Belatacept MI Patients in IM103027 at 36 Months 41
Table 18: Graft Loss and/or Death in IM103008 and IM103027 42
Table 19: Summary of PTLD Cases Observed in Belatacept Trials 008, 027 and 100 ..43
Table 20: Serious Adverse Events with Biologically Plausible Connection to Immunosuppression or MPA Exposure in at least 4% of Patients at Month 36 in IM103008 45
Table 21: Selected Serious Adverse Events with Biologically Plausible Connection to Immunosuppression or MPA Exposure in at least 4% of Patients at Month 36 in IM103027 46
Table 22: Adverse Events Leading to Treatment Discontinuation in ≥2% of Patients Up to Month 36 in IM103008* 47
Table 23: Adverse Events Leading to Treatment Discontinuation in ≥2% of Patients Up to Month 36 in IM103027* 47
Table 24: Histopathology for All BPAR Events Occurring Through Month 36* 49
Table 25: Lymphocyte Depleting Therapy For Treatment of AR Through Month 36 49
Table 26: GFR at Month 36 in IM103008 and IM103027 According to BPAR Status* ...49
Table 27: Patient and Graft Survival in IM103008 and IM103027 at Month 36 According to BPAR Status 50
Table 28: BPAR Events Occurring Between Month 24 and Month 36 50
Table 29: Mean (standard deviation) Calculated GFR in IM103008 and IM103027 53
Table 30: Slope for Calculated GFR from Month 3 to 36 in IM103008 and IM103027 ...54
Table 31: Mean Blood Pressure at Month 36 in IM103008 and IM103027 55
Table 32: Incidence of New Onset Diabetes After Transplantation at Month 36 56

Table 33: Serum Lipids at Month 36 in IM103008 and IM103027.....57
Table 34: Patients with Infections as Adverse Events up to 36 Months in IM103008 and IM103027 58
Table 35: Cases of CNS Infections in IM103008 and IM103027 through 36 Months.....59
Table 36: Cases of Tuberculosis in IM103008 and IM103027 by 36 Months.....60
Table 37: Incidence of Proteinuria Through Month 36 in IM103008 and IM103027.....60
Table 38: Development of *de novo* Anti-Donor HLA antibodies in IM1030008 and IM103027 through Month 36 62
Table 39: Selected Adverse Events Associated with Class Effects Presenting through Month 36, N (%) 64

Table of Figures

Figure 1: Trials in the Belatacept Developmental Program.....21
Figure 2: Mean Calculated GFR (mL/min) through Month 36 in IM103008.....52
Figure 3: Mean Calculated GFR (mL/min) through Month 36 in IM103027.....53

1 Recommendations/Risk Benefit Assessment

Summary of BLA 125,288 Resubmission and Review
On June 30, 2009, Bristol Myers Squibb Company (BMS) submitted a BLA requesting the approval of belatacept IV for the indication of "prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants." On May 1, 2010, the Food and Drug Administration (FDA) issued a Complete Response (CR) letter, citing both clinical and product quality deficiencies in the application. During the June 11, 2010 End of Review Conference, FDA agreed that responses to the CR letter could be provided in reviewable units. On December 15, 2010, BMS submitted an amendment (Sequence #0064) to BLA 125,288 which was determined to constitute – in combination with previous amendments to the BLA (including but not limited to Sequence #0053 on August 16, 2010, Sequence #0054 on September 9, 2010, and Sequence #0055 on September 24, 2010) – a Complete Response to the May 1, 2010 letter and started the current review cycle.

In accordance with the CR letter issued by FDA, the BMS resubmission includes the 36 month data from the Phase 3 kidney transplant trials which represented the pivotal trials supporting the original BLA application, a safety update for all the non-clinical and clinical studies of belatacept, and a revised Risk Evaluation and Mitigation Strategies (REMS) proposal. In addition, the resubmission addresses the product quality deficiencies present in the original submission.

The following review focuses on the new clinical data submitted to the BLA application to elucidate the long-term effects of belatacept with regards to post-transplant lymphoproliferative disease (PTLD), renal effects, cardiovascular effects, and patient and graft survival. While it summarizes some of the findings of the Clinical Review of the original BLA submission, the original review is not entirely reduplicated. Please refer to the original Clinical Review finalized on April 30, 2010 for detailed analyses and discussions of the 12 and 24 month clinical data, including the primary efficacy analysis. The original Clinical Review also contains detailed discussions of the data and science (including the justification of the non-inferiority margin for the biopsy-proven acute rejection efficacy endpoint, the confounding that complicated reliance on the renal function endpoint, and the epidemiology of post-transplant lymphoproliferative disease) underlying certain determinations and conclusions pertinent to both the original review and the current review but which are not fully repeated herein.

1.1 Recommendation on Regulatory Action

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 Evalutation 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)

[redacted]

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 two Phase 3 kidney transplant trials suggest that belatacept has efficacy as an immunosuppressant in the context of kidney transplantation, but that it may not be as effective as the comparator drug, CsA. Although some concerns exist regarding the consequence of a potential loss of efficacy, the regulatory standard of demonstrating efficacy is met. From a clinical point-of-view, I considered the potential loss of efficacy to represent an important concern, but ultimately judged it insufficient to withhold a recommendation for approval: immunosuppressive regimens in solid organ transplantation must balance efficacy and toxicity. As discussed below, the data supported that belatacept did not exhibit some of the toxicities of CsA (primarily those related to its acute and chronic nephrotoxicities). A regimen which may have less efficacy for the prevention of BPAR may still be preferable in certain situations if it is also less toxic.

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.

During the review of the Complete Response submission, summary data regarding a trial studying belatacept in the context of liver transplant (IM103045) was submitted to BB-IND 9,418. After review of the summary data, the Data Monitoring Committee recommended stopping the study and converting all the liver transplant recipients managed with belatacept to a standard-of-care regimen due to increased rates of graft loss and death in the belatacept arms of the trial. On the basis of these data, I also recommend labeling specifically noting that belatacept should not be used in liver transplant (see also section 5.2 and section 9.2).

In summary, I recommend approval of the belatacept LI (but not the belatacept MI) regimen 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. I also recommend that the use of belatacept should be contraindicated in patients whose EBV serostatus is negative or unknown.

1.2 Risk Benefit Assessment

The relative risks and benefits identified during the review of the BLA resubmission are largely identical 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; for that reason, only the belatacept LI regimen is recommended for approval. Please see the original Clinical Review for an extensive discussion of the importance of these risks and benefits in the context of an adult kidney transplant recipient.

Overall, the adverse events associated with using belatacept rather than CsA tended to appear early during the course of the adult kidney transplant trials: most of the BPAR occurred during the first 3 months and very few episodes occurred after 6 months; thirteen out of the fourteen cases of PTLD occurred in the first 18 months; the single event of PML in the kidney transplant trials presented in a patient 23 months after transplantation (another event of PML in a liver transplant trial – which was not submitted as part of this BLA – in a patient approximately 6 months after transplantation). No additional belatacept-treated patients developed PTLD or PML and only one additional belatacept-treated patient experienced BPAR between Month 24 and Month 36 of the Phase 3 kidney transplant trials. Some consequences of earlier

events, however, manifested in the belatacept-treated patients between Month 24 and Month 36 (including the death of a patient previously diagnosed with CNS PTLD, the death of the patient previously diagnosed with PML, and several events of graft loss and/or death among patients with a history of AR).

In contrast with the discrete adverse events associated with using belatacept rather than CsA, the acute and chronic toxicities associated with the use of CsA rather than belatacept appear to impact all patients exposed to CsA [though the impact on measured parameters may only cause some to meet the clinical definition of outcomes like new onset diabetes after transplantation (NODAT)]. In general, the benefits with regards to GFR and cardiovascular risk factors across treatment groups observed at 12 and 24 months persisted at 36 months. Differences in mean GFR across treatment groups increased slightly, differences in systolic and diastolic blood pressure across treatment groups were similar, and differences in mean triglyceride levels across treatment groups were similar. At Month 36, in addition, the belatacept patients exhibited lower mean LDL levels compared to CsA patients (a benefit not seen at earlier time points).The small difference in the incidence of NODAT across treatment groups, however, had largely eroded by Month 36.

The 36 month data from the adult kidney belatacept trials are consistent with the 12 and 24 month data in suggesting that for approximately every ten to thirty patients treated with a belatacept regimen rather than a CsA regimen, one additional patient will experience an AR episode. The data further imply that for approximately every 150 EBV+ kidney transplant recipients managed with belatacept rather than CsA, one additional patient will develop PTLD. Very rarely patients managed with belatacept may develop PML. On the other hand, the majority of patients who receive belatacept instead of CsA will not experience any of these events but may anticipate benefiting from a significantly higher GFR, better blood pressure control, and an improved metabolic profile. In addition, those patients may also potentially benefit from avoiding direct nephrotoxicities inherent to exposure to CsA (or other calcinueurin inhibitors). It is likely that, presented with the data, some patients would prefer management with calcineurin inhibitors (CNIs) despite their blanket toxicities while other patients would prefer management with belatacept despite their association with more uncommon (but sometimes catastrophic) outcomes.

In theory, it might be possible to perform a calculus that could determine whether a population of patients managed with belatacept or CsA should, on average, experience better long-term outcomes. In practice, however, limitations of the currently available data – even at 36 months – prevent a clear determination of overall risk-benefit. Belatacept patients demonstrated a predilection for developing CNS PTLD which led to several instances of death and, despite improved cardiovascular risk profiles, did not experience demonstrably fewer cardiovascular deaths. On the other hand, numerically more patients who received the proposed belatacept dosage regimen rather than CsA were alive and with a functioning graft at 36 months in the standard criteria donor kidney trial (208/226 or 92% versus 196/221 or 89%) and the extended criteria donor kidney

trial (144/175 or 82% versus 147/184 or 80%) – perhaps a reflection of the benefits accrued from avoidance of the toxicities associated with CsA.

The data from the Phase 3 trials did not suggest that the belatacept MI regimen had more efficacy than the belatacept LI regimen – in fact, there were numerically more efficacy failures among recipients of the belatacept MI regimen in comparison with the belatacept LI regimen. Some of the safety signals were more pronounced among the recipients of the belatacept MI regimen compared to the belatacept LI regimen: out of the 14 events of PTLD that presented among kidney transplant patients exposed to belatacept, eight were among recipients of the belatacept MI regimen compared to six among recipients of the belatacept LI regimen; out of the 9 events of CNS PLTD that presented among kidney transplant patients exposed to belatacept, six were among belatacept MI patients compared to three among belatacept LI patients; out of the 7 events of CNS infections that presented among kidney transplant patients by Year 3 of the Phase 3 trials, six (including the event of PML) were among belatacept MI patients compared to one among belatacept LI patients.

While the risk of PTLD was higher for recipients of the belatacept regimens than the cyclosporine regimen, the risk difference was most significant in the EBV- population. Among the belatacept patients included in the PTLD analysis, 85% had an EBV+ serostatus at baseline while only 10% had an EBV- serostatus and only 5% had an unknown EBV serostatus. However, among the 14 belatacept patients who developed PTLD, six (or 42%) were EBV+, seven (or 50%) were EBV-, and one (or 8%) was EBV unknown. Those data suggest that the risk of PTLD is approximately ten-fold higher for EBV- belatacept patients compared to EBV+ belatacept patients.

The trials, in the view of this reviewer, provide substantial evidence of the efficacy of belatacept. An analysis of both efficacy and safety endpoints favored the belatacept LI regimen over the belatacept MI regimen. Certainly, the PTLD safety signals justify a contraindication to use among EBV- and EBV unknown recipients of kidney transplants (the patient population at the highest risk for PTLD). The present data are insufficient to predict whether differences in population outcomes will ultimately emerge between the belatacept LI regimen and CsA-based treatments among EBV+ kidney transplant recipients. In the view of this reviewer, however, the data are sufficient to support a positive risk-benefit assessment for well-informed EBV+ adult kidney recipients who are willing to accept a higher risk of relatively uncommon but potentially fatal adverse events in order to avoid the well-characterized toxic effects associated with the standard of care.

Reviewer comment: UNOS data suggests that, at present, 40% of U.S. kidney transplant patients are maintained on steroid-free regimens. The vast majority of these patients receive induction with thymoglobulin and maintenance with tacrolimus and mycophenolate mofetil (as common wisdom holds that use of an IL-2 antagonist for induction or CsA as the CNI would lack sufficient potency in a steroid-free context). Such practices, while common, represent off-label use of these products as data

supporting the safety and efficacy of such approaches have never been submitted to the FDA. Given the higher rates of AR observed with belatacept in comparison to CsA and given the relative contraindication to use of thymoglobulin in conjunction with belatacept due to increased risk of PTLD, it is likely that regimens using belatacept will continue to require use of corticosteroids (which are associated with their own well-known toxicities). The risk-benefit analysis above relied on a comparison of the proposed belatacept regimen to a CsA-based regimen whose relative safety and efficacy has been established in multiple trials reviewed by FDA, but whose popularity with US transplant physicians has waned markedly over the last decade. A meaningful risk-benefit analysis of the proposed belatacept regimen in comparison to some more novel regimens (including steroid-free regimens) currently favored by the US transplant community is not possible based on available data. In the event that belatacept is approved, however, market forces will likely ensure that trials making such direct comparisons will be performed.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The review of the clinical data provided in the BLA resubmission does not alter the recommendation of the clinical review of the original BLA submission: belatacept should be approved with a REMS. The REMS should increase awareness of the increased risk of PTLD (predominantly involving the CNS) and CNS infections (including PML). The REMS should also mitigate the risk of PTLD by increasing adherence to the contraindication of the use of belatacept among patients whose EBV serostatus is negative or unknown. The REMS should include a Medication Guide and a Communication Plan. At this time, the implementation of Elements to Assure Safe Use (ETASU) does not appear warranted.

The original BLA submission included a proposed REMS which was reviewed in the original clinical review. The BLA resubmission included an amendment to the BLA on August 16, 2010 (Sequence #0053) which included a revised proposed REMS addressing the REMS-related deficiencies cited in the CR letter. The applicant and FDA met on September 27, 2010 and have interacted extensively since to align their perspectives on the REMS plans.

The Division consulted DRISK to revise the REMS document and the associated documents. Please see the DRISK reviews for more information. At the time of the writing of this review, the revised REMS have not been finalized with the applicant.

The stated goals of the revised REMS are to:

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

The proposed REMS elements include a Medication Guide, a Communication Plan, and a timetable for submission of assessments. The Communication Plan includes a Dear Healthcare Provider (DHCP) letter, an HCP Fact Sheet, a Dear Infusion Specialist letter, a Pre-Infusion checklist, a journal information piece, a webinar, and a REMS-specific landing page on the NULOJIX website).

1.4 Recommendations for Postmarket Requirements and Commitments

The original BLA submission included (b) (4) proposed protocol synopses designed to address outstanding concerns related to belatacept:

- IM103074 – Pattern of Use of Belatacept in US Transplant Recipients
- IM103075 – Belatacept and Risk of PLTD in US Renal Transplant Recipients
- IM103076 (b) (4)

(b) (4)

Postmarketing requirements (PMRs) are intended to evaluate safety signals established by the clinical trials data (b) (4)

(b) (4) (b) (4)

. The other proposed studies, however, did have the potential to further evaluate safety signals established in the clinical trials.

The Division consulted DEPI regarding the proposed postmarketing studies. Please see the DEPI review by Dr. Andy Mosholder and also the Statistical Safety team review by Dr. John Yap.

In the Clinical Review of the original BLA submission, it was noted that IM103074 and IM103075 were designed to leverage data from the Organ Procurement and Transplant Network / United Network for Organ Sharing (OPTN/UNOS) and would further elucidate the safety profile associated with the use of belatacept. IM103076, (b) (4)

On September 24, 2010, FDA provided comments to the applicant recommending the conduct of IM103074 and IM103075. In that same communication, however, FDA had the following comments regarding IM103076 "(b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted]. We recommend that instead of this proposed postmarketing study you set up a patient registry of belatacept users with the goal of enrolling the vast majority of patients, confirmed by utilization data, from as close to the time of initial marketing as feasible... Such a registry would allow a reasonably rapid and accurate estimate of the absolute incidence of PTLD, CNS PTLD, and PML among transplant patients maintained on belatacept. Such a registry would not provide a similar estimate of the absolute incidence of PTLD, CNS PTLD, and PML among transplant patients maintained on a CNI-based regimen. Nonetheless, given existing data suggesting that CNS PTLD and PML are rare among transplant patients maintained on a CNI-based regimen, accurate absolute incidences of these events among belatacept patients would have significant informative value." These recommendations were discussed further in a Type B meeting conducted with the applicant on September 27, 2010.

FDA sent an additional communication on November 12, 2010 regarding IM103075. During the review of the original BLA submission, the FDA Pharmacogenomics group noted that the percentage of belatacept-treated patients in the core kidney transplant studies who developed PTLD who were CMV seronegative at baseline was disproportionate to the percentage of the entire population of belatacept-treated patients in those studies who were CMV seronegative at baseline. For that reason, FDA provided the following comment: "While CMV serostatus has not been clearly identified as a risk factor for the development of PTLD... we recommend that IM103075 should include a sub-analysis of PTLD rates according to recipient CMV status to evaluate further whether CMS serostatus at time of transplant may represent an independent risk of the development of PLTD among kidney transplant patients maintained on belatacept."

A draft protocol for IM103074 was submitted to the BLA on November 30, 2010 (Sequence #0060) and a draft protocol for IM103075 provided on December 14, 2010 (Sequence #0063). The draft protocol for IM103075 reflected the November 12, 2010 recommendations of the FDA. A draft protocol of IM103076 was submitted to the BLA on December 21, 2010 (Sequence #0065). The applicant also adopted the suggestions of the FDA regarding IM103076: the applicant revised IM103076 as a prospective registry of adult kidney transplant patients managed with belatacept (b) (4) [redacted]. FDA provided some comments regarding the draft protocol of

IM103076 on January 25, 2010; these comments were discussed further in a January 26, 2010 teleconference with the applicant. The applicant proposes to submit complete protocols in the near future, which will be reviewed separately, as they are not required prior to the approval of belatacept.

I recommend that the following clinical Post Marketing Requirements (PMRs) shouldbe communicated in the Approval Letter. These PMRs are based on the studies that the applicant and the FDA have previously discussed.

1. [IM103074] 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 should assess the prevalence of belatacept use, characteristics of belatacept users, including EBV and CMV serostatus. In addition, the study should collect information on adult kidney-only transplant recipients who switch to or from belatacept within one year post-transplant.

2. [IM103075] Conduct a prospective observational study utilizing data from the United Network for Organ Sharing (UNOS) on the incidence rates of PTLD in 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.

3. [IM103076] Conduct a prospective registry of use of belatacept in US adult kidney-only recipients to estimate the incidence rates of PTLD, CNS PTLD, and PML. Recipients will include those initiated on belatacept at the time of transplant (de novo) and those switching to belatacept after other immunosuppressive regimens have been used ("switch"). All US adult kidney transplant centers dispensing belatacept will be asked to participate or due diligence (i.e., if a center declines to participate, the reason(s) for nonparticipation will be identified and documented). Recipient characteristics will be collected, including EBV and CMV serostatus, location of the PTLD, and outcome (survival or mortality).

2 Introduction and Regulatory Background

2.1 Product Information

2.2 Tables of Currently Available Treatments for Proposed Indications

Several products are currently used as components of a maintenance immunosuppressive regimen for the indication of prophylaxis of organ rejection in recipients of kidney transplants, including CsA, tacrolimus, sirolimus, azathioprine, mycophenolate mofetil, mycophenolate sodium, and corticosteroids, as shown in Table 1. Both mycophenolate mofetil and mycophenolate sodium are metabolized to produce the active moiety, mycophenolic acid (MPA). The products are used in a variety of combinations to form immunosuppressive regimens. The labeling across products is inconsistent: as newer products have been approved and labeled in the context of various regimens, labeling of the other components of those regimens has not always been updated. In addition, off-label use of these products is common. According to all labeling, however, immunosuppression regimens used in kidney transplant patients should include a CNI (either CsA or tacrolimus).

Table 1: Maintenance Immunosuppressants in Kidney Transplantation

Immunosuppressant	**Trade Name**
CsA	Neoral, SandImmune, and generics
Tacrolimus	Prograf
Sirolimus	Rapamune
Mycophenolate Mofetil (MMF)	CellCept
Mycophenolate Sodium (MPS)	Myfortic
Azathioprine	Imuran
Corticosteroids	Various

2.3 Availability of Proposed Active Ingredient in the United States

Belatacept is a new molecular entity not currently marketed in this or any other country.

(b) (4)

2.4 Summary of Presubmission Regulatory Activity Related to Submission

Belatacept has been developed under IND 9,418 for indications in solid organ transplant since October 2000. In August of 2005, an SPA of Study IM103008 was submitted to

FDA. While discussions were held regarding non-inferiority for the composite endpoint of death and/or graft loss and regarding the relevance of the composite renal impairment endpoint, the understanding of the science supporting both non-inferiority studies and transplant renal function have evolved at FDA since 2005. While FDA acknowledges that certain agreements were reached which may have seemed reasonable in 2005, it must also recognize that emerging science must take precedence over formal agreements.

The applicant submitted the original BLA application on June 30, 2009. FDA issued a Complete Response to that application on May 1, 2010. The applicant submitted various "reviewable units." The final unit was received December 15, 2010 and constituted a Complete Response to the BLA.

Other important regulatory activity:

- Fast track designation granted on January 26, 2005
- Orphan Drug designation granted on February 20, 2008
- Pre-BLA meetings occurred in April 2008 and May 2009
- End of Review Conference for the initial review cycle on June 11, 2010

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The BLA resubmission was well-organized and complete. The datasets provided were easily analyzed. The results of those analyses were consistent with the analyses performed and reported by the Sponsor.

3.2 Compliance with Good Clinical Practices

DSI inspections are routinely performed for New Molecular Entities (NMEs). While no data integrity issues prompted for-cause inspections, DSI inspections were therefore performed at several centers where the belatacept Phase 3 kidney trials were conducted during the review of the original BLA submission. A Clinical Inspection Summary was completed by Dr. Susan D. Thompson and Dr. Tejahsri Purohit-Sheth of the Division of Scientific Investigations (DSI) during the original review. While the DSI inspections noted some minor violations, the conclusion was that the data generated by the inspected sponsor site and clinical sites were suitable for use in support of the application. Additional clinical site visits were not performed for the BLA resubmission. Plant inspection deficiencies were noted in the first review cycle. Re-inspections were conducted in March 2011 – the final recommendations regarding those re-inspections are pending at the time of the writing of this review.

3.3 Financial Disclosures

Information regarding financial disclosures was included in the BLA submission; in the view of the clinical reviewer, the disclosures did not materially affect the apparent integrity of the submitted trial data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Complete Response letter cited a number of Product Quality deficiencies in the original BLA submission. The CMC product quality and microbiology teams state that the BLA is approvable based on the data in the resubmission. The final reviews are pending at the time of the writing of this review.

Please refer to the reviews from the CMC product quality team (Jack Ragheb, M.D., Ph.D. and Susan Kirshner, Ph.D.) and the CMC microbiology team (Bo Chi, Ph.D. and Patricia Hughes, Ph.D.) regarding the adequacy of the BLA resubmission to address the cited deficiencies.

4.2 Clinical Microbiology/Immunology

The Complete Response letter did not cite any deficiencies related to clinical micro/immunology. However, the BLA resubmission included new data regarding the development of donor specific antibodies (DSAs) among patients in the pivotal Phase 3 kidney transplant trials. The data suggest that patients treated with the belatacept regimens developed DSAs less frequently than patients treated with the CsA regimens (see also Section 7.3.5). The FDA analyses of these data are ongoing, therefore the final Microbiology/Immunology Review by Aaron Ruhland, Ph.D. is still pending at the time of the writing of this review. As data related to the development of DSAs were not cited as a deficiency in the Complete Response letter, the analysis is not a basis of action for the BLA resubmission.

4.3 Preclinical Pharmacology/Toxicology

The Complete Response letter did not cite any deficiencies related to toxicology. Two new nonclinical studies, however, were included as part of the BLA resubmission. The studies are "DS09027, BMS-224818: A One-Month Intravenous Investigative Study in Male Monkeys" and "DS09113, BMS-224818: A One-Month Combination Investigative Study with Mycophenolate Mofetil and Cyclosporin A." The studies evaluated the

penetration of belatacept into the brain and cerebral spinal fluid (CSF). Please see the review from the Pharmacology/Toxicology reviewer (Janice Lansita, Ph.D., DABT) for details. Overall, the studies indicated that belatacept does not appear to cross the blood-brain barrier or cause adverse changes in the brain of healthy cynomolgus monkeys after one month or treatment. Using MMF in combination with belatacept does not result in belatacept crossing the blood-brain barrier. However, the study did indicate that using MMF in combination with belatacept decrease systemic levels of mycophenolic acid (MPA) and increases systemic levels of mycophenolic acid glucuronide (MPAG).

Reviewer comment: In a PK substudy (IM103047) of the Phase 3 belatacept kidney transplant trials, the mean dose-normalized MPA C_{max} and AUC_{0-12} were approximately 20% and 40% higher, respectively, with belatacept co-administration compared with CsA co-administration. As CsA is known to reduce MPA exposure due to its interruption of the enterohepatic recirculation of MPA, one cannot rely on these data to deduce the precise effect of belatacept on MPA metabolism. However, these data suggest that the effect seen in the monkey study is not as pronounced in humans.

4.4 Clinical Pharmacology

The Complete Response letter did not cite any deficiencies related to clinical pharmacology. However, the three year data from the Phase 3 kidney transplant trials included some relevant pharmacology data: the mean CsA levels at Month 36 were 149 ng/ml in IM103008 and 140 ng/ml in IM103027; the mean and median doses of MMF at Month 36 were similar across treatment arms (around 1600-1700 mg/day and 1750-2000 mg/day, respectively); the median dose of corticosteroids at Month 36 were also similar across treatment arms (5 mg/day).

During this review cycle, the Clinical Pharmacology team examined the effect of belatacept of immunoglobulin levels during the first twelve months of the Phase 3 kidney transplant trials. Immunoglobulin levels at Month 6 and Month 12 were lower than baseline immunoglobulin levels in both belatacept-treated and CsA-treated patients. The decrease exhibited by patients exposed to belatacept, however, was slightly greater than the decrease exhibited by patients exposed to CsA. Analyses performed by the Clinical Pharmacology team demonstrated that lower immunoglobulin levels correlated with a variety of adverse outcomes.

The final Clinical Pharmacology review by Gerlie Gieser, Ph.D. is still pending at the time of the writing of this review. As data related to immunoglobulin levels were not cited as a deficiency in the Complete Response letter, the analysis is not a basis of action for the BLA resubmission.

Reviewer comment: Lower immunoglobulin levels at Month 6 and Month 12 in the Phase 3 kidney transplant trials also correlated with some baseline demographic data,

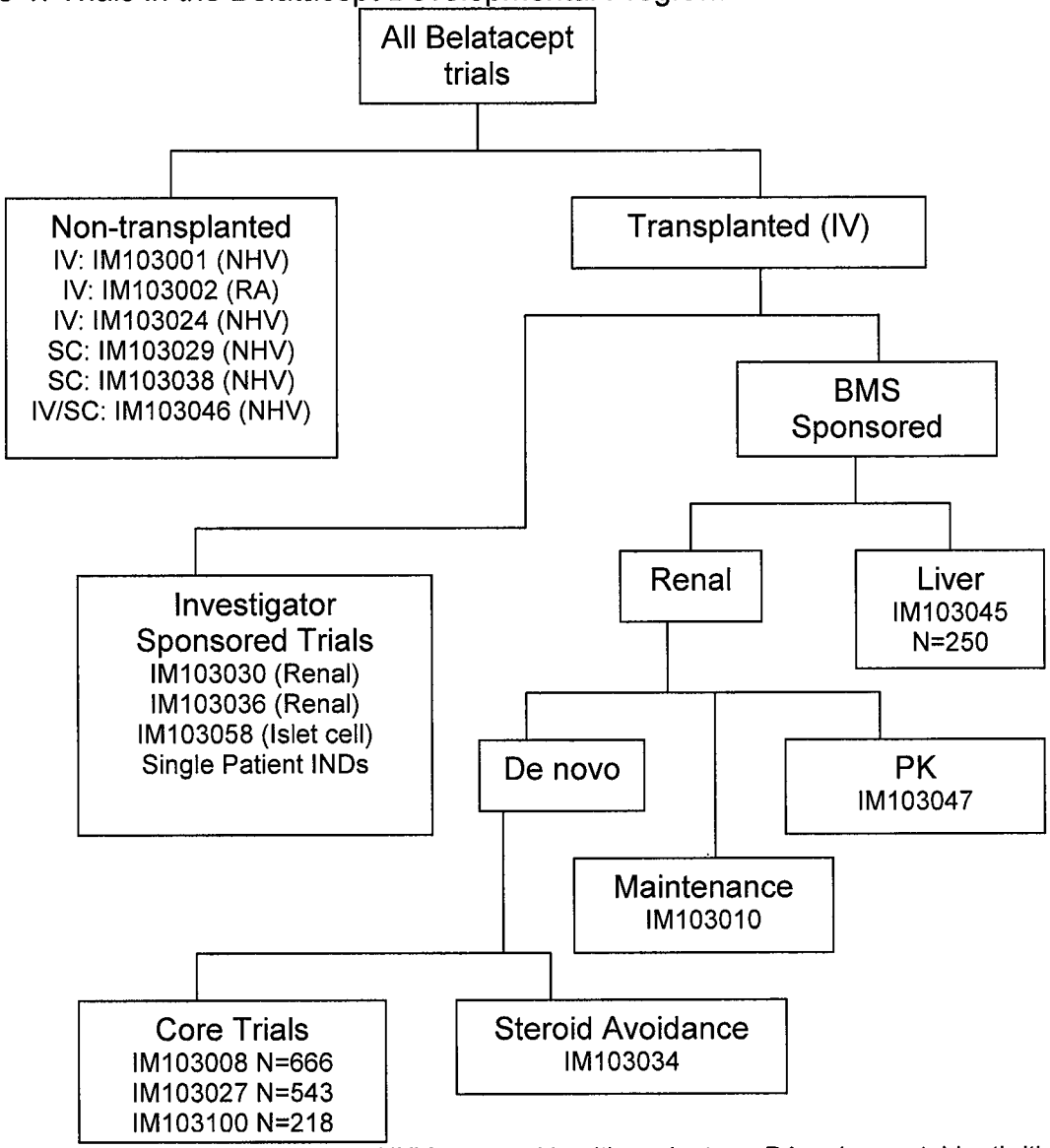
including advanced patient age and poor donor kidney quality. In addition, lymphocyte depleting agents (such as thymoglobulin) cause lower immunoglobulin levels. One reasonable explanation for the observation by the Clinical Pharmacology team that patients with lower immunoglobulin levels at Month 6 and Month 12 experienced worse outcomes is that such patients were more likely to be elderly, have received an extended criteria donor kidney, and/or have experienced a grade IIa or greater episode of acute rejection in the first 6 months after transplantation. While it is possible that the impact of belatacept and CsA on immunoglobulin levels played a causal role in the adverse outcomes experienced by these patients, insufficient evidence exists to make definitive statements in this regard.

5 Sources of Clinical Data

5.1 Studies/Clinical Trials in the Belatacept Developmental Program

The clinical development program for belatacept is shown in Figure 1 below, as adapted from the applicant's submission.

Figure 1: Trials in the Belatacept Developmental Program



IV = intravenous, SC = subcutaneous, NHV = normal healthy volunteer, RA = rheumatoid arthritis
Source: Figure adapted from Figure 3 of BMS Advisory Committee Briefing Document

The core clinical trials in support of the original BLA application were IM103008, IM103027, and IM103100, as shown in Table 2. The core clinical trials in support of the BLA resubmission are IM103008 and IM103027. IM103008 and IM103027 were both designed as three year trials, but had primary endpoints set at Month 12. The primary clinical deficiency cited in the FDA Complete Response letter was the lack of long-term follow-up data from the Phase 3 kidney transplant trials, particularly the data regarding outcomes such as mortality, graft loss, GFR, PTLD, and other serious adverse reactions. The BLA resubmission includes the three year data from IM103008 and IM103027 for those outcomes. In addition, the resubmission includes data supporting an overall safety review at the 36 month time point for those trials.

Table 2: Core clinical trials supporting the 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

[a] Belatacept MI = 10 mg/kg on Day 1 and Day 5, then every 2 weeks through Month 3, then every 4 weeks through Month 6, then 5 mg/kg every 4 weeks; Belatacept LI = 10 mg/kg on Day 1 and Day 5, then every 2 weeks through Month 1, then every 4 weeks through Month 3, then 5 mg/kg every 4 weeks
[b] Belatacept MI = 10 mg/kg on Day 1, Day 5, and Day 15, then every 2 weeks through Month 3, then every 4 weeks through Month 6, then 5 mg/kg every 4 or 8 weeks; Belatacept LI = 10 mg/kg on Day 1, Day 5, Day 15, Day 29, Day 57, and Day 85, then 5 mg/kg every 4 or 8 weeks
Source: Adapted from Applicant's AC Briefing Document

The IM103008 and IM103027 12 month study reports and datasets provided in the electronic submission were previously reviewed. These can be found in the electronic submission located at: \\cbsap58\m\eCTD_Submissions\STN125288\0000. Additional analysis datasets previously reviewed include \\cbsap58\m\eCTD_Submissions\STN125288\0006 and the 120-day safety update (2 year data) at \\cbsap58\m\eCTD_Submissions\STN125288\0013.

The IM103008 and IM103027 36 month study reports and datasets supporting the BLA resubmission are located in the electronic submission at: \\cbsap58\m\eCTD_Submissions\STN125288\0055.

5.2 Discussion of Individual Studies/Clinical Trials

IM103008, IM103027, and IM103100

IM103008, IM103027, and IM103100 were extensively discussed in the Clinical Review of the original BLA submission. All of these studies were considered supportive of the proposed dose and regimen: IM103008 and IM103027 were relied on for the determination of efficacy and all three were used for the assessment of safety. All three are randomized controlled trials of adult *de novo* kidney transplant recipients comparing belatacept-based treatment regimens to a CsA-based control treatment regimen. The regimens of all arms of all three trials also include induction immunosuppression with basiliximab and concomitant maintenance immunosuppression with mycophenolate mofetil (MMF) and corticosteroids (CS). IM103100 was designed as a 12 month Phase 2 study – although it had a long-term extension phase, few patients in the CsA control arm continued in the study beyond the first year. In addition, while IM103100 included a regimen similar to the proposed recommended regimen, it did not study a regimen identical to the proposed recommended belatacept regimen. IM103008 and IM103027 were designed as 36 month Phase 3 studies (although the primary efficacy endpoints were 12 month endpoints). IM103008 and IM103027 are the only trials which studied the proposed recommended belatacept regimen. As stated above, the 36 month data from IM103008 and IM103027 represents the core data for the BLA resubmission.

IM103045

The patient level data from IM103045 were not submitted in support of either the original BLA submission or BLA resubmission, though the BLA includes summary data regarding events of PTLD and PML which were reported in IM103045. However, during the review of the Complete Response submission (on January 18, 2011), additional summary data regarding this trial was submitted to BB-IND 9,418 (SN 513); the summary data was also accompanied by a copy of recommendations from the Data Monitoring Committee. The trial had been previously placed on a Partial Clinical Hold by FDA on November 3, 2009 due to increased rates of graft loss and death in one of the belatacept arms of the trial; the Partial Clincial Hold precluded the enrollment of additional patients into that study arm. After review of the new summary data, the Data Monitoring Committee recommended termination of the study and the conversion all the liver transplant recipients managed with belatacept to a standard-of-care regimen due to additional events of graft loss and death in the belatacept arms of the trial. These findings from IM103045 informed decisions regarding recommended labeling for belatacept, including statements in the boxed warning and in a section in Warning and Precautions regarding the safety signals detected in this liver transplant study (see Section 9.2).

IM103045 was a Phase 2 *de novo* liver transplant study that randomized patients to 5 immunosuppressive regimens: Group 1) basiliximab induction in conjunction with a belatacept more intensive (MI) regimen with MMF (N=50); Group 2) a belatacept MI

regimen with MMF (N=48); Group 3) a belatacept LI regimen with MMF (N=48); Group 4) tacrolimus with MMF (N=53); and Group 5) tacrolimus (N=50). All arms also used corticosteroids as a concomitant immunosuppressive. Enrollment into the belatacept LI regimen was stopped early on the recommendation of the Data Monitoring Committee due to an increased rate of death and/or graft loss in that study arm – these data also led to the FDA Partial Clinical Hold which also precluded additional patient enrollment. After review of the 12 month data, the Data Monitoring Committee recommended stopping the study and converting all patients from the belatacept regimens to a standard of care due to an excess number of in deaths in the belatacept groups (4 deaths in Group 1, 7 deaths in Group 2, 10 deaths in Group 3, 1 death in Group 4, and 4 deaths in Group 5). In addition to the imbalance in deaths, the belatacept regimens exhibited higher rates of efficacy failures (as measured by a composite endpoint of acute rejection and/or death and/or graft loss by Month 12): 52% for Group 1, 48% for Group 2, 53% for Group 3, 19% for Group 4, and 40% for Group 5. As discussed in Section 7, one case of PML (Group 2) and two cases of PTLD (one in Group 1 and one in Group 3) developed among patients randomized to the belatacept treatment regimens.

Reviewer comment 1: The majority of the deaths in the belatacept arms occurred early after transplantation when differences across the treatment arms were minimal (the belatacept MI regimen and belatacept LI regimen studied are identical through Week 6). The high rates of efficacy failures across the belatacept arms indicate that belatacept may not have adequate efficacy for the prevention of acute rejection in the context of liver transplantation.

Reviewer comment 2: IM103045 included two tacrolimus-based treatment regimens – Group 4 (tacrolimus + MMF) and Group 5 (tacrolimus alone). The Group 4 regimen represents the standard of care used at most US transplant centers. The Group 5 regimen reflects the current Prograf labeling for liver transplant (the de facto FDA approved comparator). Patients receiving the Group 4 regimen experienced fewer deaths, fewer graft losses, fewer acute rejection events, and fewer high grade acute rejection events than patients receiving the Group 5 regimen experienced. Various professional societies in the transplant communities (including the American Society of Transplantation and the American Society of Transplant Surgeons) have expressed concerns regarding trials that use a tacrolimus alone comparator. The data from this trial underlies some of these concerns – the safety signals regarding increased deaths and increased efficacy failures among the belatacept regimens may not have been as appreciable in the absence of the unapproved "Standard of Care" comparator arm. Registrational liver transplant trials which rely on a "tacrolimus alone" comparator may both pose safety concerns for trial patients and may also lead to inappropriate conclusions about the relative safety and efficacy of novel immunosuppressive regimens. The FDA may need to consider whether pathways exist to use data from IM103045 to reconsider the current Prograf labeling for liver transplant.

IM103034

IM103034 is not considered by the FDA to be a core study in support of either the original BLA submission or the BLA resubmission as it did not study the proposed regimen and it did not include an appropriate control arm. For that reason, IM103034 was not reviewed in full. The summary data, however, suggests findings consistent with the review of the core studies. The Complete Response did not include new data from this study.

IM103034 is a Phase 2 *de novo* adult kidney transplant trial that randomized patients to 3 immunosuppressive regimens: Group 1) thymoglobulin induction in conjunction with belatacept and MMF (N=33); Group 2) thymoglobulin induction in conjuction with belatacept and sirolimus (N=26); Group 3) thymoglobulin induction in conjunction with tacrolimus and MMF (N=30). Methylprednisolone was administered on Days 1 through Days 4, but otherwise the immunosuppressive regimens were corticosteroid-free. The belatacept regimens used were based on the belatacept MI regimen used in the other kidney transplant trials. As this trial lacked an appropriate comparator arm (as the Prograf labeling does not support the use of tacrolimus without concomitant corticosteroids and in conjunction with either thymoglobulin induction) and the trial did not study the proposed recommended belatacept dosage regimen, its results had limited usefulness during the original BLA review and also during the review of the BLA resubmission. However, it is reasonable to note that the results of IM103034 at 6 months of follow-up were consistent with the observations from the core studies: numerically more patients randomized to a belatacept regimen had experienced rejection than patients randomized to the tacrolimus regimen (4 in Group 1 versus 1 in Group 2 versus 1 in Group 3) but belatacept-treated patients exhibited higher mean GFR than tacrolimus-treated patients (57.5 ml/min/1.73 m^2 in Group 1 versus 58.7 ml/min/1.73 m^2 in Group 2 versus 50.8 ml/min/1.73 m^2 in Group 3). None of the patients in any of the groups of this trial developed PTLD or PML.

Reviewer comment: Tacrolimus, as another calcineurin inhibitor, shares many of the same acute and chronic toxicities as CsA. The data appears to suggest that belatacept may have somewhat less efficacy for the prevention of acute rejection than tacrolimus, but belatacept does not have the acute and chronic nephrotoxic effects of tacrolimus.

IM103010

IM103010 is not considered by the FDA to be a core study in support of either the original BLA submission or the BLA resubmission as it did not study the proposed regimen and its design did not allow the evaluation of any testable hypothesis. For those reasons, IM103010 was not reviewed in full. The 12 Month Clinical Study Report was submitted, however, to the BLA in November of 2009 (during the original BLA review). The summary data suggests findings consistent with the review of the core studies.

IM103010 is a Phase 2 conversion study adult kidney transplant trial that randomized 173 stable kidney transplant patients maintained on a CNI-based regimen to either converting to a belatacept-based regimen (N=84) or to staying on the CNI-based regimen (N=89). The patients who were randomized to the conversion arm received belatacept dose at 5 mg/kg on Days 1, 15, 29, 43, 57 then every 28 days thereafter. The patients reduced their dose of CNI to 40%-60% of the baseline dose on Day 15, to 20%-30% of the baseline dose on Day 22, and discontinued CNI on Day 29. At 12 Months, 6 of the patients who converted to belatacept experienced BPAR compared to none of the patients who remained on a CNI. However, the mean GFR of the patients who converted was 60.5 ml/min/1.73 m^2 compared to 56.5 ml/min/1.73 m^2 among the patients who remained on a CNI.

Reviewer comment: The data from IM103010, like those from IM103034, lead to conclusions consistent with those from the review of the core studies: belatacept may have less efficacy for the prevention of acute rejection than CNIs, but belatacept does not have the acute and chronic nephrotoxic effects of CNIs. Changing immunosuppressive regimens in stable transplant patients is inherently associated with risk of acute rejection, so it is difficult to assess the outcomes associated conversion protocol studied: while it is concerning that 6/84 (7%) of the patients who converted experience BPAR, it is unclear whether these episodes are attributable to a relative lack of efficacy of belatacept compared to CNI or whether these episodes are attributable to the approach to the conversion. Optimizing approaches to conversion would require trials which randomize patients to different conversion and dosage protocols.

6 Review of Efficacy

Efficacy Summary

The two Phase 3 kidney transplant trials, IM103008 and IM103027, were the key trials for demonstrating the efficacy of belatacept. In both trials, the control groups used a CsA-based immunosuppressive regimen. The Phase 2 trial, IM103100, did not study a regimen identical to that proposed by the applicant for approval. In addition, the Phase 2 trial lacked the statistical power to draw scientifically sound conclusions regarding efficacy. The efficacy results of IM103100, however, were noted in the initial Clinical Review to be consistent with the analysis of efficacy based of the Phase 3 belatacept trial data.

The Clinical Review of the original BLA submission described the study designs and results through 24 months of follow-up and concluded that the data supported the proposed indication of belatacept for the prevention of acute rejection. The Complete Response letter did not specifically cite a lack of adequate evidence of efficacy as a deficiency of the original BLA submission. However, it did state that 36 month data from the Phase 3 trials were required to evaluate the long-term effect of belatacept. Although the review of the original BLA submission found that the belatacept LI regimen had

evidence of efficacy for the prevention of acute rejection and that belatacept was associated with a benefit in terms of GFR, it also found that belatacept was associated with serious adverse events (including PTLD and PML). As the review of the original did not find evidence of an overall mortality benefit based on the 12 and 24 month data, the Division Director and Office Director requested the 36 month data to evaluate mortality at that time point and to determine if the clinical benefits of belatacept were sustained (see the Division Director and Office Director reviews of the original BLA submission for additional details). For that reason, the three year data from the BLA resubmission were reviewed to evaluate their consistency with the finding of efficacy based on the data provided in the original BLA submission.

The pre-specified co-primary endpoints in the Phase 3 protocols to establish efficacy were 12 month endpoints. The co-primary efficacy endpoints as pre-specified in the Phase 3 protocols were:

- The composite of patient and graft survival at 12 months, and
- The composite of renal impairment as assessed by measured glomerular filtration rate (GFR) < 60 mL/min/1.73m^2 at Month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73m^2 from Month 3 to Month 12, as measured by the cold-iothalamate method, and
- The incidence of AR, defined as a biopsy confirmed histological evidence of rejection along with clinical evidence, at 12 months (IM103008 only)

The Clinical Review and Statistical Review of the original BLA submission concluded the data supported a finding that belatacept had efficacy for the prevention of acute rejection in the context of kidney transplantation. The finding relied on an analysis of the incidence of BPAR at 12 months (where missing data due to death, graft loss, or loss to follow up was imputed as BPAR). The original Clinical Review relied on that analysis because a non-inferiority margin for the endpoint of patient and graft survival could not be established and because the data demonstrated that the composite renal impairment endpoint (which the FDA had previously agreed to in a Special Protocol Assessment of IM103008) was confounded by the effect of CsA on renal hemodynamics (and thereby GFR). Given that a BPAR endpoint with appropriate imputation for missing data [often described as the FDA composite endpoint of BPAR + death + graft loss (GL) + loss to follow up (LTF)] has served as the basis for establishing the efficacy of immunosuppressants used in solid organ transplantation (including tacrolimus, MMF, sirolimus, everolimus, basiliximab, and daclizumab), its use for evaluating the efficacy of belatacept was deemed appropriate. Based on the analysis of that endpoint, it was concluded that belatacept has efficacy for the prevention of acute rejection in recipients in kidney transplantation. The 12 month data suggest, however, that belatacept may have less efficacy than CsA for the prevention of AR at the doses of each used in the trials. Please see the original Clinical Review and original Statistical Review for details regarding the primary efficacy analysis.

An evaluation of the composite endpoint of BPAR + death + GL + LTF (see Table 7) and of various secondary efficacy endpoints using the 36 month data arrived at a similar conclusion to the evaluation of efficacy in the Clinical Review of the original submission. Likewise, observations regarding patient disposition and treatment discontinuations based on the 36 month data were very similar to the observations based on the 12 month data (see section 6.1.4).

6.1 Indication

The applicant proposed in the original BLA submission that belatacept receive an indication for "the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants." (b) (4)

(b) (4)

6.1.1 Methods

To evaluate efficacy using the 36 month data from the Phase 3 kidney transplant trial, rates of patient and graft survival and also rates of BPAR + death + GL + LTF across the treatment groups were examined. As discussed in the Clinical Review of the original BLA submission, an NI margin for the patient and graft survival endpoint at 12 months was not established. Similarly, NI margins for the primary endpoint of patient and graft survival and for BPAR + death + GL + LTF have not been established for the 36 month time point. The evaluation of efficacy in this review, therefore, does not represent a statistically rigorous exercise; the data are examined simply to evaluate whether the 36 months results appear consistent with the 12 month results. As the applicant's proposed endpoint of composite renal impairment has been determined to represent a confounded endpoint and was not a basis for the determination of efficacy in the Clinical Review of the orginal BLA submission, it was not used as an efficacy endpoint in the review of the 36 month data. However, data related to renal function at 36 months is discussed in detail in Section 7 (Safety).

6.1.2 Demographics

The baseline demographics of the Phase 3 kidney transplant trials were previously presented and discussed in the Clinical Review of the original BLA submission. They are reproduced here for the convenience of the reader.

Table 3: Demographics in the Phase 3 Kidney Transplant Trials

	IM103008			IM103027		
	MI N=219	LI N=226	CsA N=221	MI N=184	LI N=175	CsA N=184
Mean Age (years)	43.6	42.6	43.5	56.7	56.1	55.7
Gender, n (%)						
Male	151 (68.9)	146 (64.6)	165 (74.7)	119 (64.7)	129 (73.7)	116 (63.0)
Female	68 (31.1)	80 (35.4)	56 (25.3)	65 (35.3)	46 (26.3)	68 (37.0)
Race, n (%)						
White	132 (60.3)	133 (58.8)	139 (62.9)	137 (74.5)	134 (76.6)	137 (74.5)
Black	15 (6.8)	23 (10.2)	17 (7.7)	25 (13.6)	24 (13.7)	22 (12.0)
Asian	27 (12.3)	29 (12.8)	27 (12.2)	7 (3.8)	3 (1.7)	4 (2.2)
Other	45 (20.5)	41 (18.1)	38 (17.2)	15 (8.2)	14 (8.0)	21 (11.4)
Geographic region, n (%)						
North America	95 (43.4)	92 (40.7)	94 (42.5)	49 (26.6)	40 (22.9)	45 (24.5)
Rest of World	124 (56.6)	134 (59.2)	129 (57.4)	135 (73.4)	135 (73.1)	139 (75.5)
Recipient EBV serology						
Positive	194 (88.6)	199 (88.1)	184 (83.3)	169 (91.8)	156 (89.1)	168 (91.3)
Negative	25 (11.4)	27 (11.9)	37 (16.7)	14 (7.6)	19 (10.9)	16 (8.7)
Unknown	0	0	0	1 (0.5)	0	0

Source: Adapted from the Applicant's Summary of Clinical Safety; BLA 125,288

6.1.3 Subject Disposition

Clinical trials in transplantation, even randomized controlled trials intended to support the approval of a new therapy, are rarely conducted in a double blind fashion, primarily due to logistical issues and patient safety concerns regarding therapeutic drug monitoring. The belatacept Phase 3 trials were also conducted as open-label trials. There were numerically more discontinuations among CsA-treated patients than belatacept-treated patients in both studies (see Table 4 and Table 5). At Month 12, the discontinuations had been more balanced across treatment arms. There were differences in the reasons for discontinuations between belatacept and CsA groups: more belatacept patients discontinued treatment due to lack of efficacy whereas more CsA patients discontinued treatment due to adverse events. This pattern was consistent with the pattern observed at Month 12.

Table 4: Reasons for Treatment Discontinuations at 36 Months in IM103008

	IM103008		
Number randomized and transplanted	Belatacept MI N=219	Belatacept LI N=226	CsA N=221
Number Discontinued Treatment, N (%)	61 (28)	56 (25)	72 (34)
Adverse Event	16 (7.3)	16 (7.1)	32 (15)
Lack of Efficacy	29 (13)	26 (12)	18 (8.4)
Death	5 (2.3)	4 (1.8)	6 (2.8)
All Other	11 (5)	10 (4.4)	16 (7.4)

Source: Adapted from Table 5.1A, 3 Year Clinical Study Report IM103008

Table 5: Reasons for Treatment Discontinuations at 36 Months in IM103027

	IM103027		
Number randomized and transplanted	Belatacept MI N=184	Belatacept LI N=175	CsA N=184
Number Discontinued Treatment, N (%)	74 (40)	60 (34.5)	79 (44)
Adverse Event	34 (19)	35 (20)	44 (25)
Lack of Efficacy	19 (10)	15 (9)	17 (9.5)
Death	10 (5.5)	4 (2.3)	3 (2)
All Other	11 (6)	6 (3.4)	15 (8.4)

Source: Adapted from Table 5.1A, 3 Year Clinical Study Report IM103027

Reviewer comment: The high rate of treatment discontinuations among CsA-treated patients may reflect conceptions among many in the transplant community that CsA-based treatment regimens are inferior to tacrolimus-based treatment regimens. In this open-label study, physicians and patients may have been predisposed to discontinuing treatment for patients randomized to the control arm. This may explain the finding that more patients discontinued from cyclosporine than from belatacept after the first year. It may be instructive to see whether these patterns of discontinuation are repeated in future trials where belatacept-based regimens are compared to tacrolimus-based regimens.

6.1.4 Analysis of Efficacy Endpoint(s)

Patient and Graft Survival

Patient and graft survival rates at 36 months are presented in Table 6. In Study IM103008, patient and graft survival was 91.3%, 91.2% and 86.9% in the belatacept MI, belatacept LI, and CsA groups, respectively. In Study IM103027, patient and graft survival was 79.9%, 81.7%, and 77.7% in the belatacept MI, belatacept LI, and CsA groups, respectively. A non-inferiority margin was not established for this endpoint. In

addition, the 36 month time point was not the pre-specified time point for the efficacy analysis. However, the observed rates and their associated confidence intervals are compatible with the conclusion of the original Clinical Review that belatacept LI has efficacy in the context of kidney transplantation. The 36 month data regarding death and graft loss are discussed in greater detail in Section 7.3.1.

Table 6: Patient and Graft Survival at 36 months

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: Statistical Review of BLA 125,288 resubmission

Biopsy Proven Acute Rejection (BPAR)

Cumulative rates of BPAR at 36 months are presented in
Table 7. In these efficacy analyses, all patients with missing data at Month 36 (whether due to graft loss, death, or loss to follow up) are imputed to have experience BPAR. In Study IM103008, the rates at 36 months were 32%, 25.7%, and 25.7%, respectively, for the belatacept MI, belatacept LI, and CsA regimens. In Study IM103027, the rates at 36 months were 38%, 36%, and 37%, respectively, for the belatacept MI, belatacept LI, and CsA regimens. The observed rates and the associated confidence intervals are compatible with the conclusion of the Clinical Review of the original BLA submission that belatacept LI has efficacy for the prevention of BPAR in the context of kidney transplantation. The 36 month data regarding BPAR are discussed in greater detail in Section 7.3.4.

Table 7: Biopsy Proven Acute Rejection, Graft Loss, or Death at 36 Months

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: Statistical Review of BLA 125,288 resubmission

6.1.6 Other Efficacy Endpoints

The applicant analyzed and presented in the BLA resubmission a number of other endpoints as secondary efficacy endpoints. These include endpoints pertaining to renal function, new onset diabetes after transplantation (NODAT), hypertension, and dyslipidemia. (b) (4)

these analyses have been presented in the Review of Safety (see Section 7).

6.1.7 Subpopulations

EBV Serostatus
As previously discussed, a higher rate of PTLD was observed among recipients of belatacept-based immunosuppression compared to CsA-based immunosuppression in the core clinical trials. This difference was particularly pronounced among recipients who were EBV seronegative at time of transplant. EBV negative serostatus has been established as an important independent risk factor for the development of PTLD in a non-belatacept context. It is not surprising, then, that any increased risk for PTLD associated with belatacept would be particularly evident among that subpopulation. The

applicant has suggested that the overall risk-benefit profile of belatacept does not justify its use among EBV- kidney transplant recipients, but does justify its use among EBV+ kidney transplant recipients (where the absolute risk of PTLD is lower).

No biologic reason exists to believe that the efficacy of belatacept should be different among EBV+ and EBV- subpopulations. However, given that belatacept use will be be restricted to the EBV+ subpopulation, an analysis of the 36 month data supporting the efficacy of belatacept in that subpopulation was performed, as shown in Table 8 and Table 9. The observed rates and the associated confidence intervals are compatible with the conclusion of the Clinical Review of the original BLA submission that the belatacept LI regimen has efficacy in the context of kidney transplantation.

Table 8: Patient and Graft Survival at 36 months among EBV Positive Subjects

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: Statistical Review of BLA 125,288 resubmission

Table 9: BPAR, Graft Loss, Death at 36 months among EBV Positive Subjects

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: Statistical Review of BLA 125,288 resubmission

7 Review of Safety

Safety Summary

The two Phase 3 kidney transplant trials, IM103008 and IM103027, were the key trials for demonstrating the relative safety of belatacept. In both trials, the control groups used a CsA-based immunosuppressive regimen. As both of these trials were designed as 3 year trials, safety monitoring was routinely done in accordance with protocol through Month 36. A related Phase 2 kidney transplant trial, IM103100, did not study a regimen identical to that proposed by the applicant for approval. In addition, the Phase 2 trial was designed as a one year study; while a long term extension (LTE) of the trial was implemented, only a third of the 73 patients in the CsA control group part participated. In effect, then, IM103100 lacked a control group after the first year of follow-up. For both of those reasons, the safety review of the 36 month data focused on the two Phase 3 trials. The 36 Month data were also used to support labeling recommendations for the package insert.

Size of the safety database is always a limitation in the review of trials of newer therapeutic agents for indications in kidney transplantation: due to the limited number of kidney transplants performed worldwide and due to the extensive monitoring required of each patients, individual trials are rarely larger than several hundred patients. The safety population of IM103008 included 666 patients (226 randomized to the belatacept LI regimen, 219 randomized to the belatacept MI regimen, and 221 randomized to the CsA regimen). The safety population of IM103027 included 543 patients (175 randomized to the belatacept LI regimen, 184 randomized to the belatacept MI regimen, and 184 randomized to the CsA regimen). Data for outcomes including death, graft loss, and PTLD were available for all Phase 3 patients at 3 years of follow-up. Given the safety signals seen in the context of the belatacept, consideration was also given to the IM103100 kidney transplant trial data and the IM103045 liver transplant trial data in the belatacept developmental program for PTLD and PML despite concerns regarding differences in the belatacept regimens, patient populations, and indications studied .

The most significant safety concerns associated with belatacept elucidated during the Clinical Review of the original BLA submission included PTLD (predominantly PTLD involving the CNS), PML (and other CNS infections), and higher rates and grades of BPAR. As previously described, the signals pertaining to these concerns (including higher rates and grades of BPAR) were more pronounced for the belatacept MI regimen than the belatacept LI regimen – the regimen which the applicant has proposed and the regimen which I have recommended for approval.

The safety review suggested that the belatacept regimens had favorable profiles relative to CsA with regards to other important safety issues including mean GFR, blood pressure, and dyslipidemia. While the Clinical Review of the original BLA submission noted a lower rate of new onset diabetes after transplantation (NODAT) for belatacept-

treated patients than for CsA-treated patients at the 12 month time point, that difference was not as appreciable at the 36 month time point.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary data used to evaluate the long-term safety of belatacept were the 36 month data from the Phase 3 trials, IM103008 and IM103027. The review focused on those trials as they were the only ones to use the proposed belatacept LI regimen in a kidney transplant population. The Phase 2 trial, IM103100, used a similar regimen but omitted a 10 mg/kg dose on Day 5 and randomized half of the recipients to 5 mg/kg infusions every 8 weeks (instead of every 4 weeks) after Month 6. In addition, only 26 of the 73 patients in the CsA control group continued in the long-term extension study beyond Month 12 – in effect, making IM103100 an uncontrolled trial after the first year. While the Phase 3 trials represented the core of the data used in the review – specifically for endpoints such as patient and graft loss, BPAR, GFR, and cardiovascular risk factors -- additional data were considered for some safety endpoints. In particular, for some of the more rare events (such as PTLD and PML), IM103100 was included in order to capture as much safety information as possible. With regards to PTLD and PML, the trial that used belatacept in *de novo* liver transplant patients (IM103045) was also given consideration.

7.1.2 Categorization of Adverse Events

Most common and severe adverse events were categorized using the MedDRA dictionary of preferred terms. However, some safety outcomes of particular interest [including death, graft loss, BPAR episodes, PTLD, cardiovascular data (e.g., NODAT), and GFR] were identified prospectively and were specifically measured and recorded to allow analyses of these outcomes. Additional information was available in the patient narratives. Data captured in the clinical trials databases and/or narratives which specifically measured these outcomes were used preferentially to related data incidentally captured in the Adverse Events database to evaluate relevant safety outcomes.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data were pooled across IM103008, IM103027, and IM103100 to evaluate the incidence of PTLD. As stated above, the data were pooled for this purpose due to the rarity of the event. While the usual concerns regarding pooling applied to this analysis, it was deemed important to determine whether any patterns would emerge if the analyses

of these events were given greater power. Most safety issues, however, were examined within the context of the individual Phase 3 trials.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Safety analyses were performed using the ITT populations for Studies IM103008 and IM103027 as shown in Table 10 below, and included 403 patients randomized to the belatacept MI regimen, 401 patients randomized to the belatacept LI regimen, and 405 patients randomized to the CsA regimen.

Table 10: Safety Population at 36 Months for IM103008 and IM103027

Study Number	Belatacept MI	Belatacept LI	CsA
008	219	226	221
027	184	175	184
TOTAL	**403**	**401**	**405**

Source: Adapted from the 3 year Clinical study Reports, BLA 125,288

One subject in the belatacept MI group (IM103027), 1 subject in the belatacept LI group (IM103027) and 13 subjects in the CsA group (6 in IM103008, 5 in IM103027 and 2 in IM103100) were included in the safety population, but did not receive study medication. The number of subjects with at least 36 months of exposure to study medication was as follows: 158/219 (72.1%) in the IM103008 and 109/184 (59.2%) in the IM103027 for the belatacept MI groups, 170/226 (75.2%) in the IM103008 and 114/175 (65.1%) in the IM103027 for the belatacept LI groups, and 143/221 (64.7%) in the IM103008 and 99/184 (53.8%) in the IM103027 for the CsA groups.

In the following discussion of safety, adverse events (AEs) are reported by Preferred Terms (PT) and by System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs are reported through the first 36 months Phase 3 studies (IM103008, IM103027).

7.2.4 Routine Clinical Testing

In the third year of the Phase 3 kidney transplant trials, chemistry, hematology, and urinalysis panels and CsA troughs were sent to a central lab at Week 116, Week 128, Week 140, and Week 156. Fasting glucose and lipids were collected at Week 128 and Week 156. Hemoglobin A1c was measured at Week 128 and Week 156. Blood pressures were monitored at Week 128 and Week 156.

7.3 Major Safety Results

7.3.1 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- recipients and despite the impact of the imbalance in PTLD presentations across treatment groups (see Table 11).

Table 11: 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: Created by the Clinical Reviewer using the applicant's datasets and narratives, BLA 125,288
*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

Death Narratives

Patient narratives summarizing the circumstances of death were reviewed. As expected among kidney transplant recipients, most deaths appeared attributable to cardiovascular causes or infection. Several occurred in the immediate post-operative setting. The most notable difference between patient groups is the four deaths due to CNS lymphoma that occurred by the 36 month time point among belatacept-treated patients. Of these four deaths, two occurred in EBV+ patients and two occurred in EBV- patients. In addition, at least four other deaths among belatacept-treated patients appear attributable to CNS infection: one death related to West Nile Virus, one death related to Cryptococcus, one death related to PML, and one death related to an unspecified cerebral fungal infection. Table 12, Table 13, Table 14, Table 15, Table 16, and Table 17 below reflect the cause of death as inferred from the submitted death narratives by the Clinical Reviewer.

IM103008

Table 12: Narratives of Deaths among CsA Patients in IM103008 at 36 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
22-20679	1	38	M	Patient had "seizure" while driving, then died of MI in hospital
76-20171	1	55	M	Hemorrhagic shock immediately post-op, never received CsA
84-20700	1	48	F	Sepsis
89-20350	1	50	M	Cardiac arrest immediately post-operatively
98-20439	1	45	M	Suicide
118-20353	1	20	M	Pneumonia
123-20740	1	54	F	Sepsis, wound infection
10-20254	2	66	M	Cardiac arrest in setting of massive bleed on anticoagulation
41-20088	2	61	M	Cardiac arrest in setting of fever
48-20042	2	64	M	Pneumonia
84-20405	2	53	M	Pulmonary adenocarcinoma
91-20103	2	55	F	Hypoxia due to pulmonary edema
116-20453	2	37	F	Interstitial lung disease
66-20163	3	43	M	Sepsis in post-operative setting of a CABG
101-20019	3	35	M	Sudden infectious death; distant history of PTLD

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

Table 13: Narratives of Deaths among Belatacept LI Patients in IM103008 at 36 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
10-20037	1	55	M	Patient died on Day 358; distant history of wound infection, no other information available
46-20592	1	61	F	Sepsis immediately post-operatively
123-20230	1	19	F	Generalized bleeding (not witnessed)
124-20297	1	55	M	Myocardial infarction
9-20120	2	47	M	Metastatic sarcoma
25-20375	2	71	F	Non small cell lung cancer
57-20645	2	37	M	Bowel ischemia due to severe mesenteric artery occlusion
154-20618	2	26	M	No information available regarding circumstances of death
125-20504	3	59	F	Cardiac arrest in setting of admission for cellulitis
150-20482	3	39	F	Cardiac arrest; history of TB

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

Table 14: Narratives of Deaths among Belatacept MI Patients in IM103008 at 36 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
46-20330	1	77	M	Hemorrhage from vascular anastamosis on Day 12
46-20650	1	74	M	Urosepsis
84-20669	1	41	F	Sudden cardiac death
85-20526	1	71	F	CMV colitis, sepsis
124-20561	1	72	M	Lung adenocarcinoma
159-20686	1	53	M	Bronchopulmonary aspergillosis
41-20344	2	46	M	**Complications of West Nile Virus**
133-20434	3	56	M	Sepsis in setting of obstructed hernia
160-20692	3	18	M	Sudden cardiac death; history of graft loss, on dialysis

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

IM103027

Table 15: Narratives of Deaths among CsA Patients in IM103027 at 36 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
2-10002	1	56	M	"Veered off road and collapsed"
32-10077	1	63	M	Rupture of mycotic aneurysm of iliac artery
57-10086	1	64	M	Pulmonary embolus
60-10260	1	73	M	Significant intragraft bleed immediately post-op, MI; never received CsA
85-10110	1	65	F	Sepsis
85-10531	1	72	M	Obstructive uropathy, sepsis
85-10572	1	70	F	Intestinal ischemia
105-10400	1	58	F	Renal vein thrombosis, GI hemorrhage, sepsis
10-10275	2	62	M	Sepsis (MRSA); also infected with pseudomonas and aspergillosis
17-10061	2	68	F	Fungal pneumonia, disseminated CMV disease
54-10502	2	79	M	Kaposi's Sarcoma
105-10573	2	68	F	Sepsis
22-10256	3	64	M	Multiple CVA
35-10036	3	74	F	Pyelonephritis, sepsis
83-10175	3	58	M	Motor vehicle accident
91-10035	3	51	M	Septic shock
141-10579	3	52	M	Bilateral pneumonia

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

Table 16: Narratives of Deaths among Belatacept LI Patients in IM103027 at 36 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
64-10372	1	65	M	Withdrew consent on Day 42; reported to have died on Day 353
66-10516	1	68	M	Sigmoid colon perforation; sepsis
85-10569	1	66	F	Necrotizing fascitis and sepsis on Day 3
91-10089	1	42	M	Disseminated tuberculosis, invasive CMV disease, sepsis
97-10452	1	75	M	Endocarditis, sepsis
26-10440	2	55	M	Complications related to transitional cell carcinoma
29-10427	2	68	M	Myocardial infarction
69-10525	2	66	M	No information available
93-10037	2	49	M	Strongyloidiasis, CMV disease, pneumonia
101-10093	2	75	M	**CNS lymphoma (PTLD); Pt was EBV+ at baseline**
102-10186	2	55	M	No information available; had lost graft 200 days before death
124-10466	2	55	M	**Cryptococcosis, "cerebellar syndrome", seizures, coma; post-mortem cerebral cultures and biopsy were negative**
124-10527	2	44	M	Patient found dead in house on Day 426; cause unknown
64-10350	3	63	M	Sepsis
138-10593	3	38	M	**Deterioration of cognitive function, history of CNS PTLD; Pt was EBV- at baseline**

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

Table 17: Narratives of Deaths among Belatacept MI Patients in IM103027 at 36 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
22-10496	1	70	F	Cardiac arrest on Day 3
53-10399	1	63	F	Surgical wound infection
58-10390	1	68	F	Ischemic heart disease
70-10447	1	65	M	**CNS lymphoma (PTLD); Pt was EBV- at baseline**
85-10249	1	50	M	Myocardial infarction
89-10114	1	79	M	Severe post-operative MI and sepsis; Pt ultimately died on Day 96 of multi-organ failure and sepsis
93-10027	1	65	M	Myocardial infarction
102-10494	1	58	M	Post-operative renal hemorrhage; ischemic bowel
30-10184	2	72	M	Severe aortic valve disease
35-10185	2	71	M	**CNS lymphoma (PTLD); Pt was EBV+ at baseline**
97-10453	2	73	M	Withdrew consent Day 13; Pt reported to have died on Day 669
102-10164	2	61	M	Pneumonia
125-10433	2	62	M	Osteomyelitis, staph sepsis
2-10284	3	67	M	Congestive heart failure
2-10308	3	51	M	Cerebrovascular accident
10-10048	3	77	M	Sudden death; adjudicated as a cardiovascular death
15-10045	3	65	F	**Progressive multifocal leukoencephalopathy**
15-10059	3	62	M	Coronary atherosclerotic disease
20-10254	3	55	F	Cardiopulmonary arrest secondary to uremia
29-10408	3	61	F	No information available
89-10510	3	67	F	Sepsis
124-10362	3	50	F	**Cerebral fungal infection**

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

Reviewer comment: A trend toward higher rates of death related to CNS infections and/or CNS malignancies was noted among recipients of belatacept regimens – in the Phase 3 trials at the 36 month time point, 5 patients treated with the belatacept MI regimen had died secondary to a CNS infection or malignancy (1 from West Nile Virus, 1 from PML, 1 from cerebral fungal infection, and 2 from CNS PTLD), 3 patients treated with the belatacept LI regimen had died secondary to a CNS infection or malignancy (2 from CNS PTLD and 1 from cryptococcal meningitis), whereas no patients treated with the CsA regimen had died secondary to a CNS infection or malignancy.

Death, graft loss, and the combined endpoint of death and graft loss were evaluated in the Phase 3 trials IM103008 and IM103027 at 36 months. Randomized clinical trials in transplantation lack the statistical power to rigorously evaluate the combined endpoint of patient death and graft loss. Numerically, however, more belatacept patients across the Phase 3 trials were alive with a functioning graft at Month 36 (see Table 18). The numeric difference observed was driven by IM103008. Given the lack of statistical

power, one cannot determine whether the numeric difference represents chance or true benefit deriving from the favorable GFR, blood pressure, and metabolic profiles of patients on belatacept regimens compared to patients on CsA regimens. While one cannot conclude that belatacept patients had a more favorable outcome with respect to combined death and graft loss compared to CsA patients in the Phase 3 trial, it is somewhat reassuring that a numeric advantage persists at 36 months despite the greater number of PTLD events and CNS infections among belatacept patients.

Graft Loss and/or Death

Graft loss after kidney transplantation can occur secondary to patient death ("death with a functioning graft") or independently of patient death ("graft loss alone"). At the 36 month time point, the total numbers of grafts lost were generally similar across treatment arms for both IM103008 and IM103027. Numerically, patients treated with the belatacept regimens experienced the fewer graft losses than patients treated with the CsA regimen (see Table 18). In addition, there were more CsA-treated patients than belatacept-patients who graft status was unknown at the 36 month time point (in IM103008, there were two belatacept MI patients, two belatacept LI patients, and 5 CsA patients with unknown graft status at Month 36; in IM103027, there were 1 belatacept MI, 1 belatacept LI, and 5 CsA patients with unknown graft status at Month 36). It is unclear whether the small numeric differences may reflect the benefit of avoiding the acute and chronic toxicities associated with CsA or whether they may have resulted from chance.

Table 18: Graft Loss and/or Death 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/Graft Loss						
Up to Month 12	10	8	14	23	20	25
Up to Month 24	13	12	20	29	28	30
Up to Month 36	17	18	24	36	31	36
Graft Loss						
Up to Month 12	4	5	8	17	16	20
Up to Month 24	7	5	8	18	20	22
Up to Month 36	10	9	10	18	21	23

Source: Created by the Statistical Reviewer using the applicant's datasets, BLA 125,288 resubmission

7.3.2 Serious Adverse Events

PTLD

For a complete discussion regarding PTLD rates observed in the belatacept development program, please refer to the Clinical Review of the original BLA

submission. This section focuses on the impact of PTLD on the 36 month data with regards to the overall safety of belatacept in IM103008 and IM103027.

At 36 months of follow-up, two belatacept MI patients, two belatacept LI patients, and one CsA patient from trials IM103008 and IM103027 had already died from complications related to PTLD (and are therefore reflected in the total deaths presented in the 36 month efficacy and safety data). Three belatacept MI patients, four belatacept LI patients, and one CsA patient from IM103008 and IM103027 who developed PTLD remained alive and at significant risk of death and other complications at the 36 month time point (see Table 19). To date, two belatacept LI patients and one CsA patient from the Phase 3 trials have died from complications related to PTLD beyond the 36 month follow up period (and are therefore not reflected in the total deaths presented in the 36 month efficacy and safety data). A post hoc central pathology review of the PTLD cases submitted by the applicant with the original BLA application suggested the possibility that the other two belatacept LI patients who remain at risk may have been misdiagnosed with PTLD. One (PID 103008-113-20060) of those two patients, however, underwent six courses of rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP) based on the local pathology read; the other (PID 103008-122-20256) had PCR evidence of a clonal population with specific rearrangement of the heavy chain, consistent with a diagnosis of PTLD.

Reviewer comment: The slight numeric advantage in patients surviving and in patients surviving with a functioning graft exhibited by the belatacept LI group in IM103008 and IM103027 would persist even if all the patients alive at Month 36 known to have developed PTLD were imputed as deaths across treatment arms.

Table 19: Summary of PTLD Cases Observed in Belatacept Trials 008, 027 and 100

	Belatacept MI (N=477)			**Belatacept LI*** (N=472)			**CsA** (N=478)		
Trial	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		$2^{\Omega,\dagger}$							
Non-CNS PTLD			$1^{\ddagger}$						$1^{\ddagger}$
IM103008									
CNS PTLD	1^{Ω}	1^{Ω}							
Non-CNS PTLD		1^{Ω}		$2^{\Omega,\Omega}$				$1^{\dagger}$	
IM103027									
CNS PTLD	$1^{\dagger}$	$1^{\dagger}$		$2^{\dagger,\ddagger}$	$1^{\dagger}$				
Non-CNS PTLD					$1^{\ddagger}$		$1^{\ddagger}$		
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: Created by the Clinical Reviewer using PTLD narratives, BLA 125,288

At the time of the original BLA submission, fourteen PTLD events had presented among belatacept-treated patients and two PTLD events had presented among CsA-treated patients in trials IM103008, IM103027, and IM103100. After the date of the original BLA submission but before the date of the BLA resubmission, no additional PTLD events presented among belatacept-treated patients and one additional PTLD event presented in a CsA treated patient in these trials.

Narrative of the new PTLD Case Observed in the CsA Control Arm of Pivotal Kidney Transplant Trial IM103027 since the Clinical Review of the original BLA submission

IM103027-91-10020: The patient was a 36 year old EBV+, CMV- male who received a EBV unknown,CMV+ kidney on (b) (6). Patient was diagnosed in (b) (6) with PTLD in bone marrow. Patient died approximately seven weeks after diagnosis. This event occurred after database lock for the IM103027 Clinical Study Report for the BLA resubmission but was reported by the applicant in keeping with previous agreements with FDA.

Progressive Multifocal Leukoencephalopathy (PML)

A patient from the belatacept MI group in IM103027 was diagnosed with PML in Month 23; that patient died shortly after Month 24 (see summary of death narrative below). The incidence of PML in the general kidney transplant population has been estimated at 14 cases per 100,000 patient-years.[1] While the observation of even a single case of PML in IM103027, then, is remarkable, it is difficult to extrapolate too much from a single event. In addition, however, a second case of PML was diagnosed in the belatacept liver transplant program (in Study IM103045) in October of 2009. At the time of diagnosis, the patient was confused, had memory recall problems, had significant motor impairments and gait abnormalities. The patient subsequently died of complications related to PML. Two occurrences of PML in the context of a drug development program constitute a safety signal. While the impact of an increased risk of PML on the overall risk-benefit profile of belatacept is potentially small, given that the outcome remains rare, the signal is important because it supports other data suggesting that belatacept may have specific effects on CNS immunity (e.g., the increased incidence of CNS PTLD, the increased rates of CNS infections seen in the belatacept MI treatment group).

Both of these events were evaluated as part of the Clinical Review of the original BLA submission. No additional events of PML were reported as part of the BLA resubmission.

1 Neff RT, Hurst FP, Falta EM, et al. Progressive Multifocal Leukoencephalopathy and Use of Mycophenolate Mofetil after Kidney Transplantation. Transplantation 2008; 86(10): 1476-8.

Other Serious Adverse Events

Analyses of serious adverse events (SAEs), defined as events that were either life-threatening, required hospitalization, or prolonged hospitalization, reported in IM103008 and IM103027 through Month 36 were performed. The results of the analysis are presented in
Table 20 and Table 21.The major known adverse events associated with MPA exposure include leucopenia and diarrhea. Despite the 25% to 40% higher MPA exposure among the belatacept treated patients (see Clinical Pharmacology Review of the original BLA submission) the analysis did not detect any difference in serious adverse events due to leucopenia. However, in one of the two trials (IM103027), patients in the belatacept treatment groups did have a numerically higher rate of serious adverse events related to diarrhea than the CsA treatment group.

Table 20: Serious Adverse Events with Biologically Plausible Connection to Immunosuppression or MPA Exposure in at least 4% of Patients at Month 36 in IM103008

	Belatacept MI (N=219)	**Belatacept LI** (N=226)	**CsA** (N=221)
Total Patients with SAE	133 (60.7)	131 (58.0)	150 (67.9)
Infections and Infestations	62 (28.3)	73 (32.3)	73 (33.0)
Cytomegalovirus Infection	13 (5.9)	16 (7.1)	26 (11.3)
Urinary Tract Infection	12 (5.5)	12 (5.3)	7 (3.2)
Pneumonia	3 (1.4)	7 (3.1)	10 (4.5)
Renal and Urinary Disorders	29 (13.2)	25 (11.1)	42 (19.0)
Injury, Poisoning, and Procedural Complications	25 (11.4)	27 (11.9)	37 (16.7)
Graft Dysfunction	4 (1.8)	7 (3.1)	12 (5.4)
Neoplams (including cysts and polyps)	19 (8.7)	9 (4.0)	12 (5.4)
Blood and Lymphatic System Disorders	15 (6.8)	8 (3.5)	12 (5.4)
Cardiac Disorders	13 (5.9)	10 (4.4)	14 (6.3)
Vascular Disorders	11 (5.0)	13 (5.8)	22 (10.0)

Source: Adapted from 3 Year Clinical Study Report Table 8.3 for IM103008

Table 21: Selected Serious Adverse Events with Biologically Plausible Connection to Immunosuppression or MPA Exposure in at least 4% of Patients at Month 36 in IM103027

	Belatacept MI (N=184)	Belatacept LI (N=175)	CsA (N=184)
Total Patients with SAE	149 (81.0)	139 (79.4)	146 (79.3)
Infections and Infestations	89 (48.4)	71 (40.6)	84 (45.7)
Urinary Tract Infection	19 (10.3)	22 (12.6)	18 (9.8)
Cytomegalovirus Infection	17 (9.2)	16 (9.1)	12 (6.5)
Pyelonephritis	10 (5.4)	1 (0.6)	9 (4.9)
Pneumonia	9 (4.9)	4 (2.3)	6 (3.3)
Renal and Urinary Disorders	43 (23.4)	36 (20.6)	49 (26.6)
Renal Failure Acute	7 (3.8)	4 (2.3)	8 (4.3)
Gastrointestinal Disorders	29 (14.1)	22 (12.6)	28 (15.2)
Diarrhea	14 (7.6)	7 (4.0)	4 (2.2)
Neoplasms (including cysts and polyps)	16 (8.7)	15 (8.6)	16 (8.7)
Blood and Lymphatic System Disorders	18 (9.8)	14 (8.0)	14 (7.6)
Leucopenia	8 (4.3)	2 (1.1)	5 (2.7)
Cardiac Disorders	26 (14.1)	15 (8.6)	24 (13.0)
Vascular Disorders	17 (9.2)	27 (15.4)	27 (14.7)
Lymphocele	2 (1.1)	5 (2.9)	10 (5.4)

Source: Adapted from Table 8.3 from 3 Year Clinical Study Report for IM103027

7.3.3 Dropouts and/or Discontinuations

The proportions of subjects with AEs leading to study drug discontinuation up to Month 36 in IM103008 were 7.3%,in the belatacept MI, 7.1% in the belatacept LI, and 14% in the CsA groups and in IM103027 were 19% in the belatacept MI, 21% in the belatacept LI, and 24% in the CsA groups (see Table 22 and Table 23).
As previously discussed, numerically more patients receiving belatacept rather than CsA discontinued treatment in the Phase 3 trials due to efficacy failure (primarily AR).

Given that efficacy failures received separate consideration already, such events were not included in the analysis of adverse events leading to treatment discontinuation. In contrast, numerically more patients receiving CsA than belatacept discontinued treatment in those trials due to adverse events. An inspection of the reported MedDRA Preferred Terms associated with the responsible adverse events suggested that most classes of events were similar among treatment groups. In each study, however, more CsA patients discontinued due to hirsutism and therapeutic agent toxicity. In IM103027 only, more belatacept patients discontinued due to renal vein thrombosis.

Table 22: Adverse Events Leading to Treatment Discontinuation in ≥2% of Patients Up to Month 36 in IM103008*

System Organ Class Preferred Term	Belatacept MI N=219 n (%)	Belatacept LI N=226 n (%)	CsA N=221 n (%)
Total Number of Patients with AE Leading to Treatment Discontinuation	16 (7.3)	16 (7.1)	31 (14.0)
Infections and Infestations	7 (3.2)	6 (2.7)	3 (1.4)
Renal and Urinary Disorders	2 (0.9)	4 (1.8)	5 (2.3)
Injury, Poisoning and Procedural Complications	1 (0.5)	3 (1.3)	12 (5.4)
Therapeutic agent toxicity	0	0	5 (2.3)

Source: Adapted from Table S.6.1.8 from IM103008 3 Year Clinical Study Report
*Rows do not add up to totals because events with incidence rate below 2% not included

Table 23: Adverse Events Leading to Treatment Discontinuation in ≥2% of Patients Up to Month 36 in IM103027*

System Organ Class Preferred Term	Belatacept MI N=184 n (%)	Belatacept LI N=175 n (%)	CsA N=184 n (%)
Total Number of Patients with AE Leading to Treatment Discontinuation	34 (18.5)	36 (20.6)	44 (23.9)
Infections and Infestations	9 (4.0)	14 (8.0)	5 (2.7)
Cytomegalovirus infection	3 (1.6)	4 (2.3)	0
Injury, Poisioning and Procedural Complications	8 (4.2)	12 (6.9)	11 (6.0)
Graft loss	4 (2.2)	3 (1.7)	3 (1.6)
Complications of tx kidney	0	5 (2.9)	0
Neoplasms Benign, Malignant, and Unspecified	8 (4.3)	5 (2.9)	3 (1.6)
Renal and Urinary Disorders	8 (4.3)	2 (1.1)	10 (5.4)
Renal Vein Thrombosis	5 (2.7)	2 (1.1)	0
Gastrointestinal Disorders	0	1 (0.6)	9 (4.9)
Skin and Subcutaneous Tissue Disorders	0	0	4 (2.2)
Hirsutism	0	0	4 (2.2)

Source: Adapted from Table S.6.1.8 from IM103027 3 Year Clinical Study Report
*Rows do not add up to totals because events with incidence rate below 2% not included

7.3.4 Significant Adverse Events

Biopsy Proven Acute Rejection

For a complete discussion regarding BPAR rates observed in the belatacept development program and the clinical importance of BPAR in the context of kidney transplantation, please refer to the Clinical Review of the original BLA submission. This section focuses on the impact of BPAR on the 36 month data with regards to the overall safety of belatacept in IM103008 and IM103027.

As discussed in Section 6, BPAR occurred more frequently among recipients of the belatacept regimens than among recipients of the CsA regimen in IM103008: while the belatacept LI regimen met a 20% NI margin for the BPAR-based efficacy endpoint in the Clinical Review of the original BLA submission and while inspection of the 36 month BPAR data were also consistent with a conclusion that the belatacept LI regimen has some efficacy for preventing acute rejection, the comparative rates of BPAR in IM103008 suggest that belatacept regimens studied may be inferior to CsA regimen studied for the prevention of acute rejection. The analyses of the incidence rates of BPAR in IM103027 also supported conclusions that belatacept had efficacy for preventing acute rejection. In that trial, the efficacy of the belatacept regimens appeared more comparable to that of the CsA regimen.

Not all observable BPAR events experienced by kidney transplant recipients are clinically equivalent – some rejection episodes are easily resolved with a short course of corticosteroids with minimal residual damage, while others require intensive salvage treatments to rescue even minimal kidney function. The severity of a given BPAR event may be reflected in the histopathology of the BPAR lesion, the intervention required for the treatment of the episode, the impact of the event on GFR, and the impact on long-term graft survival.

As previously discussed in the Clinical Review of the original BLA submission, the data from IM103008 suggest that belatacept-treated patients not only experienced BPAR more often than CsA-treated patients, but that the BPAR events they experienced were more severe. In IM103008, belatacept-treated patients who experienced BPAR were more likely to have histopathology findings of Grade IIA or greater severity (see Table 24), to require lymphocyte depleting agents (primarily thymoglobulin) to treat the BPAR event (see Table 25), to not return to baseline GFR after treatment (see Table 26), and to died and/or lost the kidney allograft (see Table 27) than CsA-treated patients who experience BPAR. In IM103027, the severity of the BPAR events appeared more similar across treatment groups (see Table 24, Table 25, Table 26, and Table 27).

Table 24: Histopathology for All BPAR Events Occurring Through Month 36*

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

*Only the episode with the highest Banff grade for each patient is counted
Source: Created by the Statistical Reviewer using the applicant's datasets, BLA 125,288

Table 25: Lymphocyte Depleting Therapy For Treatment of AR Through Month 36

	IM103008			IM103027		
	Belatacept MI (n=219)	**Belatacept LI (n=226)**	**CsA (n=221)**	**Belatacept MI (n=184)**	**Belatacept LI (n=175)**	**CsA (n=184)**
Initial Treatment of AR	13 (5.9)	10 (4.4)	4 (1.8)	14 (7.6)	7 (4.0)	4 (2.2)
Steroid Resistant AR	15 (6.8)	12 (5.3)	1 (0.5)	2 (1.1)	1 (0.6)	2 (1.1)
Total	**28 (12.8)**	**22 (9.7)**	**5 (2.3)**	**16 (8.7)**	**8 (4.6)**	**6 (3.3)**

Source: Created by the Statistical Reviewer using the applicant's datasets, BLA 125,288

Table 26: GFR at Month 36 in IM103008 and IM103027 According to BPAR Status*

Study	Biopsy Proven Acute Rejection Status by Month 12		Belatacept MI	Belatacept LI	CsA
008	BPAR	Mean (sd) at Month 36	56.2 (32.2)	46.2 (31.6)	40.1 (23.4)
		95% CI	(46.5, 65.8)	(36.0, 56.3)	(46.5, 65.8)
		# in analysis	45	40	21
	No BPAR	Mean (sd) at Month 36	68.1 (23.6)	71.0 (23.1)	45.0 (23.6)
		95% CI	(64.2, 72.0)	(67.3, 74.8)	(41.2, 48.8)
		# in analysis	141	150	150
027	BPAR	Mean (sd) at Month 36	36.3 (28.4)	30.2 (22.5)	21.6 (21.8)
		95% CI	(24.6, 48.0)	(22.2, 38.2)	(14.0 29.3)
		# in analysis	25	33	34
	No BPAR	Mean (sd) at Month 36	43.9 (27.4)	45.5 (25.0)	34.5 (21.4)
		95% CI	(39.1, 48.7)	(41.0, 50.0	(30.5, 38.6)
		# in analysis	127	121	109

*Missing GFR at 36 months imputed as 0 if graft loss or death within first 36 months

Source: Created by the Statistical Reviewer using the applicant's datasets, BLA 125,288

Table 27: Patient and Graft Survival in IM103008 and IM103027 at Month 36 According to BPAR Status

Study	BPAR Status by Month 36		Belatacept MI	Belatacept LI	CsA
008	BPAR	Death	5/51	6/50	2/31
		Death w/ functioning graft	3/51	6/50	1/31
		Graft Loss	5/51	5/50	2/31
		Death and/or Graft Loss	8/51	11/50	3/31
	No BPAR	Death	4/160	4/176	13/190
		Death w/ functioning graft	4/160	3/176	13/190
		Graft Loss	5/160	4/176	8/190
		Death and/or Graft Loss	9/160	7/176	21/190
027	BPAR	Death	3/41	6/42	8/42
		Death w/ functioning graft	3/41	3/42	5/42
		Graft Loss	4/41	7/42	8/42
		Death and/or Graft Loss	7/41	10/42	13/42
	No BPAR	Death	19/143	9/133	9/142
		Death w/ functioning graft	15/143	7/133	8/142
		Graft Loss	14/143	14/133	15/142
		Death and/or Graft Loss	29/143	21/133	23/142

Source: Statistical Review of BLA 125,288 resubmission

As seen most clearly in the data presented in Table 27, the impact of the differences in BPAR events in IM103008 which occurred during the first six months of the trials across treatment groups may manifest in the safety outcomes of patients at later time points. Insufficient data exist to determine whether the outcomes of those patients with and without a history of BPAR will continue to diverge. However, with regards to the occurrence of events of BPAR itself, the 36 month data suggest that any differences across treatment groups stabilized after Month 24: very few new BPAR events occurred after Month 24 in either IM103008 or IM103027 (see Table 28).

Table 28: BPAR Events Occurring Between Month 24 and Month 36

Study		Belatacept MI	Belatacept LI	CsA
008	BPAR, N (%)	0	0	1 (0.5)
	Mild Acute (IA), N (%)	0	0	1 (0.5)
	Mild Acute (IB), N (%)	0	0	0
	Moderate Acute (IIA), N (%)	0	0	0
	Moderate Acute (IIB), N (%)	0	0	0
	Severe Acute (III), N (%)	0	0	0
027	BPAR, N (%)	1 (0.5)*	1 (0.6)	2 (1.1)
	Mild Acute (IA), N (%)	0	0	0
	Mild Acute (IB), N (%)	0	0	1 (0.5)
	Moderate Acute (IIA), N (%)	0	1 (0.6)	1 (0.5)
	Moderate Acute (IIB), N (%)	0	0	0
	Severe Acute (III), N (%)	1 (0.5)*	0	0

*This event occurred in a patient who had previously experienced a lower grade event
Source: Created by the Clinical Reviewer from the applicant's datasets, BLA 125,288

Reviewer comment 1: A significant limitation of this review of the 36 month data from IM103008 and IM103027 is the inability to predict the long-term outcomes of the surviving patients with functional grafts who also have a history of BPAR. The data suggest that belatacept-treated patients in IM103008 with a history of BPAR were at elevated risk of death and/or graft loss compared to the CsA-treated patients from that trial with history of BPAR at 36 months. However, the data also indicated that numerically fewer patients treated with belatacept compared to CsA experienced death and/or graft loss at 36 months. An overall long-term risk-benefit assessment of belatacept versus CsA strongly depends on whether the impact of the early BPAR events in IM103008 will continue to manifest or whether they have already had their full effect.

Reviewer comment 2: The analysis of the impact of BPAR on GFR in Table 26 relied on calculated GFRs at Month 36; in cases of missing data at Month 12, the analyses relied on an imputed GFR based on the last observed calculated GFR prior to Month 12 (last observation carried forward) unless the patient had a graft loss or died before Month 36 and then a value of 0 was imputed. Data from these same trials presented at the American Transplant Congress (ATC) in 2009 and published in the American Journal of Transplantation (AJT) suggested that differences in mean GFR at Month 12 between patients who experienced did and did not experience AR were minimal across all treatment groups.[2,3] Those analyses, however, relied on measured GFR observed at Month 12 and censored those patients with missing data at that time point. For example, data were only captured for 25 of the 39 patients with AR in the belatacept LI group in IM103008; as a result, those other analyses presented a mean measured GFR of belatacept MI patients who experienced AR of 61 mL/min compared with the mean calculated GFR of 48 mL/min determined in the analysis above. The conclusion presented at ATC and published in the AJT – that the rejection episodes observed in the belatacept trials did not have a clinically significant impact on GFR – were potentially misleading.

Reviewer comment 3: The reason(s) for the differences seen in the safety signals associated with acute rejection across the two Phase 3 trials are not entirely self-evident. Chance cannot be excluded as a possible explanation. An alternative explanation is based on the differences in recipient and donor demographics: the younger and healthier patients in IM103008 may have been more capable of mounting an effective immune response than the older patients in IM103027 (and therefore were

[2] Vincenti F, Grinyo JM, Charpentier B, et al. Primary Outcomes from a Randomized, Phase III Study of Belatacept vs CsA in Kidney Transplant Recipients (BENEFIT Study). American Transplant Congress, Boston, MA, Plenary Session I, May 31, 2009.
[3] Vincenti F, Charpentier B, Vanrenterghem L, et al. A Phase III Study of Belatacept-based Immunosuppression Regimens versus CsA in Renal Transplant Recipients (BENEFIT Study), American Journal of Transplantation 2010; 10(3): 535-46.

more capable of demonstrating the difference between the regimens) and/or the lower quality kidneys in IM103027 may have been more likely to induce rejection regardless of the immunosuppression regimen (and therefore more likely to mask the difference between the regimens).

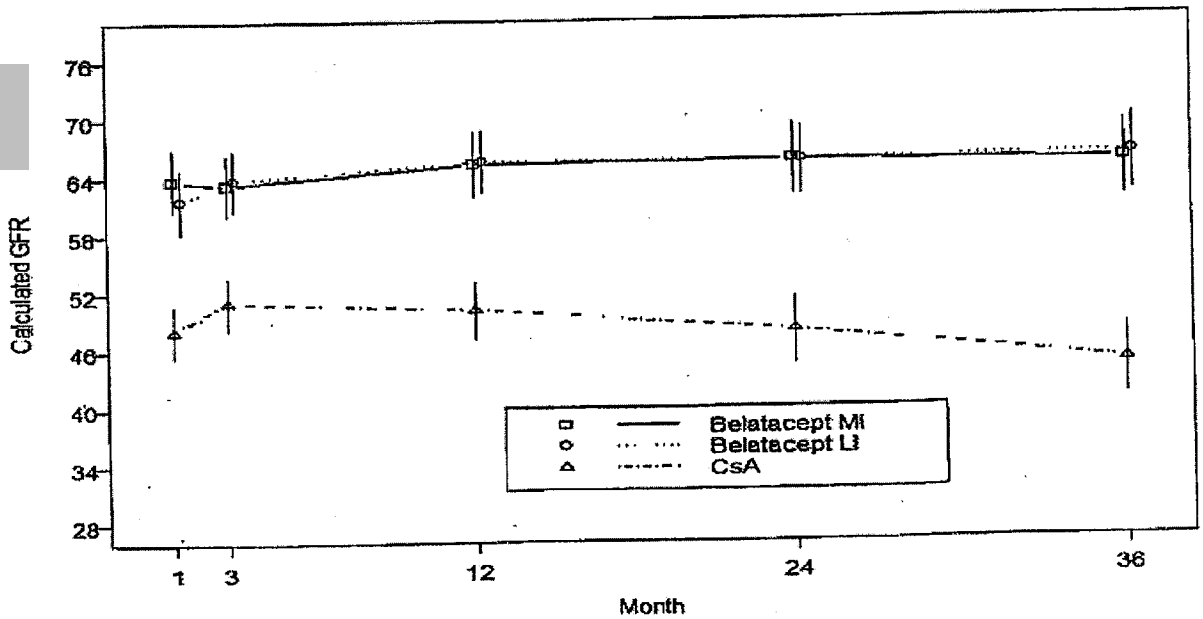
Glomerular Filtration Rate

For a complete discussion regarding GFR as observed in the belatacept development program and the clinical importance of GFR in the context of kidney transplantation, please refer to the Clinical Review of the original BLA submission. This section focuses on the evaluation of GFR in the 36 month data with regards to the overall safety of belatacept in IM103008 and IM103027.

Mean calculated GFRs were substantially higher throughout the 36 months of IM103008 and IM103027 among the belatacept treatment groups compared to the CsA treatment groups (see Figure 2, Figure 3, and Table 29). 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.

Figure 2: Mean Calculated GFR (mL/min) through Month 36 in IM103008

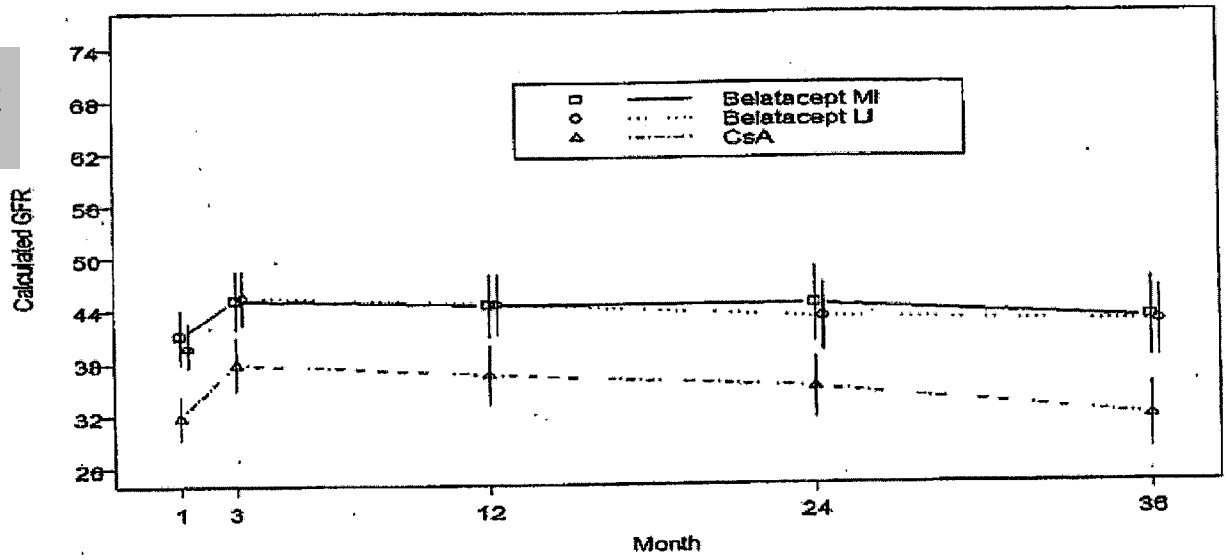
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Error bars represent 95% confidence interval of the mean
Source: Figure 1, Statistical Safety Review, BLA 125,288 resubmission

BEST POSSIBLE COPY

Figure 3: Mean Calculated GFR (mL/min) through Month 36 in IM103027



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

Table 29: Mean (standard deviation) Calculated GFR in IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
IM103008	Month 1	63.6 (23.3) n=214	61.5 (24.5) n=220	48.1 (18.9) n=214
	Month 3	63.1 (22.4) n=207	63.6 (22.9) n=211	51.0 (19.0) n=201
	Month 12	65.2 (23.5) n=201	65.4 (22.9) n=200	50.1 (21.1) n=199
	Month 24	65.5 (24.9) n=191	65.4 (25.2) n=201	47.9 (23.0) n=182
	Month 36	65.2 (26.3) n=186	65.8 (27.0) n=190	44.4 (23.6) n=171
IM103027	Month 1	41.0 (21.0) n=182	39.6 (173) n=173	31.8 (16.1) n=184
	Month 3	45.1 (21.7) n=177	45.3 (19.3) n=168	37.8 (19.2) n=172
	Month 12	44.3 (22.8) n=165	44.5 (21.8) n=158	36.5 (21.1) n=159
	Month 24	44.4 (26.7) n=152	42.8 (24.1) n=158	34.9 (21.6) n=154
	Month 36	42.7 (27.6) n=152	42.2 (25.2) n=154	31.5 (22.1) n=143

Source: Created by the Statistical Reviewer from the applicant's datasets, BLA 125,288

While a difference in measured GFRs in favor of patients in both belatacept groups relative to the CsA control group is clearly evident in both Phase 3 trials, any differences that exist between the groups with respect to their change in GFR over time are more subtle. A pre-specified calculation for slope of GFR at Month 36 based on a Month 3

starting time numerically favors the belatacept groups (see Table 30); the slopes of the belatacept groups are statistically different than that of the CsA group in IM103008.

Table 30: Slope for Calculated GFR from Month 3 to 36 in 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 m^2/year
Source: Created by the Statistical Reviewer from the applicant's datasets, BLA 125,288

Reviewer comment 1: A significant limitation of this review of the 36 month data from IM103008 and IM103027 is the inability to predict the long-term outcomes of the surviving patients with functional grafts. The data suggest that belatacept-treated patients in IM103008 are maintaining GFR better than the CsA-treated patients from that trial at 36 months, perhaps due to the avoidance of chronic nephrotoxicities. The data also indicated that numerically fewer patients treated with belatacept compared to CsA experienced death and/or graft loss at 36 months in IM103008. An overall long-term risk-benefit assessment of belatacept versus CsA strongly depends on whether the impact of avoiding the nephrotoxicity associated with CsA will translate to fewer graft losses over time.

Reviewer comment 2: The reason(s) for the differences seen in the safety signals associated with GFR across the two Phase 3 trials are not entirely self-evident. Chance cannot be excluded as a possible explanation. An alternative explanation is based on the differences in recipient and donor demographics: the allografts in IM103008 were both higher quality and placed in healthier recipients than the allografts in IM103027, perhaps suggesting that they had the highest likelihood of benefitting from a regimen that avoided direct nephrotoxicities.

Cardiovascular Risk Factors

For a complete discussion regarding cardiovascular risk factors observed in the belatacept development program and the clinical importance of cardiovascular risk factors in the context of kidney transplantation, please refer to the Clinical Review of the original BLA submission. This section focuses on the evaluation of several cardiovascular risk factors prespecified by the applicant at the 36 month time point with regards to the overall safety of belatacept in IM103008 and IM103027.

Hypertension

Mean systolic and diastolic blood pressures were significantly lower at Month 36 for patients in both belatacept groups relative to the CsA control group in both Phase 3 trials (see Table 31). These results at Month 36 are consistent with those reported at Month 12.

Table 31: Mean Blood Pressure at Month 36 in IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	Systolic Blood Pressure	126.0 (16.1)* n=166	127.7 (16.5)* n=180	133.5 (17.9) n=145
	Diastolic Blood Pressure	76.1 (11.2)* n=166	76.6 (9.7)* n=180	79.5 (9.2) n=145
027	Systolic Blood Pressure	134.9 (19.5) n=112	134.7 (21.6) n=119	140.7 (21.2) n=108
	Diastolic Blood Pressure	75.4 (11.6) n=112	75.2 (10.8) n=119	77.2 (11.8) n=108

Mean (standard deviation)
Number in analysis
*comparison of mean value of belatacept regimen to CsA p-value<0.027
Source: Created by the Statistical Reviewer from the applicant's datasets, BLA 125,288

The benefits of blood pressure control are well-established in the general population but have been shown to be particularly important in the renal transplant population. For instance, a retrospective analysis of the Collaborative Transplant Study registry data showed that renal transplant recipients with a systolic blood pressure at 1 year less than 140 mmHg had significantly reduced rates of graft loss and cardiovascular death compared with those with a systolic blood pressure at 1 year greater than 140 mmHg.[4] While it is difficult to quantify the clinical benefit in a renal transplant patient population of the differences in systolic and diastolic blood pressures observed, it is reasonable to infer that some benefit should accrue for differences of the magnitude measured in the trial.

New Onset Diabetes After Transplantation (NODAT)

As reported in the Clinical Review of the original BLA submission, a pre-specified pooled analysis across the two Phase 3 kidney transplant trials showed that the incidence of NODAT at Month 12 was lower for the belatacept MI group (4.8%) and the belatacept LI group (4.6%) than the CsA control group (9.6%). At the Month 36 time point, however, that pooled analysis shows similar rates of NODAT across all three treatment arms (see Table 32). Although a significant difference in rates of NODAT is no longer detectable, the rates of NODAT among the belatacept-treated patients remain remarkably low.

[4] Opelz G, Dohler B. Improved long-term outcomes after renal transplantation associated with blood pressure control. Am J Transplant 2005; 5: 2725-2731.

Table 32: Incidence of New Onset Diabetes After Transplantation at Month 36

Study	Belatacept MI	Belatacept LI	CsA
008	16/156 (10.3)	11/168 (6.5)	18/162 (11.1)
027	7/132 (5.3)	13/136 (9.6)	11/118 (9.3)
Pooled	23/288 (8.0)	24/304 (7.9)	29/280 (10.3)

Denominator is number of subjects with out diabetes at transplant
Source: Created by the Statistical Reviewer from the applicant's datasets, BLA 125,288

Reviewer comment: The prevalence of NODAT in the general US transplant population has been estimated at 15-20%, somewhat higher than observed in the context of the belatacept Phase 3 trials.[5,6,7] It is unclear whether the low incidence of NODAT across the treatment groups reflected the demographics of the patients studied or the use of a CsA, rather than tacrolimus, control arm. As the incidence of cardiovascular death has been estimated to be 3-fold higher among transplant patients with diabetes compared to transplant patients without diabetes,[8] the low rates of NODAT observed in the context of belatacept would be clinically significant if reproducible in the general US population.

Dyslipidemia

As reported in the Clinical Review of the original BLA submission, the mean triglyceride (but not the mean LDL or mean HDL) levels at Month 12 were significantly lower in patients in both belatacept groups relative to the CsA control group in both Phase 3 trials. At Month 36, the mean LDL and mean triglyceride (but not the mean HDL) levels were significantly lower in both belatacept groups relative to the CsA control group in IM103008; mean lipid levels at Month 36 were statistically similar across treatment groups in IM103027 – although numerically large differences in mean triglyceride levels persisted between the belatacept and CsA groups, data from too few patients were captured to make the observation statistically significant (see Table 33). While the data regarding LDL at 36 months in IM103008 suggests the possibility of a new benefit of belatacept not detected at the 12 month time point, caution must be exercised in evaluating these data: while meeting criteria for statistical significance, a large number of patients are missing data at this time point (which introduces the potential for bias into the analysis).

[5] Bodziak KA, Hricik DE. New-onset diabetes mellitus after solid organ transplantation. Transplant Int 2009; 22: 519-30.
[6] Woodward RS, Schnitzler MA, Baty J, et al. Incidence and cost of new onset diabetes mellitus among US wait-listed and transplanted renal allograft recipients. Am J Transplant 2003; 3: 590-8.
[7] Moore R, Ravindran V, Baboolal K. The burden of new-onset diabetes mellitus after transplantation. Clin Transplant 2006; 20: 755-61.
[8] Lindholm A, Albrechtsen D, Frodin L, et al. Ischemic heart disease – major cause of death and graft loss after renal transplantation in Scandinavia. Transplantation 1995; 60: 451.

Table 33: Serum Lipids at Month 36 in IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	Total cholesterol	170.7 (43.3)* n=176	171.3 (45.8)* n=184	190.7 (45.3) n=154
	HDL cholesterol	48.6 (16.9) n=176	48.9 (15.4) n=184	48.5 (14.3) n=154
	LDL cholesterol	92.5 (33.8) * n=161	96.7 (36.5) * n=170	107.6 (37.7) n=142
	Triglycerides	144.0 (81.5)* n=161	132.7 (68.7)* n=170	179.1 (97.1) n=142
027	Total cholesterol	180.3 (43.4) n=118	183.6 (48.9) n=124	195.9 (122.1) n=110
	HDL cholesterol	48.5 (14.8) n=118	49.6 (15.9) n=124	46.8 (14.0) n=109
	LDL cholesterol	102.9 (31.7) n=99	104.6 (38.1) n=104	103.7(47.0) n=100
	Triglycerides	160.1 (92.9) n=99	155.5 (84.9) n=105	180.0 (101.9) n=101

Mean (standard deviation)
Number in analysis
*comparison of mean value of belatacept regimen to CsA p-value<0.027
Source: Created by the Statistical Reviewer from the applicant's datasets, BLA 125,288

Lipid panels in ESRD patients awaiting transplantation are poorly understood: while elevated LDL and total cholesterol levels are associated with cardiovascular disease in the general population, the relationship of LDL cholesterol and cardiovascular death is less clear in the dialysis population.[9,10] Low LDL levels in patients on dialysis are common, but the significance of such LDL levels in that population is not entirely clear: generalized inflammation and poor nutrition may drive down LDL levels. Serum LDL and triglycerides typically increase after transplantation, reflecting both physiologic changes after transplantation but also adverse effects of immunosuppressive drugs.[11] Treatment of dyslipidemias in the general CKD and ESRD population remain controversial. After renal transplantation, however, management of lipids appears to improve cardiovascular outcomes.[12,13] In the context of the controversies regarding interpretation of lipid panels in these populations, it is difficult to quantify a clinical benefit but the differences in effects on triglycerides appeared favorable to belatacept.

[9] Cheung AL. Is lipid control necessary in hemodialysis patients? Clin J Am Soc Nephrol 2009; S1: S95-101.
[10] Kanbay M, Turgut F, Covic A, et al. Statin treatment for dyslipidemia in chronic kidney disease and renal transplantation: a review of the evidence. J Nephrol 2009; 22(5): 598-609.
[11] Moore R, Hernandez D, Valantine H. Calcineurin inhibitors and post-transplant hyperlipidaemias. Drug Saf 2001; 24 (10): 755-66.
[12] Holdaas H, Fellström B, Jardine AG, et al. Assessment of Lescol in Renal Transplantation (ALERT) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomized, placebo-controlled trial. Lancet. 2003; 361: 2024-31
[13] Cosio FG, Pesavento TE, Kim S, et al. Patient survival after renal transplantation: Part IV: impact of post-transplant diabetes. Kidney Int 2002; 62: 1440-6.

Infections

Overall rates of infections at 36 months appeared similar across treatment arms of the three clinical trials in an analysis of reported adverse events (see Table 34). An imbalance, however, existed with regards to herpes infections: belatacept patients had reported significantly more episodes of herpes infections at 36 months.

Table 34: 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: Adapted from Tables S.6.1.3, 8.5, S.6.5.2A, 8.6.2.1.C, 8.6.2.1.E, 8.6.2.1G and 8.6.2.2.B in the 36 Month CSRs for IM103008 and IM103027

CNS Infections

The high incidence of CNS PTLD and the single case of PML observed in the clinical trials prompted a review of all CNS infections observed in these trials in order to elucidate possible interactions between belatacept and CNS immunity. Similar rates of CNS infections were seen among the belatacept LI patients and the CsA patients (one each. Among the belatacept MI patients, however, six CNS infections were observed across the Phase 3 trials through 36 months of follow up (see Table 35). No new CNS infections were reported in the BLA resubmission. However, an additional event of CNS infection was reported among the belatacept MI patients in IM103027 in the fifth year of follow-up: a 63 year old woman transplanted in February 2006 died in October 2010 in the setting of fever, delirium, LP fluid consistent with meningitis, and CSF PCR positive for BK, CMV, and EBV.

Table 35: Cases of CNS Infections in IM103008 and IM103027 through 36 Months

Study	Belatacept MI	Belatacept LI	CsA
IM103008	Cryptococcal Meningitis Cryptococcal Meningitis/ Chagas Encephalitis West Nile Virus (Death) Cryptococcal Meningitis	--	Cryptococcal Meningitis
IM103027	Cerebral Aspergillosis (Death) PML (Death)	Cryptococcal Meningitis (Death)	--

Source: Patient Narratives for IM103008 and IM103027

Reviewer comment: Through Month 36 in the Phase 3 kidney transplant trials, there were 3 deaths due to CNS infections among recipients of the belatacept MI regimen, 1 death due to CNS infection among recipients of the belatacept LI regimen, and no deaths due to CNS infection among recipients of the CsA regimen. Since Month 36, there has been one additional death reported in a recipient of the belatacept MI regimen. Along with the signals related to CNS PTLD, the pattern suggests that belatacept may have a different impact on CNS immunity than CsA.

Tuberculosis

An imbalance in cases of tuberculosis was observed across treatment arms in the Phase 3 trials through the Month 36 time point (see Table 36). The imbalance had been previously noted, but was even more pronounced at the 36 month time point. 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.

Most of the cases of tuberculosis reported in the Phase 3 trials through 36 months involved extra-pulmonary sites: among the belatacept patients, tuberculosis presented as disseminated disease twice, laryngeal tuberculosis once, tuberculosis synovitis once, in a cervical ganglion once, in the retina once,as gastrointestinal tuberculosis twice, and as abdominal tuberculosis once. The lone case of tuberculosis among the CsA patients presented within the intra-thoracic lymph nodes. The vast majority of the patients lived in locations where tuberculosis is endemic (among the belatacept-treated patients who

developed tuberculosis, five were from India, four were from Brazil, and three were from France; the CsA-treated patient who developed tuberculosis was from India).

Table 36: 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 involvment	3	1	1	1	4	0
Death at time of database lock	1	2	0	0	1	0

Source: Patient Narratives for IM103008 and IM103027

7.3.5 Submission Specific Primary Safety Concerns

Proteinuria

As discussed in the Clinical Review of the original BLA submission, proteinuria was identified as an adverse event more frequently observed among patients receiving belatacept than CsA. The development of proteinuria is an especially important clinical event in kidney transplant recipients where its presence correlates strongly with decreased graft life. Unfortunately, however, the Phase 3 trials were poorly designed to capture data regarding proteinuria. Rather than measuring urine protein to creatinine (UP/C) ratios, proteinuria was assessed by urine dipstick assessments. According to the protocol, proteinuria was defined as 2+ on dipstick assessment on 2 consecutive visits. The imbalance in the presence of proteinuria, as defined in the protocols, persisted at 36 months (see Table 37).

Table 37: Incidence of Proteinuria Through Month 36 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)
At 12 Months	6%	4%	4%	11%	10%	7%
At 24 Months	10%	7%	5%	13%	14%	10%
At 36 Months	11%	10%	8%	14%	15%	12%

Source: Table S.7.3 in 008 and 027 Month 12 CSRs, Table S.6.10B in 008 and 027 Month 12 CSR, Table S.7.2.1 in 008 and 027 Month 36 CSRs

Like GFR, proteinuria is affected by renal hemodynamics: in the presence of CsA, proteinuria should be reduced. Insufficient data exist to conclude whether the differences in proteinuria across the treatment arms in the Phase 3 trials derive from that physiologic effect or from structural differences at the level of the glomerulus. While relatively few patients on either CsA or belatacept met the protocol definition of proteinuria, insufficient data exists to determine how many patients exhibited a clinically significant degree of proteinuria.

Immunogenicity

As discussed in the Clinical Review of the original BLA submission, a minority of patients in IM103008 and IM103027 developed anti-belatacept antibodies. The Phase 3 trial data from the original BLA submission indicated that a total of 32 out of 796 patients (4%) with a history of exposure to belatacept developed anti-belatacept antibodies by the time of the database lock for the original BLA submission. The BLA resubmission did include some new immunogenicity data from the time of the database lock of the BLA resubmission. By that time, an additional 6 patients had developed anti-belatacept antibodies (total of 4.8%). A theoretical concern exists that antibodies directed against belatacept could interfere with its immunosuppressive effects. Overall rates of acute rejection, however, were roughly similar among patients who did and did not develop anti-belatacept antibodies.

Reviewer comment 1: In addition to identifying patients who developed anti-belatacept antibodies after transplantation, the electro-chemiluminescence (ECL) assay was also reported positive in some patients at time of transplantation. It is unclear whether these positive results are false positive or whether they indicate the presence of endogenous antibodies directed against belatacept. Overall rates of rejection were also roughly similar among patients who did and did not have positive results in the ECL assay at baseline.

Autoimmunity

In addition, a theoretical concern exists that anti-belatacept antibodies could cross react with T cell receptors with homology to CTLA-4 As discussed in the Clinical Review of the original BLA submission and in the paragraphs above, a concern exists that belatacept could potentially cause autoimmune events: while there was no evidence of autoimmunity in toxicology studies with belatacept in monkeys, nonclinical studies of a related product, abatacept, showed evidence of inflammation and autoimmunity in rats (one of three animal species tested). Through 24 months, however, adverse events related to autoimmune disease were both rare and evenly distributed across the treatment groups in the belatacept kidney trials. Please refer to the Clinical Review of the original BLA submission for details.

Between Month 24 and Month 36, very few adverse events related to autoimmunity were reported in IM103008 and IM103027. In IM103008, one patient in the belatacept MI arm presented with demyelination, one patient in the CsA arm presented with hyperthyroidism, and one patient in the CsA arm presented with psoriasis. In IM103027, one patient in the belatacept MI arm and one patient in the CsA arm presented with angioedema. Cumulatively, autoimmune events were reported in 1 (<1%), 3 (1%), and 6 (3%) of patients in the belatacept LI, belatacept MI, and CsA groups respectively in IM103008 and in 6 (3%), 5 (3%), and 3 (2%) of patients in the belatacept MI, LI, and CsA groups respectively in IM103027.

Donor Specific Antibodies

The development of donor specific antibodies (DSA) after transplantation is strongly correlated with shortened graft life. The applicant submitted analyses of the 36 month data suggesting that the production of anti-donor HLA antibodies was less frequent among the belatacept arms than the CsA arms of IM103008 and IM103027 (see Table 38). The applicant presented these data as a subgroup analysis of patients with and without a history of acute rejection. However, the 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. For that reason, Table 38 presents the DSA data without regard to history of acute rejection. Nonetheless, it is a reasonable expectation that regimens that have a greater effect on limiting the development of DSAs may derive a clinical benefit from that effect.

Table 38: Development of *de novo* Anti-Donor HLA antibodies in IM1030008 and IM103027 through Month 36

	IM103008			**IM103027**		
	Belatacept MI	**Belatacept LI**	**CsA**	**Belatacept MI**	**Belatacept LI**	**CsA**
At 12 Months	6/213 (2.8%)	4/224 (1.8%)	14/210 (6.7%)	9/179 (5.0%)	7/170 (4.1%)	15/173 (8.6%)
At 24 Months	8/216 (3.7%)	8/224 (3.5%)	16/212 (7.5%)	9/179 (5.0%)	9/171 (5.3%)	21/175 (12%)
At 36 Months	14/217 (6.5%)	12/224 (5.4%)	24/212 (11%)	13/179 (7.3%)	11/171 (6.4%)	26/175 (15%)

Source: Adapted from Tables 10.1 in the IM103008 and IM103027 3 Year Clinical Study Reports

Reviewer comment: The late development of de novo DSAs has often been ascribed to medical noncompliance. It remains to be seen whether any difference between belatacept and CsA with regards to preventing the development of DSAs is intrinsic to the mechanisms of action of the two drugs or attributable to a difference in adherence in these trials comparing an intravenously infused biologic and an orally administered drug. In addition, the microbiology/immunology team has not yet completed a full review of these data at the time of this writing (see the microbiology/immunology review of the

BLA resubmission). However, these data may ultimately suffice to support a labeling supplement should the final review indicate that sufficient evidence exist to suggest a true difference in the incidence of de novo DSAs between belatacept and CsA..

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Other than the specific issues addressed above, the adverse event profile of the belatacept regimen and the CsA regimen were similar as observed by the AEs reported through Month 36 in IM103008 and IM103027. That observation is perhaps somewhat surprising as one might have anticipated more of an imbalance reflecting known class effects of CsA and mycophenolic acid (MPA). Known adverse events associated with CsA include hyperkalemia, hypertension, dyslipidemias, hyperglycemia, and tremor. One would expect the control arm to have experienced more of those adverse events. Known adverse events associated with MPA include GI toxicities (diarrhea, nausea, abdominal pain, vomiting) and bone marrow suppression (anemia and leucopenia). While the observed dosages of MMF were similar across the belatacept groups and the CsA groups, a 25 to 40% greater MPA exposure was achieved among the belatacept groups (due to the impact of CsA on the enterohepatic recirculation of MPA; see Clinical Pharmacology Review of original BLA submission) – suggesting that the belatacept arms might have been expected to have experienced more adverse events related to MPA. Therefore, in addition to carefully examining AEs associated with belatacept, particular attention was also therefore afforded to reporting of those AEs known to be associated with CsA and MPA. An analysis of these selected AEs, however, suggests that the true differences across groups were mild (see Table 39): CsA patients only appeared to experience dyslipidemia (but not hypercholesterolemia) and tremor more frequently.

Table 39: Selected Adverse Events Associated with Class Effects Presenting through Month 36, N (%)

	IM103008			IM103027		
SOC/PT	MI N=219	LI N=226	CsA N=221	MI N=184	LI N=175	CsA N=184
Metabolism and Nutritional Disorders	175 (79.9)	179 (79.2)	180 (81.4)	140 (76.1)	135 (77.1)	144 (78.3)
Hypokalemia	44 (20.1)	46 (20.4)	22 (10)	37 (20.1)	37 (21.1)	35 (19.0)
Hyperkalemia	16 (7.3)	38 (16.8)	39 (17.6)	42 (22.8)	43 (24.6)	41 (22.3)
Dyslipidemia	55 (25.6)	55 (24.3)	64 (29.0)	27 (14.7)	21 (12)	35 (19)
Hypercholesterolemia	32 (14.6)	26 (11.5)	23 (10.4)	18 (9.8)	18 (10.3)	22 (12)
Hyperglycemia	34 (15.5)	35 (15.5)	38 (17.2)	35 (19)	28 (16)	31 (16.8)
Infections and Infestations	175 (79.9)	185 (81.9)	176 (79.6)	146 (79.3)	144 (82.3)	151 (82.1)
Urinary tract infections	71 (32.4)	81 (35.8)	67 (30.3)	69 (37.5)	68 (38.9)	80 (43.5)
Gastrointestinal System Disorders	165 (75.3)	175 (77.4)	175 (79.2)	143 (77.7)	145 (82.9)	145 (78.8)
Constipation	64 (29.3)	73 (32.3)	64 (29.0)	57 (31)	59 (33.7)	77 (41.8)
Diarrhea	85 (38.8)	80 (35.4)	80 (36.2)	89 (48.4)	78 (44.6)	66 (35.9)
Nausea	55 (25.1)	56 (24.8)	65 (29.4)	49 (26.6)	40 (22.9)	46 (25)
Vomiting	37 (16.9)	45 (19.9)	44 (19.9)	32 (17.4)	44 (25.1)	38 (20.7)
Abdominal Pain	36 (16.4)	37 (16.4)	37 (16.7)	25 (13.6)	37 (21.1)	29 (15.8)
Blood and Lymphatic Systems Disorders	117 (53.4)	136 (60.2)	118 (53.4)	125 (67.9)	113 (64.6)	129 (70.1)
Anemia	77 (35.2)	88 (38.9)	76 (34.4)	94 (51.1)	91 (52.0)	101 (54.9)
Leucopenia	39 (17.8)	44 (19.5)	40 (18.1)	51 (27.7)	36 (20.6)	51 (27.7)
Nervous System Disorders	83 (37.9)	98 (43.4)	96 (43.4)	74 (40.2)	76 (43.4)	82 (44.6)
Headache	44 (20.1)	52 (23)	34 (15.4)	30 (16.3)	31 (17.7)	37 (20.1)
Tremor	12 (5.5)	15 (6.6)	42 (19)	16 (8.7)	17 (9.7)	27 (14.7)

Source: Adapted from Tables 8.5 in the 3 year Clinical Summary Reports for IM103008 and IM103027

7.4.2 Laboratory Findings

Routine clinical testing was described above in Section 7.2.4. On the basis of fasting blood glucoses, small differences in the incidence of NODAT that were observed between belatacept and CsA treatment groups in the clinical trials at Month 12 were diminished at Month 36 (see Section 7.3.4). On the basis of hemoglobin A1c, moreover, no differences were noted across treatment groups.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Other than the excess events of PTLD associated with belatacept, the incidence of malignancies appeared similar across treatment groups in IM103008 and IM103027 through Month 36. Despite the excess of PTLD events among the belatacept group, the number of patients with malignant neoplasms remained similar across all patient groups at Month 36 (8.2% of belatacept MI patients, 4.4% of belatacept LI patients, and 5.4% of CsA patients in IM103008; 8.7% of belatacept MI patients, 8.6% of belatacept LI patients, and 10.3% of CsA patients in IM103027).

7.6.2 Human Reproduction and Pregnancy Data

No data related to drug exposure in pregnant or lactating women were included in the BLA submission. The applicant has indicated that it intends to encourage participation in the National Transplant Pregnancy Registry (this is reflected in the proposed labeling).

7.6.3 Pediatrics and Assessment of Effects on Growth

Belatacept was granted Orphan Drug status. As such, the Pediatric Research Equity Act of 2003 (PREA) does not apply: the FDA has no authority to request pediatric data for such products. As the kidney transplantation trials excluded patients younger than 18 years of age, no relevant data exist.

8 Postmarket Experience

None

9 Appendices

9.1 Literature Review/References

References are incorporated in the body of the review as footnotes.

9.2 Labeling Recommendations

The BLA resubmission included new draft labeling. In the course of the review, the proposed labeling underwent multiple revisions, both by the primary review teams and also by the consult review teams (including SEALD and DDMAC).

The following summarizes major revisions recommended to the applicant as of March 19, 2011. At the time of this review, final recommendations from all disciplines have not been completed and final agreement with the applicant regarding the package insert has not been achieved.

Boxed Warning

- All immunosuppressives used in solid organ transplant have previously included a boxed warning regarding the risk of immunosuppression, stating that only physicians experienced in immunosuppressive therapy should prescribe the products. The PLR guidance, however, notes that the warnings should specify the clinical outcomes. For that reason, the "Malignancies and Serious Infections" has been recommended to replace (b) (4) in the title of the **Boxed Warning**, as those are the actual possible adverse consequences to the patient.
- The section was revised to add an additional item to the **Boxed Warning** that belatacept should not be used in liver transplant patients. Although not submitted as part of the BLA resubmission, summary data from IM103045 (a Phase 2 liver transplant trial) became available during the review of the BLA resubmission indicating that patients randomized to a belatacept regimen had higher rates of death and graft loss than patients randomized to a tacrolimus based regimen (BB-IND 9,418, SN 523). On the basis of this observation and a review of the data, the Data Monitoring Committee for Study IM103045 recommended stopping the trial and changing all patients on belatacept regimens to a standard of care. The applicant has indicated that it intends to submit the patient level data to FDA in the near future.

Indications and Usage

(b) (4)

(b) (4)

Limitations of Use

- The section has been revised to change the statement that (b) (4) (b) (4) to a statement that NULOJIX should be used only in patients who are EBV seropositive.

Dosage and Administration

- The section has been revised to start with the statement that "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. (b) (4)
- Table 1: Dosing of NULOJIX for Kidney Transplant Recipients has been modified to include more details about dosing times.
- (b) (4)

Warnings and Precautions

- Section **5.1 Post-Transplant Lymphoproliferative Disorder** was revised to such move the information regarding PTLD events in the liver transplant study to a new **Warnings and Precautions** section regarding liver transplant.
- Section **5.3 Other Malignancies** was revised to remove the phrase (b) (4) as this phrase was deemed to have a potential to minimize the impact of the overall statement.
- A revised section **5.5 Serious Infections** now includes: 1) a statement regard the role of prophylaxis against Pneumocystid jiroveci, 2) a section regarding polyoma virus nephropathy (section (b) (4) **Polyoma Virus** (b) (4) **nephropathy** in the proposed labeling) into this section as a subheading.
- Section **5.6 Liver Transplant** was added. The recommended section discusses 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 PTLD and the event of PML seen among those belatacept patients.

Adverse Reactions

- Extensive revisions to the organization of section **6.1 Clinical Studies Experience** were recommended by SEALD, including introducing all three core studies (IM103008, IM103027, and IM103100) earlier and providing more granular information regarding patient demographics and treatment discontinuation for IM103008 and IM103027 (b) (4)
- The revisions to section **6.1 Clinical Studies Experience** also included a statement that "CNS PTLD, 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 recommemended".
- It was recommended that the content of section (b) (4) should be moved to section **6.1 Clinical Studies Experience**, as all of the observations described derived from the clinical studies. This content was inserted into after the information regarding patient demographics and discontinuations, but before the information on common adverse reactions..
- Although SEALD recommended limiting the discussion of infections and adverse events to only those which were more common in the belatacept arms than the cyclosporine arms, I recommended including tables regarding the most common infections and adverse events observed in IM103008 and IM103027 for both the belatacept and CsA arms, including some events which were more common among recipients of CsA than belatacept. I believe it is important to report these data in the labeling because the data will not otherwise be available to transplant physicians. Providing data for only those events which were more common among recipients of belatacept than CsA does not provide a balanced view of the data or allow the physician to make well-informed decisions. A footnote accompanies both tables clarifying that the studies were not designed to support comparative claims for NULOJIX for the adverse reactions reported in this table.
- Although new onset diabetes, hypertension, and dyslipidemias were prespecified endpoints and should therefore be discussed in the **Clinical Studies** section according to the PLR guidance, SEALD recommended that the discussion remain in the **Adverse Reactions** section. As SEALD is the expert it this area, I defer to their judgment.
- The lists of less common adverse reactions were edited to remove items which were deemed non-specific and duplicative of the adverse events already described in this section.

Drug Interactions

- The clinical pharmacology review team recommended adding a section (**7.1 Cytochrome P450 substrates**) noting that belatacept could potentially indirectly affect the metabolism of substrates of cytochrome P450 enzymes through its effects on cytokines.

Clinical Pharmacology

- The proposed labeling in section **12.1 Mechanism of Action** includes statements that (b) (4)
- Final recommendations regarding section **12.2 Pharmacodynamics** from the clinical pharmacology review team were not available at the time of this review. The applicant did not propose any labeling for this section. The clinical pharmacology review team has indicated that they are considering proposing labeling with regards the effects of belatacept on immunoglobulin levels. Depending on the final recommendations, I will add an addendum to my review regarding the recommendations of the clinical pharmacology review team.

Nonclinical Toxicology

- The toxicology review team recommended revising a statement in section **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**. The proposed labeling noted that the nonclinical (b) (4) (b) (4) (b) (4) The toxicology review team recommended stating instead 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."
- The toxicology review team has recommended revising section **13.2 Animal Toxicology and/or Pharmacology**. At the time of this writing, the recommendations have not been finalized. Depending on the final recommendations, I will add an addendum to my review regarding the recommendations of the toxicology review team.

Clinical Studies

- Several recommendations were made regarding revisions to the introductory comments in section **14.1 Prevention of Organ Rejection in Kidney Transplant Recipients**. Exclusion criteria were added to the descriptions of IM103008 and IM103027. A statement that more efficacy failures were seen with the belatacept MI regimen was added. Information regarding patient discontinuations was added.
- The discussion of acute rejection was restricted to BPAR; (b) (4) (b) (4)
- (b) (4)

(b) (4)

- It was recommended that the statement (b) (4) should be deleted from the discussions of Study 1 and Study 2 as inadequate data exist to support the claim.
- The discussions of efficacy and GFR were conducted under separate subheadings to underline that, while comparative differences were detected for GFR across treatments, GFR was not a basis for the finding of efficacy.
- Data pertaining to the incidence of chronic allograft nephropathy across treatment arms were added to section. While the clinical significance of the findings remain uncertain, sufficient interest in the community with regards to these data exists to justify their inclusion.

Patient Counseling Information

- The section on patient counseling was revised to include the most important issues to be discussed with the patient.

9.3 Advisory Committee Meeting

A verbatim transcript of the Cardiovascular and Renal Drugs Advisory Committee held on March 1, 2010 is available at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm192863.htm
The Advisory Committee Meeting discussed the original BLA submission. An Advisory Committee was not convened to discuss the BLA resubmission.

Office Director Decisional Memo

Date	May 1, 2010
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
BLA #	125,288
Applicant Name	Bristol-Myers Squibb Company
Date of Submission **Date of Receipt**	June 30, 2009 July 1, 2009
PDUFA Goal Date	May 1, 2010
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:	Complete Response

Belatacept is a recombinant soluble fusion protein of the extracellular domain of human CTLA-4 and a fragment of a modified domain of IgG1. Belatacept interferes with CD28:CD80/CD86 interactions thereby interfering with a key co-stimulatory activity for T cell activation. BMS developed belatacept as an alternative to the cyclosporine component of a regimen to prevent rejection in kidney transplant recipients.

The review team has reviewed the issues in detail in their respective disciplines. For a detailed discussion, the reader is referred to the individual discipline specific reviews, the Cross-Discipline Team Leader (CDTL) Review, and the Division Director Review. I concur with the CDTL and Division Director Reviews. This memorandum will focus on selected issues from the application.

The evaluation from the Chemistry Manufacturing Controls standpoint is that there are deficiencies in Product Quality and Product Quality Microbiology. The Product Quality deficiencies are that there is inadequate control in manufacturing the drug substance, process controls and specifications, quality and stability protocols, stability standards, stability studies, in use stability, and immunogenicity issues. The Product Quality Microbiology deficiencies include insufficient information on the (b) (4) the container closure integrity test, (b) (4) validation, shipping validation, drug product endotoxin specification and data to support (b) (4) There are also

Compliance deficiencies; the inspections on the manufacturing facilities in East Syracuse and Manati, Puerto Rico are classified as withhold.

The Pharmacology/Toxicology, Clinical Pharmacology, and Clinical Microbiology reviewers find the application to be approvable from the standpoint of their respective disciplines. The safety signals identified from the pharmacology/toxicology review of nonclinical studies include risk of infections, autoimmunity, and carcinogenicity. The analyses of exposure-response relationships by the Clinical Pharmacology reviewers finds that higher belatacept trough concentrations on Day 5 are associated with a lower incidence of acute rejection during Month 1 post transplant and higher belatacept trough concentrations were associated with a lower proportion of patients with a reduction in glomerular filtration rate of ≥ 10 mL/min/1.73m^2. For exposure response relationships for safety findings, an analysis was performed to evaluate risk for post-transplant lymphoproliferative disorder (PTLD). Belatacept treated patients were at greater risk for development of PTLD than Cyclosporine A treated patients; an analysis of belatacept troughs to explore the risk of developing PTLD was performed but the number of events was small and hence meaningful exposure response relationships could not be derived. It was noted that two patients that developed PTLD during months 6 to 12 had higher trough levels.

The applicant performed two phase 3 trials that included 2 dosing regimens of belatacept as part of an immunosuppressive drug regimen compared to a cyclosporine A based drug regimen. The applicant seeks approval of the LI (less intensive) regimen. The FDA analysis of the study evaluated the study based upon the endpoint of biopsy proven acute rejection, graft loss, death or loss to follow-up at 12 months with the goal of showing non-inferiority to the cyclosporine regimen. As described in the Statistical review, the M1 for the treatment effect of the cyclosporine in this setting was estimated at 21.9%. The results for the study are shown in the tables below.

Study IM103008: BPAR, Graft Loss, Death, or Loss to Follow-up at 12 Months

	Belatacept MI	**Belatacept LI**	**CsA**
Met Endpoint	60/219 (27.4)	49/226 (21.7)	37/221 (16.7)
Biopsy Proven Acute	52	45	23
Rejection	3	3	7
Graft Loss	4	1	6
Death	1	0	1
Unknown			
Difference from CsA (97.3% CI)	10.7 (1.6, **19.8**)	5.0 (-3.7, **13.7**)	

Study IM103027: BPAR, Graft Loss, Death, or Loss to Follow-up at 12 Months

	Belatacept MI	**Belatacept LI**	**CsA**
Met Endpoint	62/184 (33.7)	51/175 (29.1)	52/184 (28.3)
Biopsy Proven Acute	40	37	34
Rejection	14	11	12
Graft Loss	6	3	5
Death	2	0	1
Unknown			
Difference from CsA (97.3% CI)	5.4 (-5.8, **6.6**)	0.8 (-10.3, **11.9**)	

The results are largely driven by acute rejection. The upper bound of the 97.3% confidence intervals for the study results for the LI regimen extend to 13.7 and 11.9 in studies IM103008 and IM103027, respectively.

The applicant's proposed indication was prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving kidney transplants. The indication of prophylaxis of organ rejection in kidney transplant recipients has been the indication that other similarly studied products have received. The added claim of preservation of allograft function has not been previously granted. (b) (4)

(b) (4)

The safety of belatacept is reviewed in detail in the Clinical and other reviews. The safety database from the clinical studies included over 900 patients, approximately half of whom received the MI regimen. Of particular note in the safety reviews is the finding of more cases of PTLD in belatacept-treated patients and 2 cases of progressive multifocal leukoencephalopathy (PML) (one at month 23 in a patient on the MI (more intensive regimen) and one in a phase 2 liver transplant study). Also of note is that there were cases of CNS PTLD in the belatacept arm. Given the cases of PTLD and the higher risk in EBV seronegative patients, the drug would only be indicated for use in patients who are EBV seropositive. For additional discussion of hypertension, dyslipidemias, new onset diabetes mellitus and cardiovascular mortality, the reader is referred to the Medical Officer's review.

Given the results for the BPAR endpoint with the 97.3% confidence bounds extending beyond 10% and the PTLD and PML events in the safety database, additional safety 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 are needed to evaluate benefit and risk. The 36-month data from the Phase 3 studies, particularly data on outcomes such as mortality, graft loss, GFR, PTLD and other serious adverse reactions can provide

additional information to further assess risk and benefit for belatacept for prophylaxis of organ rejection in kidney transplant recipients.

In addition, given the risks for PML and PTLD, a REMS is necessary for belatacept, if approved, to ensure that the benefits of the drug outweigh the risks of PTLD and PML.

Summary

Based upon the available information in the application, the application cannot be approved in its present form. The deficiencies that need to be addressed are enumerated in the Complete Response Letter. The deficiencies include Chemistry, Manufacturing and Controls (CMC) deficiencies, Compliance deficiencies, Clinical deficiencies, and a deficiency regarding the need to develop a REMS. For the primary efficacy endpoint, the upper bound of the 97.3% confidence intervals in the two phase 3 studies for the LI regimen are 13.7 and 11.9. Given the results for the BPAR endpoint and considering the safety issue of PTLD observed with belatacept and the cases of PML in the safety database, additional safety data are needed to further characterize the risk benefit of belatacept for prophylaxis of rejection in kidney transplant recipients. In addition, the identified CMC and Compliance deficiencies will need to be resolved and a REMS developed.

Edwlof 5/1/2010

Edward Cox, MD MPH
Director, OAP

Summary Review for Regulatory Action

Date	See ~~electronic~~ stamp date on page 25
From	Renata Albrecht, MD
Subject	Division Director Summary Review
BLA Number	BLA 125,288
Related IND **Belatacept** **Abatacept**	 IND 9418 IND 9391
Related NDA	BLA 125118, Abatacept (Orencia®)
Applicant Name	Bristol-Myers Squibb (BMS)
Date of Submission **Date of Receipt**	June 30, 2009 July 1, 2009
PDUFA Goal Date	May 1, 2010 (standard review)
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	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Patrick Archdeacon, Joette Meyer TL
CDTL Review	Bill Taylor/Joette Meyer
Statistical Review	Cheryl Dixon, Karen Higgins TL
Statistics Safety Consult Review	Eugenio Andraca-Carrera, Antonio Paredes, John Yap (TL) – *consult pending*
Statistics DB7 PTLD review	Anita Abraham, LaRee Tracy, Aloka Chakravarty
Biometrics DB6 Consult to CMC	Yi Tsong, Jinglin Zhong – *consult pending*
Pharmacology Toxicology Review	Ying Mu, Janice Lansita, Bill Taylor TL (CDTL)
CMC/OPS/OBP/DTP Review	Susan Kirschner TL, Barry Cherney *Jack Ragheb, Edward Max, Norihisa, Sakamoto, Joao Pedras-Vasconcelaos,*
Microbiology 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	
Interdisciplinary QT Review Team	Suchitra Balakrishnan, Christine Garnett
DSI	Susan Thompson, Tejashri Purohit-Sheth
OSE/DMEPA	Denise Toyer, Carol Holquist
OSE/DPV II (re: abatacept autoimmunity)	Peter Diak, Martin Pollock, Robert Boucher, Karen Townsent (PM)
OSE/DRISK	Tselaine Jones-Smith, Kristina Arwine, Mary Dempsey
Compliance/DMPQ/MAPCB/BMT	Bo Chi, Patricia Hughes, Michelle Clark-Stuart

CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
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 Pre-Approval Compliance Branch/ Biotech Manufacturing Team
OPS/OBP/DTP = Office of Pharmaceutical Sciences/Office of Biologics Products/Division of Therapeutic Proteins
DB = Division of Biometrics

Table of Contents:

Table of Contents: 3
1. Recommendations (Introduction) 4
1.1 Deficiences to be Communicated to Applicant: 4
2. Background 5
2.1 Belatacept Product Development and Submission Milestones 6
3. CMC/Product Quality Microbiology 7
4. Nonclinical Pharmacology/Toxicology 8
5. Clinical Pharmacology/Biopharmaceutics 10
6. Clinical Microbiology/Immunology 12
7. Clinical/Statistical-Efficacy 13
7.1 Biopsy Proven Acute Rejection Analyses: 15
7.2 Noninferiority Margin: 15
7.3 Glomerular Filtration Rate 16
8. Safety 17
8.1 REMS 20
9. Advisory Committee Meeting 21
10. Pediatrics 22
11. Other Relevant Regulatory Issues 22
11.1 Compliance Inspection 22
11.2 DSI Audits 22
11.3 Debarment certification 22
11.4 Orphan Status 22
11.4 Other Regulatory Issues 22
12. Labeling 23
13. Decision/Action/Risk Benefit Assessment 23
13.1 Regulatory Action 23
13.2 Risk Benefit Assessment 24
13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies 25
13.4 Recommendation for other Postmarketing Requirements and Commitments 25

1. Recommendations (Introduction)

BLA 125288 for Nulojix (belatacept) lyophilized powder for intravenous infusion 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. The proposed regimen is the low intensity (LI) regimen consisting of 10 mg/kg infusions on days 1, 5, 14, 28, 56 (month 2), 86 (month 3), and then 5 mg/kg at month 4 and thereafter. Based on the review of the data by all disciplines, the application cannot be approved at the present time and should be issued a *Complete Response* action letter due to a number of outstanding deficiencies which include

1.1 Deficiences to be Communicated to Applicant:

CMC Deficiencies:
The Product Quality reviewers determined that the application does not contain sufficient data on the (b) (4), process control and specifications, qualification and stability protocols for new reference standards, stability studies, in use stability and immunogenicity assays.

The Product Quality Microbiology reviewers determined that the application does not contain sufficient data on product quality from a microbiology perspective. Specifically, the data or information on the (b) (4) the container closure integrity test, (b) (4), shipping validation, drug product endotoxin specification, and (b) (4)

Compliance Deficiencies:
Both the East Syracuse NY facility and the Maniti Puerto Rico facility were recommended withhold approval because the facilities have unacceptable compliance status.

Clinical Deficiency:
For the indication of prophylaxis of organ rejection in kidney transplant recipients, because in clinical trials the incidence of acute rejection and post-transplant lymphoproliferative disorder (PTLD) was higher in the belatacept arms, safety data from the 36-month follow up from the Phase 3 studies will be requested prior to approval, focusing on overall death, graft loss, reports of serious events such as PTLD and PML, as well as information on GFR. The information should also help address whether the lower rate of cardiovascular and metabolic adverse reactions associated with belatacept translates to a lower overall mortality and graft loss.

(b) (4)

(b) (4)

[redacted]

REMS:
Based on the conclusions of the review team and recommendations of the Advisory Committee, belatacept needs a REMS to assure the benefits of the product outweigh the risks; BMS needs to provide revisions to their proposed REMS program which will include a Medication Guide and Communication plan to manage the risk of PTLD and progressive multifocal leukoencephalopathy (PML). The Division is continuing to work on labeling, and as part of this process, will provide advice to BMS on the Medication Guide.

2. Background

Belatacept is a fusion protein of human cytotoxic T-lymphocyte antigen-4 (CTLA-4) extracellular domain and modified human IgG_1 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 costimulatory pathway to T lymphocyte activation via CD28, and this blocks interleukin-2 (IL-2), IL-4, TNF-α and INF-γ production. This is the co-stimulatory signal needed for T-cell activation and inhibition of this signal leads to immunosuppression.

Belatacept it is related to abatacept (two amino acid difference [redacted] (b) (4)) which is marketed as Orencia® for rheumatoid arthritis and JRA; both products have the same mechanism of action but different potencies (see Pharmacology/Toxicology section).

The proposed indication is for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving kidney transplants.

Comment: The Division has previously reviewed and approved a number of products for prophylaxis of organ rejection in kidney transplant patients, including azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, mycophenolic acid, sirolimus and most recently everolimus. However, the Division has not previously reviewed or approved an indication of "preservation of functioning allograft." (b) (4)

[redacted]

[1] MDRD = modification of diet in renal disease' CKD-EPI = chronic kidney disease epidemiology collaboration,

(b) (4)

The indication of prophylaxis in kidney transplant patients is based on two Phase 3 studies, both of which evaluated so called moderate intensity (MI) and so-called low intensity (LI) regimens 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 sought for approval and consists of belatacept 10 mg/kg on days 1, 5, 14, 28 and month 2, month 3; then belatacept 5 mg/kg every month starting at Month 4.

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 including acute rejection and chronic allograft nephropathy (CAN) analyses. 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 whether blocking co-stimulation of pre T cells in the 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.

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.

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 CAN. 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. (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 this letter. The 74-day letter issued September 11, 2009 identifying multiple information requests. Between the time of submission and 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 advisory committee (AC) meeting. A number of teleconferences were held, including one to discuss the standard review designation.

3. CMC/Product Quality Microbiology

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

During the course of the review, the CMC/Product Quality Microbiology reviewer identified a number of deficiencies regarding the drug product so a facsimile requesting further information on 22 items was sent to BMS on January 29, 2010; an amendment of approximately 500 pages was submitted on February 24, 2010. Other requests on CMC manufacture had been sent January 22, 2010, and December 23, 2010.

Based on the reviews by both product quality and product quality microbiology, there are a number of deficiencies that need to be resolved before approval. CMC reviewers have also identified other issues that can be addressed as post-marketing commitments.

Dr. Kirschner of DTP/OBP/OPS (Product Quality) does not recommend approval because the data are considered inadequate to support the conclusion that manufacture of Nulojix is well controlled and leads to a product that is pure and potent. Deficiencies include (b) (4) (b) (4) stability protocols, release specifications, in use stability, immunogenicity assays.

Dr. Hughes and colleagues of OC/DMPQ/MAPCB/BMT (Product Quality Microbiology) note that there are a number of deficiencies that preclude approval from their perspective. Specifically, the data or information on the (b) (4), the container closure integrity test, (b) (4) validation, shipping validation, drug product endotoxin specification. (b) (4)

Dr. Ragheb, the CMC reviewer, has identified a different issue, a potential clinical concern related to the mechanism of action of belatacept. His concern is that belatacept may interfere with normal maturation of T regulatory cells needed for normal immune function, and autoimmunity may develop if a fetus is exposed to belatacept in utero. The concern is based in part on evidence that,

> "genetic mutations in the gene encoding Foxp3 …in both humans and mice…provide the most striking evidence that regulatory T cells play a critical role in maintaining normal immune system function. Humans with mutations in Foxp3 suffer from a severe and rapidly fatal autoimmune disorder known as **I**mmune dysregulation, **P**olyendocrinopathy, **E**nteropathy **X**-linked (**IPEX**) syndrome. The IPEX syndrome is characterized by the development of overwhelming systemic autoimmunity in the first year of life resulting in the commonly observed triad of watery diarrhea, eczematous dermatitis, and endocrinopathy seen most commonly as insulin-dependent diabetes mellitus. Most individual have other autoimmune phenomena including Coombs positive hemolytic anemia, autoimmune thrombocytopenia, autoimmune neutropenia, and tubular nephropathy."[2]

This issue is further discussed under nonclinical pharmacology/toxicology, and will be addressed by providing information in labeling (b) (4)

Comment: The application cannot be approved from a CMC standpoint until the deficiencies identified have been addressed.

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.

[2] Regulatory T Cell: http://en.wikipedia.org/wiki/Regulatory_T_cell

Drs. Mu and Lansita write:

> "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."

The drug is pregnancy category C. In animals fetal loss was noted but not teratogenicity. There were no concerning findings from the adults monkey toxicology studies. However, the question of autoimmunity was raised and was evaluated in a number of studies which are briefly mentioned here: Study DN07013 was a 13-week SC/IV trial of abatacept in juvenile rats dosed from postnatal day (PND) 4 to 94, and resulted in inflammation and changes to lymph nodes, and following a three month recovery period most changes showed partial to complete recovery. Abatacept is more potent in rats and mice, while belatacept has higher binding and potency in monkeys and humans, which is why toxicology studies used the more potent of the two products in each species tested. The reviewer comments that infections were seen more in juvenile rats than in the adult rat study (DN07166). Abatacept increased T helper and decreased T regulatory cells (CD4+CD25+Foxp3+) but these recovered by PND 183. Abatacept specific antibodies were not detected until PND 125 (1 month after drug stopped). Histology showed changes in spleen and lymph nodes that recovered by PND 183. Inflammation in the thyroid was seen in 24% of juvenile rats on PND 93 and increased to 75% by PND 183. Pancreatic inflammation of islets (insulitis) was seen in 9% of juvenile rats on PND 93 and 29% by PND 183. These are the findings that have raised concern about the risk of autoimmunity in infants exposed to belatacept in utero. Another study DS07156 evaluated 3 month intemittent SC/IV dosing of abatacept in juvenile rats and in this trial apparently similar changes were seen and autoimmunity with lymphocytic infiltration of pancreatic islet cells and thyroid were see which persisted through the recovery period and increased in incidence and severity. Study DS07166 was conducted in adult rats showing similar toxicities, indicating the autoimmunity is not just in juvenile rats. Such findings were not seen in adult monkeys studies with belatacept; juvenile monkey studies were not done.

Comment:
The reproducibility of the thyroiditis and insulitis finding in rat indicates this is a real finding – based on literature, the inhibition of the co-stimulatory signal (prevent activation) may lead

to autoimmunity with target organs being thyroid and pancreatic islets. However, it was also noted that the effect was not reproduced in other species (although juvenile studies in other species were not done, only adult studies). For this reason, information on these findings will (b) (4) *and a pregnancy registry will be developed to follow infants exposed in utero – in rats, the autoimminity manifested once the drug stopped and progressed over time. Therefore, there may be a latency period to this effect,* (b) (4) *. However, the duration of potential risk period in infants would also need to be discussed and defined.*

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.

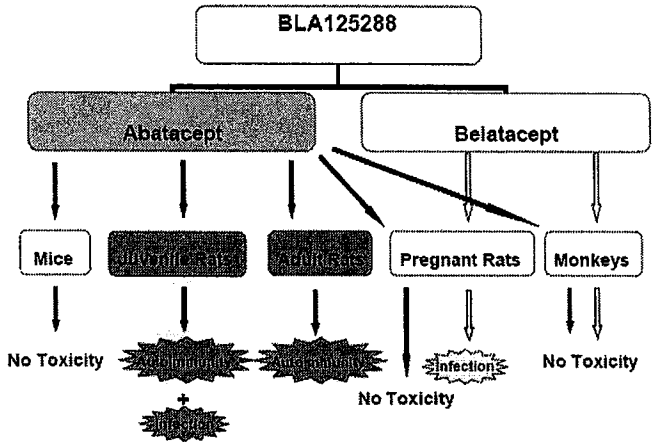


Figure 4: A summary of the significant toxicities observed in each animal study by treatment. The solid black arrows signify the abatacept studies and outcomes. The open-hatched arrows signify the belatacept studies and outcomes.

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Comment: The application can be approved from a pharmacology/toxicology standpoint; labeling revisions have been proposed. Further investigation of the autoimmunity signal is warranted as discussed above.

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 pharmacokinetics is reproduced from their review, page 4.

Table 1. Pharmacokinetic parameters (Mean ± SD [Range]) in Healthy Subjects and *de novo* Kidney Transplant Patients

Pharmacokinetic Parameters	Healthy Subjects (After 10 mg/kg Single IV Infusion) N=15	Kidney Transplant Patients during the Maintenance Phase (After 5 mg/kg Multiple IV Infusions) N=14	Kidney Transplant Patients during the Initial Phase (After 10 mg/kg Multiple IV Infusions) N=10
Peak concentration (C_{max}) [µg/mL]	300 ± 77 (190-492)	139 ± 28 (80-176)	247 ± 68 (161-340)
AUC[a] [µg•h/mL]	26398 ± 5175 (18964-40684)	14090 ± 3860 (7906-20510)	22252 ± 7868 (13575-42144)
Terminal half-life (T½) [days]	9.8 ± 2.8 (6.4-15.6)	8.2 ± 2.4[b] (3.1-11.9)	9.8 ± 3.2 (6.1-15.1)
Systemic clearance (CL) [mL/h/kg]	0.39 ± 0.07 (0.25-0.53)	0.51±0.14[b] (0.33-0.75)	0.49 ± 0.13 (0.23-0.70)
Volume of distribution (Vss) [L/kg]	0.09 ± 0.02 (0.07-0.15)	0.12±0.03[b] (0.09-0.17)	0.11 ± 0.03 (0.07-0.17)

[a] AUC=AUC (INF) after single dose and AUC (TAU) after multiple dose, where TAU=4 weeks
[b] TAU=8 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 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 two 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. 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 a 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.

Comment: The application can be approved from a clinical pharmacology/ pharmacometric/ pharmacogenomic standpoint; some labeling revisions have been proposed. Further investigation of the interactions noted above and possible TDM are warranted but are not needed before approval.

6. Clinical Microbiology/Immunology

Belatacept inhibits the activation of T cells, lymphocytes involved in mediating immunologic rejection of allografts. Dr. Rhuland noted that in primate models of kidney transplantation, and in transplanted islet cells, belatacept along with other immunosuprresants prolonged graft survival. He also summarized the findings from animals studies showing there was no effect on toxicity or 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 ($CD25^+$, $FOX3^+$) 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.

Comment: No autoimmunity was reported in the clinical trials; however, given that all patients in the studies were on immunosuppression to prevent graft rejections, it is not clear whether such events would be readily identified. There was a 5% incidence of diabetes mellitus in belatacept patients, which was lower than the 10% rate in the CsA arm. A consult was requested from DPVII regarding abatacept – 19 post marketing cases were identified and reviewed. The patients had SLE or RA and comorbid conditions; the consult reported that no autoimmune events were noted (5 patients had diabetes mellitus).

T cells are important in mediating immune responses, and T cell activation depends on several signals: CTLA-4 inhibits activation of T cells while CD28 augments activation of T cells when it bind CD80/06 on APC. Belatacept is not inhibitory like CTLA-4 but interferes with CD28:CD80/86 interaction. Dr. Bala summarizes that,

(a) The T-cell receptor (TCR) binding to the MHC receptor on the APC, representing the first signal.
(b) The interaction between the CD 28 receptor and CD80/CD86 receptor represents the co-stimulatory signal needed for activation. As written in Dr Bala's review,
   - **CD28:** CD28 is expressed on both resting and activated T-cells and binds CD80 and CD86 (B7-2) on the surface of APC. CD28 signals are important for cytokine (IL-2, IL-4, IL-5, IL-13, interferon-γ, GM-CSF, and IL-8) and chemokine (e.g., CCL5 that interacts with CCR1 CCR3, and CCR5 receptors) production that may promote type-2 T-helper response and T-cell survival by promoting BCL-X that belongs to BCL-2 family. TCR binding in the absence of CD28 ligation leads to apoptosis or anergy/tolerance.
   - **CD152:** CD152 (also called as CTLA-4), is expressed on activated T-cells and is

considered a T-cell inhibitory or regulatory receptor. CD152 binds CD80 and CD86 with higher affinity than CD28. Studies also suggest that interaction of CD80 and CD152 may mediate a stronger signal than CD152 and CD86. Interaction of CD152 with CD80/86 expressed on the APC also initiates reverse signaling in the APC that induces expression of indoleamine-pyrrole 2, 3-dioxygenase (IDO). IDO catalyzes the degradation of tryptophan, an essential amino-acid to N-formyl kynurenine. Depletion of tryptophan may inhibit the growth of microbes and proliferation of T-cells. Studies suggest that in models of transplantation, IDO can down-regulate the T-cell alloresponse *in vitro* and promote tolerance in murine models of pancreatic islet transplantation and allogeneic T-cell transfer[3]. However, the physiologic role of IDO in transplantation has not been determined.

There were fewer patients with donor specific antibodies (DSA) in the belatacept arm, and there was no 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 that 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), 6 were EBV positive (of 805 total EBV positive patients on belatacept) and 1 was of unknown status; 9/14 had CNS PTLD, which is an uncommon site for PTLD presentation. Among the CsA patients who developed PTLD, in one EBV serostatus was unknown and the other patient was EBV negative; neither patient developed CNS PTLD. In these trials, there were 108 assays used to detect EBV status, 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. It must not be used (contraindications) 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 standpoint; some labeling revisions have been proposed, including a contraindication regarding EBV negative and unknown-status, and the importance of using reliable EBV assays and interpretation of results.

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 analysis. Details of these trials are provided in the statistical review by Dr. Dixon and the clinical review by Dr. Archdeacon. The Phase 3 studies were evaluated for efficacy; both were multicenter, prospective studies of 36 months in duration; the agreement was that 12 month data would be submitted to support a regulatory decision.

- 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.

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

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 Cmax 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 m^2 at Month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73 m^2 from Month 3 to Month 12. The incidence of acute rejection by 12 months 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 noninferiority (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 set of

patients because their risk of PTLD is lower than for EBV negative patients (see safety discussion), and showed that the efficacy results were similar. Tables from the Statistical Review are presented below.

7.1 Biopsy Proven Acute Rejection Analyses:

Study IM103008: BPAR, Graft Loss, Death, or Loss to Follow-up at 12 Months

	Belatacept MI	**Belatacept LI**	**CsA**
Met Endpoint	60/219 (27.4)	49/226 (21.7)	37/221 (16.7)
Biopsy Proven Acute	52	45	23
Rejection	3	3	7
Graft Loss	4	1	6
Death	1	0	1
Unknown			
Difference from CsA (97.3% CI)	10.7 (1.6, **19.8**)	5.0 (-3.7, **13.7**)	

Study IM103027: BPAR, Graft Loss, Death, or Loss to Follow-up at 12 Months

	Belatacept MI	**Belatacept LI**	**CsA**
Met Endpoint	62/184 (33.7)	51/175 (29.1)	52/184 (28.3)
Biopsy Proven Acute	40	37	34
Rejection	14	11	12
Graft Loss	6	3	5
Death	2	0	1
Unknown			
Difference from CsA (97.3% CI)	5.4 (-5.8, **6.6**)	0.8 (-10.3, **11.9**)	

7.2 Noninferiority Margin:

As summarized by Dr. Dixon, in the current trial, 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 (B) + MMF + corticosteroids (CS)
Control:	CsA + basiliximab + MMF + corticosteroids
Putative Placebo:	basiliximab + MMF + corticosteroids

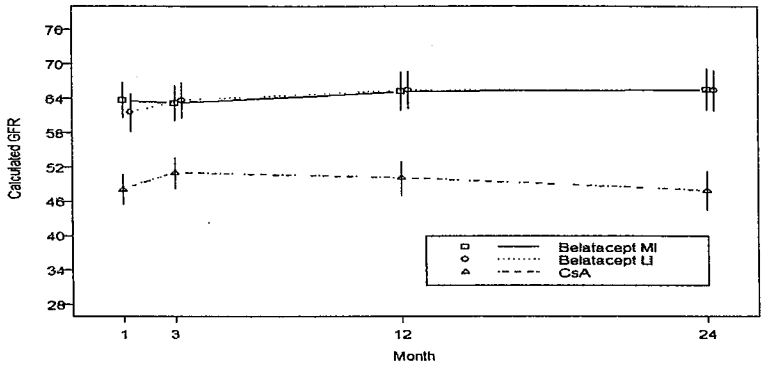
One trial examined a regimen of daclizumab + MMF + corticosteroids (the putative placebo with a different IL-2 blocker) and showed a 58% BPAR rate, 95% CI (**47.9**, 68.4). Four studies examined CsA + basiliximab + MMF + corticosteroids regimens similar to the one in the belatacept studies, and the pooled 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 (M1) is preserved in LI regimens of the two studies.

7.3 Glomerular Filtration Rate

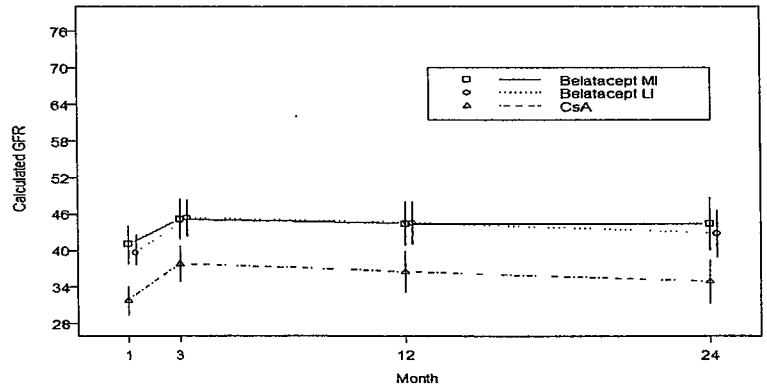
GFR was measured by the iothalamate method and also calculated. The GFR was approximately 15 mL/min higher in 008 (SCD kidney) and 8 mL/min higher in 027 (ECD kidney) in the belatacept arm compared to the CsA arm.

Study IM103008: Mean Calculated GFR through 24 months



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Study IM103027: Mean Calculated GFR through 24 months



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. The slope of the renal function curves was positive in the belatacept arm of study 008 (1.19) but negative for the CsA arm in study 008 (-1.73), belatacept arm in study 027 (-.0.93) and CsA arm in study 027 (-1.88), suggesting there may be a beneficial effect of belatacept on renal function in study 008, but a benefit of belatacept is not evident in study 027. Both CsA arms (lines) have a negative slope, suggesting a small loss in GFR.

The composite renal endpoint showed the belatacept arms to be superior in study 008 ($p<0.001$) but not significant in study 027 (p value = 0.0995).

Overall graft and patient survival at 24 months on belatacept LI versus CsA was 93.8% (212/226) versus 89.6% (198/221) in study 008 and 83.4% (146/175) versus 80.4% (148/184) in study 027. (MOR p 74) While these differences are not statistically significant, it is noted that the rates are slightly numerically higher in the belatacept arms.

Thus efficacy was demonstrated on the primary endpoint of BPAR, graft loss, death and loss to follow up, and met the pre-specified NI margin of 20% (actually preserved 30-40% of benefit of the margin). This endpoint was supported by information from the analysis of death and graft loss which was a pre-specified endpoint but for which the proposed 10% NI margin could not be justified, and a GFR endpoint that showed superiority for belatacept but was confounded by the known renal toxicity of CsA; as noted by Dr. Archdeacon, it is not clear that absence of toxicity should be interpreted as evidence of efficacy.

Comment: Although the results of efficacy show that the NI margin was met in both studies, because of the benefit/risk considerations, patient data from the 36 month follow up will be requested to see whether the benefits on GFR, lipids, hypertension and NODAT may translate to a benefit in terms of graft and patient survival, given the concern regarding PTLD, notably in EBV negative patients, and PML (see Safety below).

8. Safety

Safety data were available from over 900 patients treated with belatacept in studies of kidney transplantation as shown in the table below.

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

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

belatacept arm). 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)

The main safety signal of PTLD was looked at across the Phase 2 and Phase 3 studies. As noted by Dr. Dixon, up to December 14, 2009, there were 8 cases (1.7%) of PTLD in the belatacept MI group, 6 cases (1.3%) in the belatacept LI group, and 2 cases reported (0.4%) in the CsA group. Nine of the 16 cases presented with CNS involvement (6 belatacept MI, 3 belatacept LI and 0 CSA). The distribution of PTLD cases across the trials was as follows:

- IM103008: 3 belatacept MI, 2 belatacept LI, and 1 CsA
- IM103027: 2 belatacept MI, 4 belatacept LI, and 0 CsA
- IM103100: 3 belatacept MI, 0 belatacept LI, and 1 CsA

IM103008, IM103027, and IM103100 Summary of PTLD Cases

	Belatacept MI (N=477)			Belatacept LI* (N=472)			CsA (N=478)		
Trial	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		$2^{\Omega,\dagger}$							
Non-CNS PTLD			$1^{\dagger}$						$1^{\ddagger}$
IM103008									
CNS PTLD	1^{Ω}	1^{Ω}							
Non-CNS PTLD		1^{Ω}		$2^{\Omega,\Omega}$				$1^{\ddagger}$	
IM103027									
CNS PTLD	$1^{\dagger}$	$1^{\dagger}$		$2^{\Omega,\dagger}$	$1^{\ddagger}$				
Non-CNS PTLD					$1^{\ddagger}$				
					2			*1*	
Total	***2 (0.5)***	***5 (11.1)***	***1 (3.6)***	***4 (1.0)***	***(3.9)***	***0***	***0***	***(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 24 months; ‡ = Patient died after first 24 months
Table from Dr. Archdeacon and Dr. Dixon

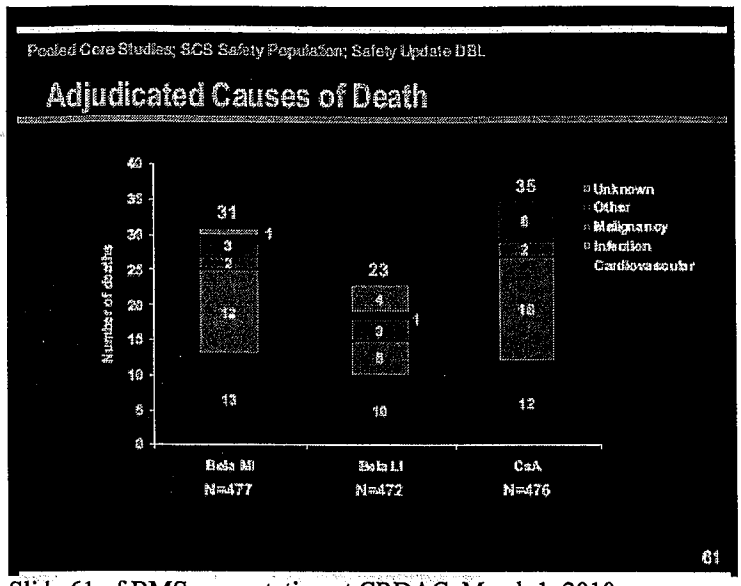
EBV negative status (or unknown status) was associated with higher PTLD, accounting for 6/8 cases in MI arms, 2/6 cases in LI arms and 2/2 cases on CsA. Therefore, it was concluded that PTLD risk was still increased, and by examining other clinical trials, as well as registry data from OPTN/UNOS and CMS claims data in the USA and Collaborative Transplant Study (CTS) Europe, it was calculated that the number needed to treat/harm (NNTH) was approximately 145-170 patients which means that for each 145-170 patients treated with belatacept instead of CsA in a two year period, one extra case of PTLD would likely be reported (see Dr. Abrahim and Dr. Tracy's review). Although it was recognized that there are many limitations to the study, all analyses of (a) pivotal studies, (b) other randomized studies, (c) registry data from USA and Europe suggested that the rate of PTLD would be higher on belatacept compared to CsA – based on these analyses, the application will need to contraindicate use in EBV negative patients, and will need a REMS to manage the risk of PTLD, and PML as noted below.

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

There were two cases of PML in the database; one in an MI treated patient and one in a liver transplant patient from an ongoing Phase 2 study. 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.



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Slide 61 of BMS presentation at CRDAC, March 1, 2010.

Immunogenicity: There were 34/857 (4%) patients who developed antibodies to belatacept; about 1/3 were considered neutralizing antibodies. There was some suggestion that death, graft loss and acute rejection were higher in patients with antibodies than those who were seronegative; some of the associations may be signals, other on closer look showed some improbable associations – e.g., the 4 graft losses were during first week due to graft thrombosis. The incidence of antibody-mediated acute rejections appears lower on belatacept compared to CsA.

8.1 REMS

Based on the concerns regarding PTLD and PML, and based on input from the Advisory Committee as well as consultants in OSE, belatacept will need a REMS if approved, as authorized under Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) to ensure that the benefits of the drug outweigh the risks of PTLD and PML. The REMS will need to include a Medication Guide (21 CFR 208), a communication plan including a Dear Healthcare Provider Letter and education material to be distributed by BMS detail representatives, and a timetable for risk assessment. After approval, each REMS assessment report would need to include the following type of information:

a. A survey of healthcare providers' and patients' understanding of the serious risks of belatacept.
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
c. A report on failures to adhere to distribution and dispensing requirements of the Medication Guide, and corrective actions taken to address noncompliance.
d. A summary of all reported cases of PTLD and PML during the preceding reporting period.

e. An analysis of prescribers' compliance with the labeled contraindication regarding the use of belatacept in EBV negative patients and patients in whom EBV-status is unknown.
f. A plan to monitor prescription data to evaluate:
   - Number of patients treated, reported by transplant organ received
   - Number of units shipped, reported by year and type of healthcare setting (e.g., transplant center, infusion center, hospital

Comment: Based on the benefit risk consideration, in addition to obtaining patient data from the 36 month follow to assess graft and patient survival, GFR, PTLD and PML, a REMS will be necessary to assure that the benefits outweigh the risks of belatacept.

9. Advisory Committee Meeting

The application was discussed before the Cardiovascular and Renal Drugs Advisory Committee on March 1, 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 was 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 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. The issue of whether to write a pediatric written request can be revisited once a decision about approval in adults has been made.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection

As summarized by Dr. Hughes in the most recent Compliance review from April 27, 2010, the recommendation is to withhold BLA approval based on need for additional information from the East Syracuse, NY facility and the OAI classification of the Manati, Puerto Rico facility. Both sites are considered to have an unacceptable compliance status.

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 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.

11.4 Other Issues

Because the application is not ready for approval, a number of consults, particularly reviews of labeling, are pending at this time.

12. Labeling

The applicant submitted a package insert, a Medication Guide, and carton and container labeling. Although the Division has started some labeling discussion with the applicant, the consulting groups have deferred review until near-final labeling is available: DDMAC and OSE (DMEPA, DRISK) reviews of labeling are pending at this time.[4] The Division has also determined that belatacept would need a REMS to be approved, and continues to work with DRISK to address this part of the application.

- **Package insert (PI):** The PI was submitted in PLR format. The review team has considered the major sections and provided preliminary comments to BMS. Although a draft PI will not be sent with the CR letter, the Division will continue to discuss labeling with BMS.

- **Medication Guide (MG)**: A draft MG has been submitted. The Division has asked DMEPA/DRISK to begin review of the MG based on the current elements and safety issues within the PI.

(b) (4)

- **REMS**: The REMS is under discussion with DRISK.

- **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 will be re-reviewed within 90 days prior to approval to determine whether it is still acceptable.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

A *Complete Response* letter is recommended because of outstanding CMC Product Quality and Microbiology deficiencies, which include deficiencies in the (b) (4) , process control and specifications, qualification and stability protocols for new reference standards, stability studies, in use stability and immunogenicity assays (product quality) and the microbial challenge test, (b) (4) shipping product during summer months, the quantity of endotoxin present in the product, and (b) (4) (product quality microbiology). Furthermore, neither the East Syracuse, NY facility that makes the drug substance, nor the Maniti, Puerto Rico facility that makes the drug product have been recommended to be approved; the recommendation for the latter is OAI.

[4] 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.

The data from other disciplines is considered sufficient for approval, however I am requesting that the company submit the 36 month data from the Phase 3 studies to obtain data on mortality, graft loss, PTLD, serious events, and to assess whether the benefits seen on GFR, lipids, hypertension, and NODAT translate into a survival benefit, and whether the number of PTLD cases stabilizes or increases. The current recommendation is that belatacept will need a REMS to manage the risk of PTLD and PML to assure the benefits of the product outweigh the risks. This means in addition to the package insert, a Medication Guide and communication plan will be developed. Finally, the Division and BMS will discuss a number of post-marketing requirements (PMRs) to collect data on the use of belatacept and detection of PTLD, PML and other serious CNS (b) (4)

13.2 Risk Benefit Assessment

In transplantation, even immunosuppressants that show efficacy 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, and patient management involves several agents with optimization of the regimen to maximize efficacy and minimize toxicity. Belatacept was developed as an alternative to currently available products, mainly cyclosporine, a calcineurin inhibitor, with the goal of minimizing the toxicity. A number of products, including cyclosporine, need to be used with therapeutic drug monitoring (TDM) to minimize toxicity. Although clinical pharmacology suggests that TDM be evaluated for belatacept, this 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: "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. Dr. Archdeacon's review includes a detailed and quantitative discussion of the individual 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 (evidence of efficacy or absence of toxicity?)
- Less toxicity related to lipids, hypertension, and NODAT

- 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
- IV administration (approximately weekly, then monthly)

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Please see section 8.1 above to mitigate PTLD and PML.

13.4 Recommendation for other Postmarketing Requirements and Commitments

BMS has submitted brief outlines for four proposed post marketing studies which will be classified as postmarketing requirements (PMR) and include

- IM103074 – Pattern of Use of Belatacept in US Transplant Recipients using UNOS/OPTN data base
- IM103075 – Belatacept and Risk of PLTD in US Renal Transplant Recipients
- IM103076 – (b) (4)

(b) (4)

(b) (4)

A consult will be/has been sent to OSE/Division of Epidemiology (DEPI).

4/30/2010
Renata Albrecht, MD
Director, DSPTP

5/1/2010
Edward Cox, MD, MPH
Director, OAP

Cross-Discipline Team Leader Review

Date	April 30, 2010
From William H Taylor 4/30/10 Joette M. Meyer 4/30/10	William Taylor, Ph.D., Pharmacology/Toxicology Team Leader Joette M. Meyer, Pharm.D., Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
BLA #	125,288
Applicant	Bristol-Myers Squibb Company
Date of Submission	June 30, 2009
PDUFA Goal Date	May 1, 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:	Complete Response, due to CMC and REMS deficiencies

TABLE OF CONTENTS

1. Introduction....3
2. Background....9
3. CMC....10
4. Nonclinical Pharmacology/Toxicology....11
5. Clinical Pharmacology/Biopharmaceutics....14
6. Clinical Microbiology....19
7. Clinical/Statistical - Efficacy....22
8. Safety....36
9. Advisory Committee Meeting....42
10. Pediatrics....46
11. Other Relevant Regulatory Issues....47
12. Labeling....51
13. Recommendations/Risk Benefit Assessment....52
Appendix I – REMS Deficiencies....59
Appendix II – Drug Substance Deficiencies....62
Appendix III – Drug Product Deficiencies....66

1. Introduction

Belatacept (Nulojix®) is a recombinant soluble fusion protein consisting of the extracellular domain of human CTLA-4 and a fragment (hinge–CH2–CH3 domains) of a modified Fc domain of human IgG1 developed by Bristol-Myers Squibb Company (BMS). CTLA-4 is a member of the immunoglobulin superfamily with structural similarities to CD28. While both CTLA-4 and CD28 bind CD80/86 on antigen presenting cells, CTLA-4 inhibits activation of T cells whereas CD28 augments activation of T cells. As a soluble fusion protein, belatacept does not transmit inhibitory signals like CTLA-4, but it interferes with CD28:CD80/CD86 interactions, key costimulatory signals required for T cell activation. T cells require at least 2 signals for full activation. The first signal is delivered by the T cell receptor and the second via costimulatory molecules like CD28. By preventing signaling through CD28, belatacept modulates immune responses and acts as an immunosuppressant.

The proposed indication is 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."

Regulatory History
An End-of-Phase 2 (EOP2) meeting was held between BMS and FDA representatives from CBER/ODE VI in September 2004, during which key elements of the Phase 3 studies, including the co-primary endpoints of non-inferiority on the composite of death and graft loss with a 10% margin, and superiority on the composite renal impairment endpoint were discussed. In addition, the definition and analyses of acute rejection (AR) and other cardiovascular and metabolic endpoints of clinical importance were discussed.

(b) (4)

The applicant noted that AR was not included as a co-primary endpoint in IM103027 due to a stipulation in the protocols that CsA subjects, but not belatacept subjects, could receive T cell depleting therapies for anticipated delayed graft function (DGF), a provision which could bias the assessment of AR against belatacept as a result of expected high rates of DGF in recipients of extended criteria donor (ECD) kidneys.

The protocol for Study IM103008 was submitted to FDA for a Special Protocol Assessment (SPA) in September 2005, when trial endpoints and margins were agreed upon. As discussed further in Section 6, while discussions were held regarding non-inferiority margins for the composite of death and graft loss and regarding the relevance of the composite renal impairment endpoint, the understanding of the science supporting both non-inferiority studies and renal function in transplant patients have evolved within the Division and the FDA since

2005. Therefore, the endpoints used to provide evidence of efficacy during the BLA review, were not the same as those agreed upon during these earlier meeting.

The clinical pharmacology program was also discussed at the EOP 2 meeting and subsequently agreed upon as adequate to support the filing for belatacept in kidney transplantation. An additional request was made by the FDA (December 2007) for BMS to assess mycophenolic acid (MPA)/MPAG (the glucoronide metabolite of MPA) levels in belatacept-treated subjects, which the applicant agreed to conduct.

Belatacept was granted a Fast Track Designation by the FDA (January 26, 2005) on the basis of its potential to address a serious aspect (renal function) of a serious disease (organ transplant). Belatacept was also granted orphan drug designation in February 2008, by the Office of Orphan Products Development.

In April 2008, a pre-BLA meeting was held during which FDA agreed to the format and content of the BLA submission. A final pre-BLA meeting with FDA occurred in May 2009, at which several aspects of the data to be included in the BLA and the approach to benefit-risk assessment were discussed.

The BLA was submitted June 30, 2009. (b) (4)

(b) (4)



(b) (4)

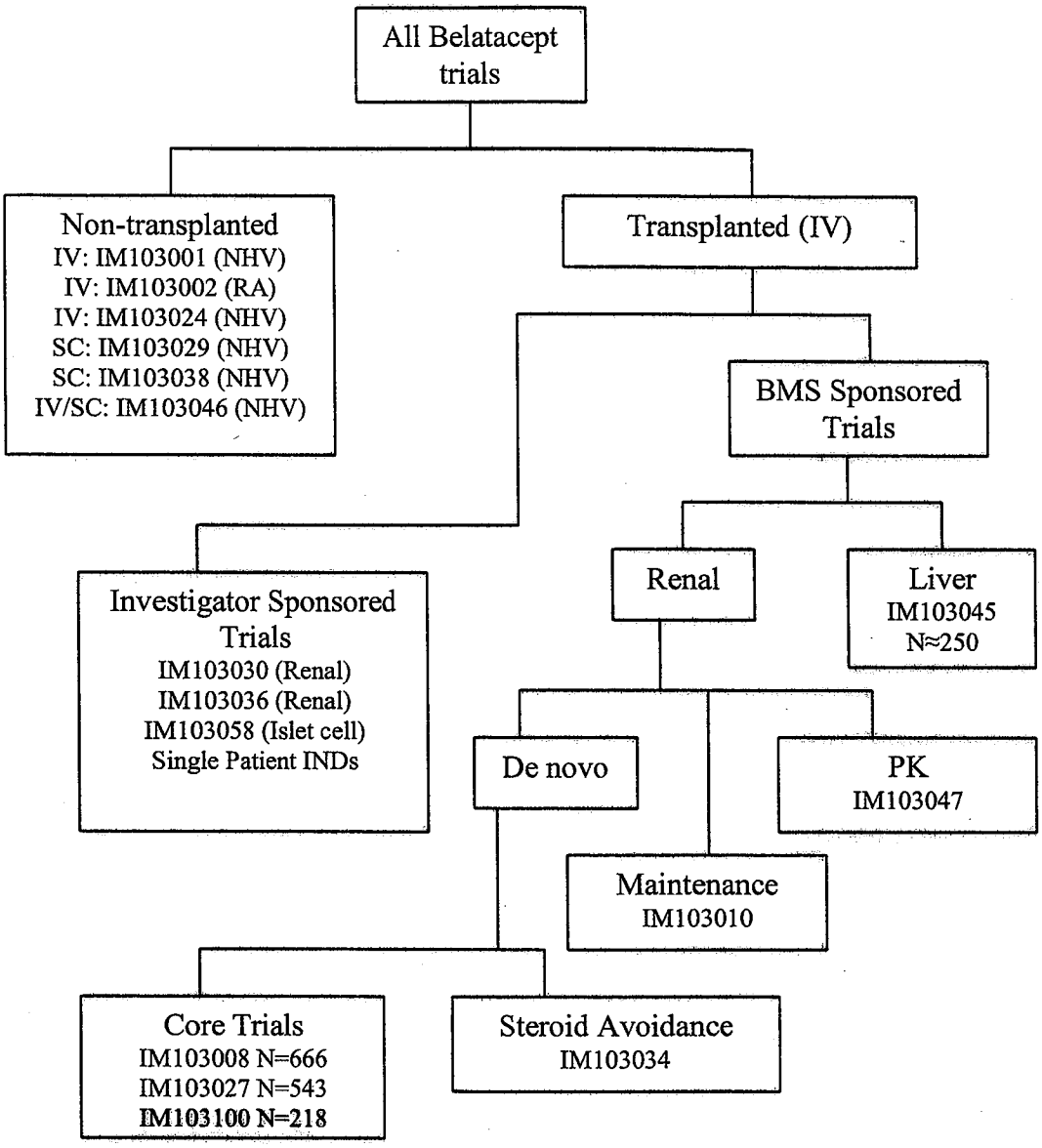
(b) (4)

On August 28, 2009 the applicant was notified in the 60-day filing letter that BLA 125,288 would receive a standard 10 month review.

Overview of the Clinical Development Program

The clinical development program for belatacept is shown in Figure 1 below, as adapted from the applicant's submission.

Figure 1: Belatacept Clinical Development Program



IV = intravenous, SC = subcutaneous, NHV = normal healthy volunteer, RA = rheumatoid arthritis

The safety and efficacy of belatacept for the prevention of organ rejection and preservation of allograft function following *de novo* kidney transplantation were assessed in two randomized, multicenter, controlled Phase 3 trials. These studies compared two dose regimens of belatacept (MI and LI, discussed below) versus CsA when administered in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids in recipients of living donor and standard criteria deceased donor organs (Study IM103008) or extended criteria donor organs (Study IM103027). Standard criteria donor (SCD) organs were defined as organs from a living donor, or a deceased donor with anticipated cold ischemia time of <24 hours and not meeting

the definition of extended criteria donor organs. Extended criteria donors (ECD) were defined as deceased donors with at least one of the following: (1) donor age ≥60 years; (2) donor age ≥50 years and other donor comorbidities (≥2 of the following: stroke, hypertension, serum creatinine >1.5 mg/dL); (3) donation of organ after cardiac death; or (4) anticipated cold ischemia time of the organ of ≥24 hours.

A Phase 2 trial (IM103100) with a similar design and dosing regimens to the Phase 3 trials, but which excluded ECD kidneys, was also conducted and was considered a supportive trial.

Together these three trials constituted the "core" clinical studies for evaluation in the BLA.

Dosing Regimen

Two dosage regimens were studied during the development of belatacept: a less intensive (LI) regimen and a more intensive (MI) regimen. In the current BLA application, BMS is seeking approval for the belatacept LI regimen studied in the Phase 3 trials for kidney transplantation.

As shown in **Table 1**, the belatacept LI regimen in the Phase 3 trials consisted of belatacept (10 mg/kg IV) administration on Day 1 (the day of transplantation, prior to implantation); and on Days 5, 14, and 28; then every 4 weeks through 3 months after transplantation. Starting at Month 4 after transplantation, belatacept was administered at the maintenance dose of 5 mg/kg every 4 weeks (± 5 days). This regimen is provided in the table below.

Table 1: Dosing for Belatacept LI Regimen (Phase 3 trials)

Dosing for Initial Phase	**Dose**
Day of transplantation, prior to implantation (Day 1)	10 mg/kg
Day 5, Day 14, and Day 28 (1 month after transplantation)	10 mg/kg
Month 2 and 3 after transplantation	10 mg/kg
Dosing for Maintenance Phase	**Dose**
Monthly, starting at Month 4 after transplantation	5 mg/kg

The LI regimen in the Phase 2 trial (IM103100) was different from the regimen in Phase 3 in that there was no dose given on Day 5. The following is the applicant's rationale for changing the dosing between Phase 2 and Phase 3:

> In the Phase 2 study, IM103100, the MI regimen demonstrated acceptable efficacy while the LI regimen was associated with an elevated rate of subclinical rejection. As a result, the MI regimen studied in Phase 2 was taken forward into the Phase 3 trials to further characterize its efficacy and safety. However, a Day 5 dose was added to the Phase 2 LI regimen to ensure that target drug concentrations were achieved in the early transplant period and to reduce the rates of subclinical rejection. This updated LI regimen was then studied in Phase 3 to determine if it would provide comparable efficacy to the MI regimen, but reduce the overall burden of immunosuppression and offer an improved safety profile. In addition, maintenance dosing was established at 5 mg/kg every 4 weeks based upon the higher rates of subclinical rejection noted with the every 8 week schedule in IM103100.[1]

The Phase 2 LI regimen consisted of belatacept (10 mg/kg) administration on Days 1, 15, 29, 57, and 85; patients were then reallocated to a 5 mg/kg maintenance dose every 4 weeks or

[1] Clinical Overview, Belatacept BLA 125,288.

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- The incidence of acute rejection (AR), defined as a biopsy confirmed histological evidence of rejection along with clinical evidence, at 12 months (IM103008 only)

The incidence of AR was a secondary endpoint in IM103027. Mean GFR at 12 months and incidence of chronic allograft nephropathy (CAN) were also secondary endpoints in both trials.

The protocol specified that the endpoints of patient and graft survival and of AR were to be assessed for noninferiority (NI), whereas the endpoint of composite renal impairment was to be assessed for superiority. The endpoints were to be examined sequentially in the order of hierarchy stated above.

2. Background

Belatacept was developed by BMS as a new therapeutic agent for immunosuppression in kidney transplant recipients; it was studied as a replacement for CsA in an immunosuppressive regimen that also included an IL-2 antagonist, MMF and corticosteroids.

Calcineurin inhibitors (CNIs), starting with the advent of CsA, have been largely responsible for the high rates of one-year patient and graft survival presently observed among kidney transplant patients compared to the historically low survival rates observed from those eras where transplantation was performed without immunosuppression or with azathioprine and steroids only. While one-year survival rates have substantially improved, two leading causes of long term adverse outcomes among kidney transplant patients are death with a functioning graft and late graft loss due to cumulative immunologic and non-immunologic injuries to the allograft. Despite their beneficial effect on short-term survival, CNIs may contribute in part to poor long-term outcomes due to their renal, cardiovascular, and metabolic toxicities, which can cause renal impairment, hypertension, hypercholesterolemia, and diabetes mellitus. CNIs have been associated with a direct nephrotoxic effect whose mechanisms have not been clearly elucidated. This calcineurin inhibitor nephrotoxicity (CIN) may contribute to the cumulative allograft injuries that result in late graft loss.

Transplantation has been established as the preferred therapeutic intervention in end stage renal disease (ESRD). Beyond its impact on quality of life, transplantation clearly imparts a significant survival benefit over the other renal replacement therapies (peritoneal dialysis, hemodialysis).[2] While an ever increasing number of Americans (now over 500,000) meet the criteria for ESRD, the number of kidney transplants performed annually has remained stable at around 17,000 for the past several years.[3] Given the shortage of available kidneys for transplantation (and the immunologic and non-immunologic barriers to performing repeat transplants), increasing graft life is of critical importance to improving patient outcomes.

[2] Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. NEJM 1999; 341(23): 1725-30.
[3] http://www.usrds.org/

Bristol Myers Squibb (BMS) has submitted a BLA requesting the approval of belatacept for the indications of prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving kidney transplants. While a number of products have been approved for the prophylaxis of organ rejection in patients who received an allograft (e.g. kidney, heart, or liver), the indication of preservation of a functioning allograft has not been previously considered or granted by the Agency. The applicant has suggested that by avoiding the use of CNIs, patients treated with belatacept may avoid the consequences of CNI-related adverse effects (including cardiovascular and metabolic toxicities, as well as direct renal toxicities). It should be noted, however, that the absence of a renal toxicity attributed to CNIs, while an important safety consideration, can not constitute evidence of the efficacy of belatacept.

Foreign Marketing Experience
Belatacept is not approved in any country at the current time. (b) (4)

3. CMC

The CDER Office of Compliance, Division of Manufacturing and Product Quality, Manufacturing Assessment and Pre-Approval Compliance Branch, Biotech Manufacturing Team does not recommend approval at this time, although the drug substance manufacturing controls for sterility are acceptable, based on a review of the BLA.

Compliance deficiencies leading to the recommendation of non-approval include (1) unsatisfactory facility inspection findings arising from the November 2009 inspection of the BMS East Syracuse, New York facility, where drug substance is manufactured; (2) unsatisfactory facility inspection findings arising from the March 2009 inspection of the Manati, Puerto Rico facility, where drug product is manufactured; and (3) inadequacy of drug product microbiologic (sterility) information submitted to the BLA. Other manufacturing and testing facilities listed in the BLA are currently in compliance with CGMP requirements. Additional details follow which include itemized deficiencies and a recommended Post-Marketing Commitment.

I. The CMC (drug substance) team recommends BLA approval from a product quality/ microbiology controls perspective, based on a review of the BLA, as amended. The belatacept drug substance manufacturing process was evaluated for microbial control strategy, and contamination/cross-contamination controls related to the drug substance and facilities and equipment. Questions arising from review of the initial BLA submission and inspections were adequately addressed by the applicant and no additional inspectional follow-up items are identified. Adequate microbial controls are described in the amended BLA for the drug substance manufacturing process.

II. The CMC (drug substance) team *does not* recommend BLA approval from a product quality and sterility assurance perspective. The East Syracuse, NY facilities November 2009 inspection resulted in an FDA Form 483 (Inspectional Observations) issued to BMS; items

included in the Form 483 were subsequently addressed by the applicant and determined by reviewers to be adequate. However, the CDER Office of Compliance determined additional process problems described in the Establishment Inspection Report still need addressing before approval can be recommended. For a listing of those items, please see **Appendix II**.

III. The CMC (drug product) team *does not* recommend BLA approval from a product quality and sterility manufacturing perspective. Following the March 2010 inspection of the Manati, Puerto Rico facility, an FDA Form 483 (Inspectional Observations) was issued to BMS. Items included in the Form 483 are not currently available, but they will need to be addressed before CDER/OC will recommend approval of the NuLojix® (belatacept) BLA.

IV. The CMC (drug product) team *does not* recommend BLA approval from a product quality and sterility assurance perspective. The microbiology team has determined the applicant should address six deficiencies based on a review of the BLA, as amended, prior to recommending approval. For a listing of those deficiencies, please see **Appendix III**. Additionally, the drug product review team recommends the applicant should agree to one post-licensing commitment, which is listed in **Section 14** (Recommendations/Risk Benefit Assessment).

4. Nonclinical Pharmacology/Toxicology

The applicant submitted nonclinical toxicology studies and *in vivo* and *in vitro* pharmacology studies of belatacept and abatacept to the BLA. Belatacept and abatacept target the same receptors; however, belatacept has greater potency in humans and nonhuman primates than abatacept, and abatacept has greater potency in rodents and rabbits than belatacept. Therefore, adverse safety findings in rodent studies of abatacept may be conservatively considered as potential hazard indicators for belatacept in humans, and abatacept studies in rodents are relevant to the belatacept clinical safety assessment.

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 were a risk of infections, autoimmunity, and carcinogenicity; and each of these are described in the proposed product label. All adverse findings except for autoimmunity are related to the expected pharmacology of belatacept. No effects on reproductive function and no terata were observed in animal studies of either belatacept or abatacept. Models in which infections and autoimmunity were observed are diagrammed below.

Infections
In the pre- and postnatal development study (Study# DN06002) in female rats, belatacept was given at doses of 20, 65 and 200 mg/kg/day, IV, from gestation day (GD) 6 to lactation day (LD) 20. In all treated groups, 3.8% - 9.6% of the dams presented with opportunistic infections, leading to moribundity or death, impairment of maternal care and partial or complete litter losses.

Infections were not observed in pregnant rats and rabbits treated with belatacept over a shorter dosing duration (study# DN06032, DN06008, and DN06056), or in pregnant rats treated with abatacept (study# DS07166, DN01060) .

A small percentage of pathogenic bacterial infections leading to moribundity or death was also observed in two 3-month juvenile toxicity studies with abatacept (study# DN07013 and DS07165).

Results suggest that pregnant rats and juvenile rats treated with these compounds are more susceptible to infections than nonpregnant adult rats. Susceptibility to infections might be exacerbated with pregnancy, dose frequency, dose duration or dose volume (10 mL/kg, IV). In juvenile rats, a potential mechanism may include suppressed development of memory immune response.

Autoimmunity
Autoimmunity was only observed in nonclinical studies of abatacept. Autoimmunity was observed in pups exposed to abatacept *in utero* and during lactation in a peri- post-natal study (Study# DN01060), in two abatacept 3-month juvenile rat toxicity studies (study# DN07013 and DS07165), and in an abatacept 3-month adult rat toxicity study (study# DS07166).

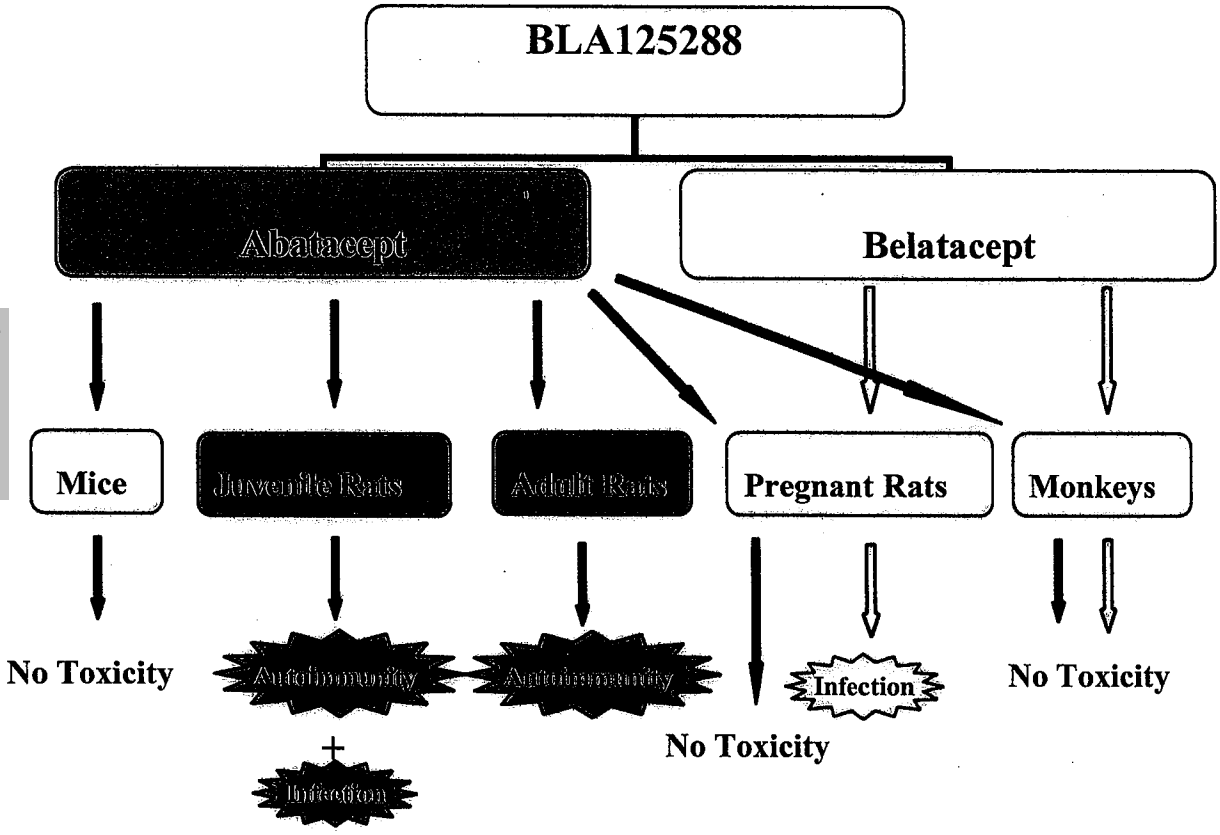
Autoimmunity of the thyroid (thyroiditis) was identified in one out of twenty rat off-spring at 112 days of age exposed to abatacept in utero and during lactation from a dam dosed at 200 mg/kg (Study# DN01060). The dam's thyroid status was not examined; therefore, it is unknown whether the thyroiditis originated in the maternal animal (and may have been transferred to the off-spring via anti-thyroid antibodies). Additionally, female pups dosed at 200 mg/kg in this study showed a 9-fold increase in T-cell dependent antibody-mediated response (TDAR).

In the rat juvenile toxicity studies abatacept was administrated SC from postnatal day (PND) 4 to 28 and IV from PND 31 to 94 at doses up to 200 mg/kg every 3 days. The autoimmunity was identified by histopathology as lymphocytic infiltration of the thyroid (thyroiditis) and pancreatic islet cells (insulitis). Other treatment-related findings included infections (described above), significant decreases in TDAR, decreases in serum IgG, increases in T-helper cells, decreases in T-regulatory cells, and morphological changes in lymphoid organs. The severity and incidence of findings were generally not dose-dependent. Although most immunological changes were partially or completely reversible, including a complete recovery of T-regulatory cell counts, the thyroiditis and insulitis persisted and progressed in incidence and/or severity throughout the 3-month recovery period. T-regulatory cells are important in maintaining immune self-tolerance. However, the relationship between decreased T-

regulatory cells and the observed autoimmunity remains unclear. Additionally, although anti-CTLA4 antibodies have been associated with autoimmunity, no correlation between immunogenicity and autoimmunity could be determined in the nonclinical studies with abatacept.

Finally, autoimmunity was also seen in a 3-month adult rat toxicology study with abatacept (study# DS07166) but was not observed in a 6-month chronic mouse toxicology study or in a 1-year chronic monkey toxicology study with abatacept. Belatacept has not been associated with autoimmune signals in a 6-month chronic monkey study or in human patients to date. Therefore, the autoimmunity finding may be a rat-specific effect of abatacept.

Diagram: Infections and Autoimmunity in Nonclinical Safety Studies.



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Carcinogenicity

The applicant did not conduct carcinogenicity studies with belatacept. However, a carcinogenicity study in mice with abatacept (study# 97610) showed increased incidences of mammary tumors (female only) and lymphomas (both sexes). The tumors were associated with endogenous mouse mammary tumor virus (MMTV) and murine leukemia virus (MLV), respectively. In the clinic, belatacept is associated with malignancy through an increased risk of post-transplant lymphoproliferative disease (PTLD), specifically in the central nervous system (CNS) and is described in the product label.

In summary, the pharmacology and toxicology studies support the proposed use of belatacept in the prophylaxis of organ rejection in kidney transplant patients. The Pharmacology/ Toxicology team has no post-marketing requirements or post-marketing commitments for the applicant.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review team agrees that the clinical pharmacology information presented in the BLA is acceptable to support the approval of belatacept for the proposed indication of prophylaxis of organ rejection (b) (4) Based on the efficacy and safety findings observed in the pivotal clinical trials, the reviewers agree with the sponsor's proposal to recommend the less intensive (LI) belatacept regimen for the prophylaxis of kidney transplant rejection.

See complete Clinical Pharmacology review by Gerlie Gieser, PhD, Seong Jang, PhD, Jiang Liu, PhD, Shashi Amur, PhD, and Li Zhang, PhD.

General Clinical Pharmacokinetics
The pharmacokinetics (PK) of belatacept are linear and plasma exposures (C_{max} and AUC) increase dose proportionally in healthy subjects following single escalating intravenous (IV) infusion doses from 1 to 20 mg/kg.

Table 2 summarizes the PK parameters of belatacept in healthy subjects after a single 10 mg/kg IV infusion and in *de novo* kidney transplant patients after multiple 5 mg/kg and 10 mg/kg IV infusions. Similar to healthy subjects, mean C_{max} and AUC increased dose proportionally in *de novo* kidney transplant patients following multiple IV doses of 5 mg/kg and 10 mg/kg every 4 weeks. Mean estimates of systemic clearance (CL) and volume of distribution (Vss) of belatacept in kidney transplant patients were also comparable to those in healthy subjects. Likewise, the mean estimates of belatacept half-life (T½) were similar between kidney transplant patients (approximately 8 to 10 days) and healthy subjects. The between subject variability in the PK estimates from Table 1 (as %CV) is less than 30% in healthy subjects (range 18-28%), and is slightly higher in kidney transplant patients (range 27-35%).

Table 2 Pharmacokinetic parameters (Mean ± SD [Range]) in Healthy Subjects and de novo Kidney Transplant Patients

Pharmacokinetic Parameters	Healthy Subjects (After 10 mg/kg Single IV Infusion) N=15	Kidney Transplant Patients during the Maintenance Phase (After 5 mg/kg Multiple IV Infusions) N=14	Kidney Transplant Patients during the Initial Phase (After 10 mg/kg Multiple IV Infusions) N=10
Peak concentration (C_{max}) [µg/mL]	300 ± 77 (190-492)	139 ± 28 (80-176)	247 ± 68 (161-340)
AUC[a] [µg•h/mL]	26398 ± 5175 (18964-40684)	14090 ± 3860 (7906-20510)	22252 ± 7868 (13575-42144)
Terminal half-life (T½) [days]	9.8 ± 2.8 (6.4-15.6)	8.2 ± 2.4[b] (3.1-11.9)	9.8 ± 3.2 (6.1-15.1)
Systemic clearance (CL) [mL/h/kg]	0.39 ± 0.07 (0.25-0.53)	0.51±0.14[b] (0.33-0.75)	0.49 ± 0.13 (0.23-0.70)
Volume of distribution (Vss) [L/kg]	0.09 ± 0.02 (0.07-0.15)	0.12±0.03[b] (0.09-0.17)	0.11 ± 0.03 (0.07-0.17)

[a] AUC=AUC (INF) after single dose and AUC (TAU) after multiple dose, where TAU=4 weeks
[b] TAU=8 weeks

Pathway of Elimination
A mass balance trial was not conducted for belatacept. Belatacept is an Fc fusion protein. Mass balance studies are not generally performed for proteins because they are degraded into amino acids that are then recycled into other proteins.

Pharmacokinetics Specific Populations
No formal PK studies were conducted in subjects with hepatic impairment, renal impairment, or in geriatric and pediatric populations. Population PK analysis showed that there was a trend toward higher CL of belatacept with increasing body weight, supporting a weight-based dose of belatacept. Age, gender, race, renal function (measured by calculated glomerular filtration rate [GFR]), hepatic function (measured by albumin), diabetes, and concomitant dialysis did not affect clearance of belatacept.

Drug-Drug Interactions
Traditional *in vitro* and *in vivo* drug interaction studies were not conducted. See request for additional studies below.

QT Assessment
Belatacept is a large fusion protein with a molecular weight of approximately 91 kDa and with high specificity for its target; therefore a Thorough QT trial (TQT) was not required and not conducted by the applicant. Non-clinical evaluations have suggested no evidence of cardiovascular or hemodynamic abnormalities. The QT-IRT was consulted to evaluate the clinical trials database to see if a QT signal was detected (See **Section 11**)

Exposure-Response Relationships for Efficacy
The relationship between exposure (belatacept trough concentrations) and response (AR and renal function) was assessed and the results are summarized below.

Acute Rejection (AR): Higher belatacept trough concentrations on Day 5 appeared to be related to a lower incidence of AR during Month 1 post transplant. However, the incidence of AR during Month 1 post transplant only accounts for ~1/3 of the total AR episodes. Overall, no apparent relationship of belatacept trough concentrations with AR was observed in the Phase 3 trials IM103008 and IM103027.

Renal Function: In the Phase 3 trials IM103008 and IM103027, renal impairment was defined as a measured GFR (mGFR) < 60 mL/min/1.73 m^2 or a decrease in measured GFR ≥ 10 mL/min/1.73 m^2 from Month 3 to Month 12 (mGFR10). The exposure-response analysis was conducted with mGFR10 because it is not influenced by the observed difference in baseline mGFR values in each patient. Overall, the proportion of patients with mGFR10 decreased with increasing belatacept trough concentrations in Studies IM103008 and IM103027 (see **Table 3**). Data from the LI and MI regimens in IM103008 and IM103027 were combined for the quartile analysis.

Table 3: Relationship between Belatacept Trough Concentrations (Median; 10-90th percentile) and Proportion of Patients with a Decrease in Measured GFR ≥ 10 mL/min/1.73 m^2 from Month 3 to Month 12

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Month 1[a]				
Median (10-90th percentile) belatacept C_{trough} (µg/mL)	25.5 (18.9 – 28.8)	32.9 (30.5 – 35.5)	38.7 (36.5 – 41.8)	49.9 (43.4 – 62.8)
Percentage of patients with mGFR10 (%; n/N)	22.4 (40/179)	24.0 (43/179)	25.1 (45/179)	18.0 (32/178)
Months 2 to 4				
Median (10-90th percentile) belatacept C_{trough} (µg/mL)	6.1 (3.6 – 8.1)	12.1 (9.7 – 16.0)	22.3 (17.8 – 26.1)	34.4 (28.5 – 49.5)
Percentage of patients with mGFR10 (%; n/N)	31.3 (57/182)	23.1 (42/182)	21.4 (39/182)	19.4 (35/180)
≥ Months 6				
Median (10-90th percentile) belatacept C_{trough} (µg/mL)	2.4 (1.1 – 3.1)	4.0 (3.4 – 4.7)	5.7 (5.0 – 6.7)	8.5 (7.3 – 17.0)
Percentage of patients with mGFR10 (%; n/N)	28.4 (46/162)	28.4 (46/162)	23.5 (38/162)	20.5 (33/161)
All Months				
Median (10-90th percentile) belatacept C_{trough} (µg/mL)	7.5 (5.1 – 9.3)	11.3 (9.9 – 12.8)	15.6 (13.9 – 18.7)	27 (20.9 – 42.7)
Percentage of patients with mGFR10 (%; n/N)	31.4 (61/194)	21.7 (42/194)	22.7 (44/194)	14.1 (27/192)

[a] taken on day 5 post-transplant

C_{trough} = trough concentration

mGFR10 = decrease in measured GFR ≥ 10 mL/min/1.73 m^2 from Month 3 to Month 12

Exposure-Response Relationships for Safety

The relationship between exposure (belatacept trough concentrations) and response (PTLD, infections, and other adverse events of interest) was assessed and the results are summarized below.

Post-transplant lymphoproliferative disorder (PTLD): Epstein-Barr virus (EBV) – induced PTLD is a life-threatening complication following organ transplantation in high-risk patients receiving immunosuppressive therapy. The primary risk observed with belatacept was PTLD, with the central nervous system (CNS) being the predominant site of presentation. Belatacept-treated patients were found to be at a higher risk for developing CNS-PTLD compared with CsA-treated patients. Based on visual inspection of graphical analyses comparing belatacept trough concentrations in patients with PTLD, belatacept trough concentrations in patients with PTLD were not substantially different from those in patients without PTLD. In the Phase 3 studies, the incidence of CNS-PTLD with onset in Month 6 to 12 was 0.6% (2/312) in the patients with higher C_{trough} (i.e., > 4.4 μg/mL) whereas no PTLD (0/312) occurred in the patients with lower C_{trough} (i.e, ≤4.4 μg/mL). Overall, the number of clinical cases was not adequate to derive meaningful exposure-response relationships.

Non-Exposure-Related Risk Factors of PTLD: Receiver Operating Characteristic (ROC) analyses using data from Studies IM103100, IM103008 and IM103027 were conducted by the Pharmacogenomic reviewers to identify potential factors associated with PTLD risk in belatacept-treated patients. The results showed that (a) EBV negative serostatus was the strongest risk factor, followed by CMV negative serostatus, and (b) among EBV positive patients (the population to which belatacept is likely to be restricted if approved), a significant imbalance of PTLD was observed in CMV negative patients (6-fold higher risk compared to CMV positive patients [OR 5.75 [1.05-31.66]] (see **Table 4**), suggesting that CMV negative serostatus should be considered as an additional risk factor when considering belatacept as a treatment option.

Table 4: Belatacept-induced PTLD rates among EBV seropositive patients as a function of CMV serostatus

		PTLD-No[a]	PTLD-Yes[a]	Total[a]	PTLD Rate
CMV	+	590	2	592	0.34%
	-	205	4	209	1.91%
Total		795	6	801	0.75%

[a]: Number of Patients

Infections: Serious infections occurred more frequently in the first 6 months following transplantation. From Month 2 to Month 6, belatacept exposure in subjects on the MI regimen is generally higher than those on the LI regimen. However, the incidence rate of serious infections does not appear to be substantially different between the MI regimen and the LI regimen in that period. The incidence of some infections, such as BK virus and herpes virus infections, tend to be higher in patients with higher belatacept trough concentrations. However, overall incidence of these infections is too low to draw definite conclusions.

Other Adverse Events: There was no apparent association between the incidence of new onset diabetes mellitus after transplant (NODAT), hypertension, dyslipidemia, or congestive heart failure and belatacept trough concentrations.

Immunogenicity
A total of 34 of 857 patients (4.0%) developed antibodies during treatment with intravenous belatacept in the two Phase 3 trials and during the long-term extension (LTE) phase of the 4-week cohort of the key Phase 2 trial; an additional 7 of 124 (5.6%) developed antibodies within 7 belatacept half-lives after treatment discontinuation.

There appears to be a trend towards higher rates of graft loss, death, and acute rejection in those patients who were seropositive or indeterminate than in those who were seronegative to anti-belatacept antibodies. However, the complexity and the small numbers of clinical cases, and the limited immunogenicity and belatacept concentration data taken around the time of the event of interest do not support a causal or temporal association between the development of anti-belatacept antibodies and any of these events.

In terms of mean and median belatacept clearance, there was no significant difference among seropositive, seronegative and indeterminate patients, as well as among neutralizing antibody (NAB)-positive and other patients.

Clinical Pharmacology Requests for Additional Trials
The following requests for additional trials as Post-Marketing Requirements were made by the Clinical Pharmacology review team.

Drug-Drug Interaction
Belatacept is an inhibitor of the production of cytokines and, in turn, may potentially affect mRNA expression and functional activities of hepatic CYP450 metabolizing enzymes. Thus, we recommend the sponsor investigate the safety/efficacy/dose regimen of additional medications which are metabolized through the hepatic CYP450 enzyme system and were co-administered with belatacept in ongoing clinical trials as well as in the previously conducted Phase 3 studies IM103008 and IM103027. Examples of such co-administered drugs are HMG-CoA reductase inhibitors (statins), anti-hypertensive drugs (beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB)), oral hypoglycemic drugs, triazole antifungal and anti viral drugs metabolized through CYP450. Depending on the results of these investigations, further studies may be needed to evaluate the effect of belatacept on concomitant medications which are metabolized through CYP450 enzymes.

Relationship between PLTD and CMV Serostatus
We recommend that future studies be designed to elucidate the differential risk of development of post-transplant lymphoproliferative disorders (PTLD) based on CMV serostatus in EBV seropositive kidney transplant recipients treated with belatacept.

CDTL Comment: The applicant has proposed a post-marketing study to further investigate the risk of PLTD in kidney transplant patients using the UNOS database. Information on CMV

*and EBV serostatus will be collected in this study (See **Section 13** for more information on the applicant's proposed PM studies).*

6. Clinical Microbiology

The applicant submitted *in vitro* and *in vivo* mechanism of action studies to the BLA. *In vitro* studies examined the effects of belatacept on T-cell proliferation, cytokine production, complement and antibody mediated cellular cytotoxicity, and receptor occupancy. *In vivo* studies included studies of kidney transplants and pancreas transplant in rhesus monkeys.

Additionally, issues related to (1) the development of PTLD and Epstein Barr virus (EBV) serostatus, and (2) belatacept effects on immune cells and function are discussed in the Clinical Microbiology reviews and summarized below. Finally, Clinical Microbiology has recommendations for testing EBV serostatus for inclusion in the product label.

Mechanism of action, in vitro studies

Effect on T-cells and autoimmunity

Belatacept IC_{50} values are lower than abatacept suggesting belatacept is a more active blocker than abatacept. Blocking CD28 signaling by belatacept will predominantly prevent activation of naïve T-cells, since memory T-cells are not entirely dependent on a CD28 costimulatory signal for activation. The effect of blocking CD28 interaction with CD80/CD86 expressed on thymic APCs could potentially lead to the escape of self-reactive T-cells or the inhibition of T_{reg} development and promote autoimmunity. This may be of higher importance in juvenile or young adult patients in whom the thymus is more active. However, in patients, the immunosuppressive drug regimen may suppress autoimmune effector mechanisms and autoimmunity may not be relevant. Autoimmunity in human patients in clinical trials has not been substantiated; however a theoretical risk may still exist in patients who discontinue immunosuppression (i.e. return to dialysis).

Effect on cytokine production

Belatacept decreased the production of IL-2, IL-4, IFN-γ and TNF-α in mixed lymphocyte reaction cultures of human peripheral blood T-cells and irradiated human B-cell line cells (PM-LCL). Effect were concentration dependent. Belatacept IC_{50} values required for CD86 occupancy appear to correlate with function. Overall, the results suggest that belatacept is more effective than abatacept in inhibiting cytokine production in response to alloantigen.

Effect on complement and antibody mediated cellular cytotoxicity

Belatacept does not mediate human complement-dependent cellular cytotoxicity and antibody dependent cellular toxicity; this could be due to the fact that the hinge region of the Fc portion (IgG1) of belatacept (b) (4)

Effect on receptor occupancy

Receptor occupancy by belatacept was evaluated using commercially available anti-CD86 antibodies that compete for CD86 receptor expressed on monocytes. Saturation of the receptors by belatacept occurred at a concentration of approximately (b) (4)

for CD80 and CD86, respectively. The saturation level of CD86 on the APC appears to correlate with the activity of belatacept in blocking T-cell response to stimulation in a mixed lymphocyte reaction. The clinical relevance of saturating or more proportionally inhibiting one receptor over another is unknown, but it may be informative to correlate the relative ratio of CD80/86 expression to clinical experience such as infection or acute rejection.

Mechanism of action, in vivo studies

Kidney transplant model

The activity of belatacept alone or as part of an immunosuppressive regimen was measured in a primate orthotopic transplant model. The rhesus monkeys underwent bilateral nephrectomy with the donor kidney anastomosed to the recipient vena cava (renal vein) and distal aorta (renal artery). Monkeys were treated with belatacept alone or in combination with mycophenolate mofetil (MMF) and steroids or basiliximab. The kidney graft survival was measured by serum creatinine, BUN and serum chemistries. Kidney allograft histology was conducted at the time of necropsy. Belatacept alone or in combination with MMF + steroids or basiliximab extended the survival of kidney allografts (Figure 3).

No detectable anti-donor antibody responses were reported in monkeys treated with albumin (control group) or those treated with basiliximab; however, the monkeys (2 per group) died by 8 days post-transplantation. None of the monkeys treated with belatacept alone or in combination with MMF+steroids or basiliximab developed antibodies until day 100 i.e., 30 days after the last dose. About 40 % of the monkeys developed antibodies between days 100 and 130. Similarly, in monkeys treated with belatacept + basiliximab about 40% of the monkeys developed anti-donor antibodies. In monkeys treated with MMF or steroids significant anti-donor antibodies were detected in about 80% of the monkeys by day 25. Overall the results suggest that belatacept is effective in prolonging graft survival and inhibiting the development of anti-donor antibodies.

In another experiment, the effect of 2 different (low and high) maintenance regimens of belatacept in combination with MMF, steroids and basiliximab was measured. Low and high maintenance regimens are similar in improving graft survival (except for one animal in the low maintenance group that showed survival >625 days) compared to the control group.

Pancreatic transplant model

The activity of belatacept + sirolimus + basiliximab as part of an immunosuppressive regimen was measured in a primate pancreatic transplant model. The rhesus monkeys underwent pancreatectomy and a week later were intra-hepatically implanted with allogeneic pancreatic cells by injecting into the colic vein. Allograft function was measured daily by glucose tolerance test (insulin and c-peptide production). Sirolimus + basiliximab were not effective in prolonging graft survival, whereas belatacept + sirolimus + basiliximab prolonged graft survival. Shortened graft survival in the control group (sirolimus + basiliximab) was associated with early (day 11) production of IFN- γ. In the group treated with belatacept + sirolimus + basiliximab, IFN- γ production was suppressed until day 185; IFN- γ production was restored about a month after discontinuation of therapy thereby indicating reversal of the effect of belatacept on T-cells.

Additional nonclinical observations
In an animal model of transplantation (which model was not located in review), the applicant stated that there was no effect of belatacept on lymphocyte count or its subsets.

Clinical microbiology, PTLD and EBV serostatus
Post-transplant lymphoproliferative disorder (PTLD) is described as an abnormal proliferation of lymphocytes following transplant and includes B-cell neoplasia and hyperplasia. Most cases of PTLD occur as the result of host immune failure to control progressive infection with Epstein Barr virus (EBV), a consequence of the impaired host T-cell immune responses that normally control the proliferation of EBV-infected B-cells. PTLD typically presents as a tumor consisting of B-cells (CD20+) which also test positive for EBV. Patients who test serologically negative for EBV antibodies prior to transplant and the initiation of immunosuppression are considered to be at a higher risk for PTLD. However PTLD has occurred in both EBV^+ and EBV^- recipients. The applicant recommends that only patients who test as serologically positive for EBV be treated with belatacept.

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 trial. PTLD developed in 16 patients, including 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. Neither of the 2 patients in the CsA arm developed CNS PTLD. Based on the clinical trial results, there was no association between EBV serostatus and development of CNS PTLD.

One of the limitations of EBV testing of samples from patients enrolled in the clinical trial is the variety of EBV serological tests employed by the different study centers involved in the clinical trials. Overall, 108 different assays were combined into 81 different panels and used in the clinical trials at 95 different laboratories. A majority of the testing was done at the site laboratories. Ninety-seven of the assays were noted as "FDA cleared" in the dataset provided by the sponsor. The sponsor provided product brochures for 31 of the assays and also provided the specificity and sensitivity of many of the assays as well. The performance of the assays was variable with some assays being less specific than others. The specificity of the IgG antibody based EBV tests in the 14 PTLD patients with known EBV status was ≥96% (for details see Dr. Ruhland's review).

To determine a current or active infection, a typical panel includes testing for IgM antibodies to EBV viral capsid antigen (VCA) or use the Paul-Bunnell heterophile antibody test. To determine past infection and convalescence, several assays are available and cleared by the FDA that test for IgG antibodies to VCA, EBV nuclear antigen (EBNA) and EBV early antigen (EA). IgG antibodies to VCA and EBNA persist for life in most people. IgG antibodies to EA may also be present, but this titer tends to decrease to an undetectable level within months of clearing the primary infection. Reappearance or rising titers of antibody to EA is indicative of reactivation of EBV if noted in the presence of clinical signs of disease.

False-positive antibody titer results may occur on the basis of cross-reactivity with several viruses (e.g. CMV, rubella, and adenovirus) and some parasites such as *Toxoplasma gondii*.

Since the risk of developing PTLD is life-threatening and irreversible, the Clinical Microbiology team recommends that EBV testing should be based on a panel of tests with high specificity that can detect IgG antibodies against VCA and EBNA to ensure a high positive predictive value. The Division consulted with the Center for Devices and Radiological Health (CDRH), Office of In Vitro Devices, regarding the appropriateness of the EBV assays. The CDRH microbiology reviewers, Mr. Peter Summers and Mr. Li Li, agreed with the Division's assessment and recommendation.

Clinical microbiology, immune response

- A lower incidence of anti-donor HLA antibodies was reported in patients in the belatacept regimen compared to the comparator arm. There was no correlation between the presence of anti-donor HLA antibodies and antibody mediated rejection.

- CD4 T-cells were isolated from a group of patients treated with belatacept and stimulated with a nonspecific mitogen, phytohemagglutinin, *in vitro* to measure lymphoproliferation. No significant changes over time in ATP levels following belatacept administration were observed for any of the subjects, and there was no correlation between the alteration in ATP levels and belatacept concentrations or clinical response.

- The effect of belatacept treatment on indoleamine-pyrrole 2, 3-dioxygenase (IDO) activity was measured in a small number of patients in study IM103100. IDO catalyzes the degradation of tryptophan, an essential amino-acid, and depletion of tryptophan may inhibit the growth of microbes and proliferation of T-cells. In the samples tested, there was no monitorable effect on IDO activity.

- Whole blood samples were collected from patients in three clinical trials. CD86 receptor occupancy was similar post dose in both short term (< 6 months) and long term (> 1 year) treatment groups post dose, but in blood samples collected just before the next dose, there was a higher CD86 occupancy in short term patients than the long term patients.

Clinical microbiology, conclusions and recommendations

The BLA is approvable pending an acceptable version of the labeling. Labeling should specify the increased risk of developing PTLD in EBV negative patients, and certain standards should be maintained for the testing EBV serostatus. The EBV tests used should be highly specific for IgG antibodies against VCA and EBNA antigens. These clarifications should be made in appropriate sections of the labeling so that the message goes to the prescribing physicians and the clinical microbiology laboratories responsible for EBV testing.

7. Clinical/Statistical - Efficacy

The efficacy portion of the BLA was reviewed by the Statistical Team. It was concluded that efficacy was demonstrated for the endpoint of biopsy proven acute rejection (BPAR), graft

loss, death or lost to follow-up at 12 months in the Phase 3 trials. The results of other efficacy endpoints pre-specified by the applicant demonstrated additional evidence of benefit. The Reviewer also noted the higher rate of PTLD in the belatacept groups compared to the CsA group and the results being mainly driven by the event of CNS PTLD. Given that the applicant is proposing to contraindicate the use of belatacept in EBV- patients and only recommend use in EBV+ patients, the Reviewer concludes that efficacy is still demonstrated when restricting the efficacy analyses to the EBV+ subgroup in the Phase 3 trials.

See complete review by Cheryl Dixon, Ph.D.

Statistical Issues and Endpoints

The co-primary endpoints in the Phase 3 trials (see **Section 1**) were agreed to in principle during protocol design and discussions between the applicant and the FDA. However, further clinical consideration has called into question the ability of these endpoints to prove the efficacy of belatacept.

First, the assessment of patient and graft survival was to be made based on showing that belatacept was non-inferior to CsA. Due to relatively high rates of patient and graft survival seen at 12 months and the choice of control regimen, an estimate of the size of the effect of CsA given the current standard regimen including induction, corticosteroids, and MMF on patient and graft survival is not easily estimated and therefore a NI margin can not be defined for this endpoint.

CDTL Comment: For these reasons, the endpoint of patient and graft survival in the belatacept trials was not viewed as a primary endpoint for the demonstration of efficacy by the Statistical/Clinical Reviewers; however, it was important secondary efficacy and safety endpoint.

Second, interpretation of differences with respect to renal function (GFR in general and the definition of the composite renal function endpoint) are confounded due to differential effects of the treatments on renal hemodynamics. CsA has a known toxicity profile that causes a decrease in GFR whereas belatacept does not have this hemodynamic effect. Thus, comparison of a treatment with a known toxicity to a treatment without this known toxicity does not necessarily prove the efficacy of the treatment without the known toxicity. Additionally, one component of the composite renal impairment endpoint was measured GFR < 60 mL/min/1.73 m^2 at Month 12 and recipients of ECD kidneys rarely achieve a GFR > 60 mL/min. Therefore, given the limitations of the composite renal impairment endpoint in the setting of incomparable renal hemodynamics across treatment groups and in the setting of a trial of ECD kidneys, it is difficult to understand the significance or relevance of this endpoint as an endpoint to prove efficacy of belatacept.

CDTL Comment: In fact, the majority of patients in all arms in IM103027 started out with GFRs less than 60 mL/min. As a result, the composite renal endpoint did not detect a significant difference between the belatacept and the CsA treatment groups despite a considerable difference in mean GFRs observed between these same groups.

Given the imbalance, then, in starting GFRs (post-transplantation once therapy was started) between the belatacept arms and the CsA control arms, due to incomparable renal hemodynamics, and the limitations of the composite renal endpoint in the setting of a trial of ECD kidneys, the composite renal endpoint was not viewed by the Statistical/Clinical Reivewers as a primary efficacy endpoint. However, because GFR remains an important measure of renal function, differences in mean GFR at Month 12 were given consideration both as a secondary efficacy endpoint and a safety endpoint.

Acute rejection has been the traditional endpoint used by the FDA for assessing the efficacy of other products for the indication of prophylaxis of rejection in kidney transplant recipients. However, the definition of AR used by the FDA is slightly different from that used by the applicant. The applicant defined AR as central biopsy proven rejection that was either clinically suspected by protocol defined reasons or clinically suspected by other reasons and treated. The FDA's traditional assessment of AR is based on any biopsy proven acute rejection (BPAR), regardless of the reason for performing the biopsy. Additionally, patients who experience graft loss, death, or are lost to follow-up are not considered as having a positive outcome (i.e. no rejection) and treated as failures in the analysis. Therefore, this endpoint has been referred to as the "efficacy failure" endpoint which is the composite of BPAR, graft loss, death, or lost to follow-up.

A non-inferiority margin of 20% was able to be justified from a data driven standpoint for an assessment of AR, as assessed by the applicant and as analyzed by the FDA, to allow for the demonstration of efficacy of belatacept.

CDTL Comment: A justification of the 20% NI margin for the AR endpoint was made on the basis of data from a trial of an IL-2 receptor antagonist plus MMF plus corticosteroids[4] and an estimate obtained from six other publications that CsA-based regimens are expected to result in a 15% rate of AR. See Statistical Review for a complete discussion of the methods and analysis.

Therefore, given the limitation in the ability to justify a non-inferiority margin for patient and graft survival at 12 months and the limitations regarding the use of the composite renal impairment endpoint, the Statistical/Clinical Reviewers used AR as traditionally assessed by the FDA (i.e., efficacy failure defined as BPAR, graft loss, death, or lost to follow-up) as the primary proof of efficacy of belatacept for both of the Phase 3 trials.

Both belatacept groups were non-inferior to CsA for the endpoint of biopsy proven acute rejection, graft loss, death, or lost to follow-up in both trials, based on a 20% non-inferiority margin. The rates of BPAR, graft loss, death, or lost to follow-up were 27.4%, 21.7%, and 16.7% in the belatacept MI, belatacept LI, and CsA groups respectively in IM103008; 33.7%, 29.1%, and 28.3%, respectively in IM103027. The upper bounds of the 97.3% confidence intervals about the difference (belatacept - CsA) were for IM103008: 19.8% for the belatacept

[4] Vincenti et al. Multicenter Trial Exploring Calcineurin Inhibitors Avoidance in Renal Transplantation. Transplantation 2001; 71:1282-7.

MI comparison and 13.7% for the belatacept LI comparison and for IM103027: 16.6% for the belatacept MI comparison and 11.9% for the belatacept LI comparison.

In IM103008, patient and graft survival was 95%, 96.5%, and 93.2% in the belatacept MI, belatacept LI, and CsA groups respectively. The patient and graft survival rates in IM103027, which evaluated extended criteria donor kidneys, were lower than those seen in IM103008 and are 85.9%, 88.6%, and 84.8% in the belatacept MI, belatacept LI, and CsA groups, respectively. The lower bounds of the 97.3% confidence interval about the difference between belatacept regimen and CsA were greater than -5% for all comparisons with the exception of the belatacept MI vs. CsA comparison in IM103027 which was -7.6%.

Mean GFR was substantially higher through 24 months among the belatacept treatment groups compared to the CsA group in both Phase 3 trials. Differences between the belatacept groups and CsA were seen at Month 1, the first measurable time point, and was maintained through 24 months. Due to the vasoconstrictive effects of CsA, it is unclear whether the higher GFRs observed among belatacept treated patients reflect a healthier kidney, more favorable renal hemodynamics, or both.

Primary Efficacy Results

Patient and Graft Survival

Patient and graft survival at 12 months is presented in **Table 5.** In Study IM103008, patient and graft survival at 12 months was 95%, 96.5%, and 93.2% in the belatacept MI, belatacept LI and CsA groups, respectively. The patient and graft survival rates were lower in Study IM103027 than those seen in IM103008; IM103027 evaluated recipients of ECD kidneys and rates are 85.9%, 88.6%, and 84.8% in the belatacept MI, belatacept LI and CsA groups, respectively. The lower bound of the 97.3% confidence interval about the difference between belatacept regimen and CsA was greater than -5% for all comparisons with the exception of the belatacept MI versus CsA comparison in Study IM103027 which was -7.6%. It should be noted that these results are slightly different than those presented by the Applicant since all patients with unknown survival status at Month 12 are treated as failures.

Table 5: Patient and Graft Survival at 12 months

Study		Belatacept MI	Belatacept LI	CsA
008	Surviving with a functioning graft	208/219 (95.0)	218/226 (96.5)	206/221 (93.2)
	Graft Loss	4 (0 died)	5 (1 died)	8 (1 died)
	Death w/ functioning graft	6	3	6
	Unknown status	1	0	1
	Difference from CsA (97.3% CI)	1.8 (**-3.6**, 7.2)	3.3 (**-1.8**, 8.4)	
027	Surviving with a functioning graft	158/184 (85.9)	155/175 (88.6)	156/184 (84.8)
	Graft Loss	17 (2 died)	16 (1 died)	20 (3 died)
	Death w/ functioning graft	6	4	5
	Unknown status	3	0	3
	Difference from CsA (97.3% CI)	1.1 (**-7.6**, 9.8)	3.8 (**-4.7**, 12.3)	

Source: Adapted from Tables 3 and 13, Statistical Review, BLA 125,288

Composite Renal Endpoint

The proportions of subjects meeting the composite renal impairment endpoint as well as the reasons for meeting the composite endpoint are presented in **Table 6**. The difference in the proportion of subjects meeting the composite endpoint was statistically significantly better for a belatacept versus CsA comparisons with the exception of the belatacept LI versus CsA comparison in Study IM103027. It should be noted that the analyses presented here are slightly different from that presented by the applicant in that subjects with missing measured GFR data for reasons other than death or graft loss are also included as failures of the endpoint. The conclusions drawn, however, are not different.

Table 6: Composite Measured GFR Endpoint

Study		Belatacept MI	Belatacept LI	CsA
008		(n=219)	(n=226)	(n=221)
	Composite endpoint	125 (57.1)	128 (56.6)	174 (78.7)
	Reason for meeting composite:			
	-M12 < 60 and Decrease ≥ 10 from M3 to 12	33	34	52
	-M12 < 60 only	58	58	92
	-Decrease ≥ 10 from M3 to M12 only	15	16	8
	-Imputed due to GL or death	9	8	14
	-Missing	10	12	8
	p-value	<0.0001	<0.0001	
027		(n=184)	(n=175)	(n=184)
	Composite endpoint	132 (71.7)	135 (77.1)	157 (85.3)
	Reason for meeting composite:			
	-M12 < 60 and Decrease ≥ 10 from M3 to 12	27	41	37
	-M12 < 60 only	71	64	83
	-Decrease ≥ 10 from M3 to M12 only	4	6	7
	-Imputed due to GL or death	22	19	24
	-Missing	8	5	6
	p-value	.0022	.0575	

Source: Adapted from Tables 4 and 14, Statistical Review, BLA 125,288

Acute Rejection

Table 7 summarizes the incidence of AR, as defined by the applicant, at 12 months. Noninferiority of all belatacept regimens to CsA based on a NI margin of 20% was shown, as demonstrated by an upper bound of the 97.3% confidence interval (CI) of less than 20%, with the exception of the belatacept MI regimen in Study IM103008.

However, it should also be noted that there were numerically more ARs in the belatacept-treated subjects than in the CsA-treated subjects. In Study IM103008 for both the belatacept regimens the lower bound of the 97.3% CI was above zero, indicating a significant increase in the number of ARs compared to CsA. In addition, the severity of rejection was greater in the belatacept groups, which will be discussed further in the safety discussion (see **Section 8**).

Table 7: Acute Rejection (as Defined by the Applicant) at 12 months

Study		Belatacept MI	Belatacept LI	CsA
008	Acute Rejection	49/219 (22.4)	39/226 (17.3)	16/221 (7.2)
	Mild IA	7	4	3
	Mild IB	3	8	5
	Moderate IIA	17	16	6
	Moderate IIB	20	10	2
	Severe III	2	1	0
	Difference from CsA (97.3% CI)	15.2 (7.4, **23.0**)	10.1 (2.9, **17.3**)	
027	Acute Rejection	33/184 (17.9)	31/175 (17.7)	26/184 (14.1)
	Mild IA	0	4	2
	Mild IB	7	2	2
	Moderate IIA	10	17	17
	Moderate IIB	16	8	5
	Severe III	0	0	0
	Difference from CsA (97.3% CI)	3.8 (-5.2, **12.8**)	3.6 (-5.5, **12.7**)	

Source: Adapted from Tables 5 and 15, Statistical Review, BLA 125,288

As discussed previously, the Clinical and Statistical Reviewers felt there were limitations with the applicant's evaluation of AR, specifically that events of death, graft loss, or loss to follow up were imputed as successes. Therefore, the FDA also conducted another analysis of AR through the traditional combined endpoint of BPAR, graft loss, death or lost to follow-up.

The results of the FDA's composite endpoint analysis using the FDA definition of BPAR are presented in **Table 8**. Of note, a similar analysis to that in **Table 8** was also conducted using the applicant's definition of AR and similar results were obtained (data not shown). Using a margin of 20%, NI of all belatacept regimens to CsA for the FDA endpoint was shown. While the upper limit of the 97.3% CI for the LI arms is 13.7% and 11.9% for the two studies and thus each trial meets the 20% margin, the upper bound of the CI for the belatacept MI arm in IM103008 was essentially 20%.

Table 8: FDA's Analysis of Biopsy Proven Acute Rejection, Graft Loss, and Death at 12 Months

Study		Belatacept MI	Belatacept LI	CsA
008	Met Endpoint	60/219 (27.4)	49/226 (21.7)	37/221 (16.7)
	Biopsy Proven Acute Rejection	52	45	23
	Graft Loss	3	3	7
	Death	4	1	6
	Unknown	1	0	1
	Difference from CsA (97.3% CI)	10.7 (1.6, **19.8**)	5.0 (-3.7, **13.7**)	
027	Met Endpoint	62/184 (33.7)	51/175 (29.1)	52/184 (28.3)
	Biopsy Proven Acute Rejection	40	37	34
	Graft Loss	14	11	12
	Death	6	3	5
	Unknown	2	0	1
	Difference from CsA (97.3% CI)	5.4 (-5.8, **16.6**)	0.8 (-10.3, **11.9**)	

*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 death.

Source: Adapted from Tables 6 and 16, Statistical Review, BLA 125,288

Additional Efficacy Results

GFR measured at Month 12

Measured GFR at Month 12 was significantly higher for both belatacept regimens compared to CsA in Study IM103008 as shown in **Table 9**. In the trial of ECD kidneys, Study IM103027, measured GFR at Month 12 was higher for belatacept treated patients compared to CsA but the finding was statistically significant only for the belatacept MI versus CsA comparison.

Table 9: Measured GFR at Month 12

Study		Belatacept MI	Belatacept LI	CsA
008	Mean (sd) at Month 12	65.0 (30.0)	63.4 (27.7)	50.4 (18.7)
	# in analysis	200	206	199
	Difference from CsA (97.3% CI)	14.6 (8.9, 20.4)	13.0 (7.3, 18.7)	
	p-value	<0.0001	<0.0001	
027	Mean (sd) at Month 12	52.1 (21.9)	49.5 (25.8)	45.2 (21.1)
	# in analysis	154	151	154
	Difference from CsA (97.3% CI)	6.9 (1.1, 12.7)	4.3 (-1.5, 10.2)	
	p-value	0.0089	0.0995	

Source: Adapted from Tables 7 and 17, Statistical Review, BLA 125,288

As noted previously, similar differences were also detected as early as 1 month after transplantation. These early differences may reflect hemodynamic (rather than structural) differences due to the vasoconstrictive effects of CsA on the renal artery. The CsA group likely received less renal blood flow, resulting in lower GFR.

Impact of AR on GFR

In order to determine the impact of the difference in the number and severity of AR events, analyses of calculated GFR at 12 months by rejection status were conducted. This analysis was conducted because it has been suggested that recovery of GFR following an episode of aR correlates with better longer term graft outcomes. Analyses based on recovery of GFR to baseline could not be performed since many of the AR episodes occurred early in the trial before a true baseline GFR could be established. **Table 10** presents the mean calculated GFR at 12 months for patients who experienced an epidose of AR and for those who didn't. In patients with AR and in subjects without AR, mean calculated GFR was higher in the belatacept groups than in the CsA group. Mean calculated GFR was lower for patients who experienced an episode of AR compared to those who did not experience an episode of AR. The differences in calculated GFR for those who did and did not experience AR were greatest for belatacept treated patients.

Interpretation of these analyses should be made with caution because of limitations in the data due to the following reasons: missing GFR at 12 months for some patients even with applying imputation; not all patients remained on study therapy for the entire 12 months and those who didn't may have switched to a regimen containing a CNI; and these subsets of patients are based on an outcome variable that is affected by treatment.

Table 10: Calculated GFR at 12 Months by Acute Rejection Status at 12 Months

Study	Acute Rejection Status by Month 12		Belatacept MI	Belatacept LI	CsA
008	AR	Mean (sd) at Month 12	58.2 (23.3)	48.0 (21.6)	44.3 (17.8)
		95% CI	(51.5, 64.9)	(41.0, 55.0)	(34.8, 53.8)
		# in analysis	49	39	16
	No AR	Mean (sd) at Month 12	66.2 (23.0)	67.7 (21.7)	49.8 (21.5)
		95% CI	(62.7, 69.7)	(64.5, 70.9)	(46.8, 52.7)
		# in analysis	170	184	203
027	AR	Mean (sd) at Month 12	36.1 (17.0)	38.9 (20.5)	25.2 (18.8)
		95% CI	(30.0, 42.1)	(31.4, 46.5)	(17.6, 32.8)
		# in analysis	33	31	26
	No AR	Mean (sd) at Month 12	44.3 (22.7)	45.0 (21.5)	37.6 (20.3)
		95% CI	(40.7, 48.0)	(41.4, 48.5)	(34.4, 40.7)
		# in analysis	150	144	158

Missing GFR at 12 months imputed as 0 if graft loss or death within first 12 months and last observation carried forward otherwise.
Source: Table 10, Statistical Review, BLA 125,288

Efficacy Results by Subgroups of Age/Gender/Race

Results of patient and graft survival at 12 months, biopsy proven acute rejection, graft loss, death, or lost to follow-up at 12 months, and measured GFR at 12 months are presented by gender, age, and race in **Tables 11, 12 and 13**, respectively, for both Phase 3 trials. For many of the subgroups, the results should be interpreted with caution due to small sample sizes. In IM103008, results for gender are fairly consistent with those seen for the overall population with the exception of female CsA patients who have slightly worse patient and graft survival at 12 months and higher biopsy proven acute rejection, graft loss, death, or loss to follow-up at 12 months compared to belatacept females and their male CsA counterparts. In IM103027, female belatacept patients have lower patient and graft survival at 12 months and higher

biopsy proven acute rejection, graft loss, death, or loss to follow-up at 12 months than female CsA patients. In IM103008, there were too few patients ≥ 65 to make and meaningful comparisons with respect to age groups. In IM103027, patient and graft survival is slightly lower for patients ≥ 65 than patients < 65. There appears to be a larger difference between age groups for the belatacept LI group than the belatacept MI and CsA groups and belatacept LI patients ≥ 65 have the lowest patient and graft survival at 12 months.. Biopsy proven acute rejection, graft loss, death, or lost to follow-up at 12 months is fairly similar between age groups for the belatacept MI and CsA groups but is greatest for patients ≥ 65 in the belatacept LI group. As for measured GFR at 12 months, older patients tend to have lower GFR but the difference between treatment groups is consistent for both age groups. In general where the sample sizes are sufficient, the results for race are consistent with those seen for the overall population.

Table 11: Patient and Graft Survival at 12 Months By Gender, Age, and Race IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	**Gender**			
	Male	144/151 (95.4) 2 GL, 4 Died, 1 missing	140/146 (95.9) 4 GL, 2 Died	156/165 (94.6) 5 GL, 5 Died*
	Female	64/68 (94.1) 2 GL, 2 Died	78/80 (97.5) 1 GL, 2 Died*	50/56 (89.3) 3 GL, 2 Died, 1 missing
	Age			
	< 65	193/200 (96.5) 4 GL, 2 Died, 1 missing	208/216 (96.3) 5 GL, 4 Died*	195/209 (93.3) 7 GL, 7 Died*, 1
	≥ 65	15/19 (79.0) 4 Died	10/10 (100.0) -	missing 11/12 (91.7) 1 GL
	Race			
	White	123/132 (93.2) 4 GL, 5 Died	130/133 (97.7) 1 GL, 2 Died	130/139 (93.5) 6 GL, 4 Died*
	Black	15/15 (100.0) -	22/23 (95.7) 1 Died	16/17 (94.1) 1 GL
	Asian	26/27 (96.3) 1 Died	27/29 (93.1) 2 GL	27/27 (100.0) -
	Others	44/45 (97.8) 1 missing	39/41 (95.1) 2 GL, 1 Died*	33/38 (86.8) 1 GL,3 Died, 1 missing
027	**Gender**			
	Male	103/119 (86.6) 9 GL, 5 Died*, 3 missing	117/129 (90.7) 9 GL, 4 Died*	96/116 (82.8) 15 GL, 5 Died**, 3
	Female	55/65 (84.6) 8 GL, 3 Died*	38/46 (82.6) 7 GL, 1 Died	missing 60/68 (88.2) 5 GL, 3 Died
	Age			
	< 65	106/120 (88.3) 11 GL, 3 Died*, 1 missing	116/125 (92.8) 9 GL, 1 Died*	109/126 (86.5) 13 GL, 4 Died*, 1
	≥ 65	52/64 (81.3) 6 GL, 5 Died*, 2 missing	39/50 (78.0) 7 GL, 4 Died	missing 47/58 (81.0) 7 GL, 4 Died^, 2 missing
	Race			
	White	115/137 (83.9) 14 GL, 7 Died^, 3 missing	118/134 (88.1) 12 GL, 5 Died*	118/137 (86.1) 14 GL, 6 Died**, 2
	Black	21/25 (84.0) 3 GL, 1 Died	21/24 (87.5) 3 GL	missing 17/22 (77.3)
	Others	21/21 (100.0) -	16/17 (94.1) 1 GL	3 GL, 2 Died 21/25 (84.0) 3 GL, 1 missing

*Includes 1 patient who experienced GL prior to death
^Includes 2 patients who experienced GL prior to death
**Includes 3 patients who experienced GL prior to death
Source: Table 30, Statistical Review of BLA 125,288 by Cheryl Dixon, Ph.D.

Table 12: Biopsy Proven Acute Rejection, Graft Loss, Death, or Lost to Follow-up at 12 Months By Gender, Age, and Race IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	**Gender**			
	Male	45/151 (29.8)	33/146 (22.6)	24/165 (14.6)
	Female	15/68 (22.1)	16/80 (20.0)	13/56 (23.2)
	Age			
	< 65	55/200 (27.5)	45/216 (20.8)	35/209 (16.8)
	≥ 65	5/19 (26.3)	4/10 (40.0)	2/12 (16.7)
	Race			
	White	43/132 (32.6)	32/133 (24.1)	27/139 (19.4)
	Black	5/15 (33.3)	5/23 (21.7)	2/17 (11.8)
	Asian	2/27 (7.4)	5/29 (17.2)	1/27 (3.7)
	Others	10/45 (22.2)	7/41 (17.1)	7/38 (18.4)
027	**Gender**			
	Male	45/119 (37.8)	36/129 (27.9)	35/116 (30.2)
	Female	17/65 (26.2)	15/46 (32.6)	17/68 (25.0)
	Age			
	< 65	41/120 (34.2)	31/125 (24.8)	34/126 (27.0)
	≥ 65	21/64 (32.8)	20/50 (40.0)	18/58 (31.0)
	Race			
	White	52/137 (38.0)	42/134 (31.3)	36/137 (26.3)
	Black	8/25 (32.0)	8/24 (33.3)	9/22 (40.9)
	Others	2/21 (9.5)	1/17 (5.9)	7/25 (28.0)

Source: Table 31, Statistical Review of BLA 125,288 by Cheryl Dixon, Ph.D.

Table 13: Measured GFR at 12 Months By Gender, Age, and Race IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	**Gender**			
	Male	63.1 (29.7) n=137	62.6 (27.3) n=131	50.0 (18.9) n=150
	Female	69.0 (30.6) n=63	64.7 (28.4) n=75	51.6 (18.2) n=49
	Age			
	< 65	64.3 (29.3) n=186	63.6 (27.8) n=200	50.6 (18.6) n=188
	≥ 65	74.7 (38.6) n=14	57.5 (24.7) n=6	46.6 (21.1) n=11
	Race			
	White	64.7 (30.1) n=114	63.1 (28.6) n=121	51.2 (18.7) n=124
	Black	70.3 (27.1) n=15	63.0 (18.1) n=21	51.1 (16.8) n=16
	Asian	46.7 (32.6) n=26	59.9 (40.6) n=26	35.3 (15.9) n=26
	Others	74.4 (24.7) n=45	66.8 (16.5) n=38	58.7 (15.0) n=33
027	**Gender**			
	Male	49.9 (20.9) n=99	51.0 (27.6) n=113	43.7 (19.7) n=96
	Female	56.0 (23.2) n=55	45.2 (19.1) n=38	47.8 (23.1) n=58
	Age			
	< 65	51.7 (20.9) n=103	50.8 (22.6) n=113	47.4 (21.5) n=108
	≥ 65	52.9 (24.0) n=51	45.8 (33.5) n=38	40.1 (19.3) n=46
	Race			
	White	49.9 (22.6) n=112	49.6 (25.7) n=115	43.7 (19.9) n=117
	Black	61.4 (18.9) n=21	50.7 (29.5) n=20	50.2 (21.7) n=17
	Others	54.0 (19.1) n=20	47.8 (22.8) n=16	49.7 (26.6) n=20

Source: Table 32, Statistical Review of BLA 125,288 by Cheryl Dixon, Ph.D.

Efficacy Results by EBV Serostatus

Analyses by EBV serostatus were conducted for the endpoints of patient and graft survival at 12 months; BPAR, graft loss, death, or lost to follow-up at 12 months; and measured GFR at 12 months. Treatment comparisons are presented in **Tables 14, 15 and 16**, respectively, for the EBV+ group only since this is the population of patients for which belatacept is being considered. In IM103027, there is one belatacept MI patient who had unknown EBV status and is not presented in any of the tables. The conclusions drawn for the EBV+ patients are similar to those drawn for the overall population.

Table 14: Patient and Graft Survival at 12 months by EBV Serostatus

Study			Belatacept MI	Belatacept LI	CsA
008	EBV+	Surviving with a functioning graft	184/194 (94.8)	195/199 (98.0)	170/184 (92.4)
		Graft Loss	3	1	7 (1 died)
		Death w/ functioning graft	6	3	6
		Unknown status	1	0	1
		Difference from CsA (97.3% CI)	2.4 (**-3.7**, 8.5)	5.6 (**0.2**, 11.0)	
	EBV-	Surviving with a functioning graft	24/25 (96.0)	23/27 (85.2)	36/37 (97.3)
		Graft Loss	1	4 (1 died))	1
		Death w/ functioning graft	0	0	0
		Unknown status	0	0	0
027	EBV+	Surviving with a functioning graft	144/169 (85.2)	139/156 (89.1)	143/168 (85.1)
		Graft Loss	17 (2 died)	14 (1 died)	19 (3 died)
		Death w/ functioning graft	5	3	4
		Unknown status	3	0	2
		Difference from CsA (97.3% CI)	0.1 (**-9.1**, 9.3)	0.4 (**-4.8**, 12.8)	
	EBV-	Surviving with a functioning graft	13/14 (92.9)	15/19 (78.9)	13/16 (81.3)
		Graft Loss	0	2	1
		Death w/ functioning graft	1	1	1
		Unknown status	0	1	1

Source: Table 36, Statistical Review, BLA 125,288

Table 15: Biopsy Proven Acute Rejection, Graft Loss, Death at 12 months By EBV Serostatus

Study			Belatacept MI	Belatacept LI	CsA
008	EBV+	Met Endpoint	57/194 (29.4)	42/199 (21.1)	31/184 (16.8)
		Biopsy Proven AR	49	40	18
		Graft Loss	3	1	6
		Death	4	1	6
		Unknown	1	0	1
		Diff from CsA (97.3% CI)	12.6 (2.6, **22.6**)	4.3 (-5.0, **13.7**)	
	EBV-	Met Endpoint	3/25 (12.0)	7/27 (25.9)	6/37 (16.2)
		Biopsy Proven AR	3	5	5
		Graft Loss	0	2	1
		Death	0	0	0
		Unknown	0	0	0
027	EBV+	Met Endpoint	57/169 (33.7)	45/156 (28.8)	47/168 (28.0)
		Biopsy Proven AR	36	32	31
		Graft Loss	14	10	11
		Death	5	3	4
		Unknown	2	0	1
		Diff from CsA (97.3% CI)	5.7 (-6.0, **17.4**)	0.8 (-10.9, **12.5**)	
	EBV-	Met Endpoint	5/14 (33.7)	6/19 (31.6)	5/16 (31.3)
		Biopsy Proven AR	4	5	3
		Graft Loss	0	1	1
		Death	1	0	1
		Unknown	0	0	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 37, Statistical Review, BLA 125,288

Table 16: Measured GFR at Month 12
By EBV Serostatus

Study			Belatacept MI	Belatacept LI	CsA
008	EBV+	Mean (sd) at Month 12	67.3 (30.0)	64.7 (27.9)	51.7 (18.1)
		# in analysis	177	183	165
		Diff from CsA (97.3% CI)	15.6 (9.3, 21.8)	13.0 (6.8, 19.2)	
		p-value	<0.0001	< 0.0001	
	EBV-	Mean (sd) at Month 12	47.5 (24.4)	52.8 (23.8)	43.9 (20.4)
		# in analysis	23	23	34
027	EBV+	Mean (sd) at Month 12	51.5 (20.7)	48.5 (25.5)	45.2 (20.7)
		# in analysis	141	135	140
		Diff from CsA (97.3% CI)	6.3 (0.4, 12.2)	3.3 (-2.7, 9.3)	
		p-value	0.0184	0.2250	
	EBV-	Mean (sd) at Month 12	59.3 (33.9)	58.7 (27.5)	45.4 (25.2)
		# in analysis	12	16	14

Source: Table 38, Statistical Review, BLA 125,288

Summary of Efficacy

Non-inferiority based on a 20% non-inferiority margin, of both belatacept regimens to CsA was demonstrated for BPAR, graft loss, death, or lost to follow-up at 12 months. If a smaller margin were to be deemed more appropriate from a clinical standpoint, then the belatacept LI comparison to CsA in both Phase 3 trials would make a 15% margin. The results of this endpoint constitute the proof of efficacy for belatacept.

There were similar rates of patient and graft survival at 12 month between the belatacept regimens and CsA in both trials. In IM103008, the rates of patient and graft survival at 12 months were 93 to 96%. In IM103027, the rates were slightly lower, 85 to 88%, but as may be expected for a trial of ECD kidneys. The lower bounds of the confidence interval about the difference in the rate of patient and graft survival (belatacept- CsA) were all greater than -5% with the exception of the belatacept MI vs. CsA comparison in IM103027 which was -7.6%.

The difference in the proportion of patients meeting the composite renal impairment endpoint was statistically significantly less for belatacept compared to CsA with the exception of the belatacept LI vs. CsA comparison in IM103027. The trend however was in favor of belatacept LI.

There were numerically more patients who experienced AR by 12 months in belatacept-treated patients than in CsA-treated patients. The severity of rejection was also more severe in the belatacept groups. (See additional discussion in **Section 8** below.)

The mean measured GFR at 12 months in the belatacept-treated patients was higher (13 to 14 mL/min in IM103008 and 4 to 7 mL/min in IM103027) than in CsA-treated patients. Additionally, calculated GFR was higher for belatacept treated patients starting at the first measureable time point and was maintained through 24 months.

The results for patient and graft survival at 12 months; BPAR, graft loss, death, or lost to follow-up at 12 months; and measured GFR at 12 months are consistent for the EBV+ subgroup as compared to the overall population.

8. Safety

The safety portion of the BLA was reviewed by the Medical Officer (MO), who also evaluated the efficacy in conjunction with the Statistical Reviewer. The MO concluded that substantial evidence of the effectiveness of belatacept was demonstrated through an examination of the FDA's composite efficacy endpoint in the two randomized Phase 3 trials. However, it was also noted that while belatacept has efficacy as an immunosuppressant, it may not be as effective as the comparator drug, CsA, for the prevention of acute rejection episodes at the doses tested: while the belatacept groups met a scientifically justified NI margin of 20%, patients receiving belatacept experienced both numerically more events of AR and higher grades of AR. From a clinical point-of-view, the potential loss of efficacy was an important consideration, but not necessarily a contraindication to approval: 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.

Supportive evidence of the efficacy of belatacept was also provided from additional endpoints from the pivotal Phase 3 kidney transplant trials. The data showed that more patients on belatacept regimens than cyclosporine regimens were alive with a functioning graft at 12 and 24 months. The data also showed that patients on belatacept regimens had higher mean GFRs and similar preservation of GFR at 12 and 24 months. The findings were consistent with the substantial evidence of the effectiveness of belatacept provided by analysis of the endpoint based on AR.

The relative safety of belatacept, compared to that of CsA, was performed by the MO by evaluating both pre-specified endpoints and observed safety signals. Belatacept was associated with higher rates and grades of AR, with a higher incidence of post-transplant lymphoproliferative disorder (PTLD) – particularly among EBV- patients and with a preponderance of central nervous system (CNS) presentations, and with the development of progressive multifocal leukoencephalopathy (PML).

On the other hand, patients maintained on belatacept avoided the toxic effects of cyclosporine on GFR, blood pressure, lipids, and glucose. Differences in GFR for the belatacept regimens compared to CsA were apparent in the first month after transplant and maintained up to 24 months (the latest time point of the study for which complete follow-up on all patients was available by the 120-day safety update for the BLA submission). Slopes of the calculated GFR curves from Month 3 (the time when post-transplant GFR appeared to stabilize) to Month 24 were calculated. For the CsA group, the slope was -1.88 mL/min/1.73m^2/year indicating a slight annual decline in renal function. For the belatacept regimens, the slopes were also negative but to a lesser extent (-0.93 mL/min/1.73m^2/year for belatacept LI). Mean systolic and diastolic blood pressures were significantly lower for patients in both belatacept groups relative to the CsA group in both trials. Mean non-HDL cholesterol and mean triglyceride levels at Month 12 were significantly lower for patients in both belatacept groups relative to the CsA group in both trials. The differences in non-HDL cholesterol between the belatacept and CsA groups appeared to be driven by the contribution of triglycerides, as the LDL levels at Month 12 were more similar across groups. New onset diabetes after transplant (NODAT) was defined in the trials 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. Numerically fewer belatacept treated patients compared to CsA treated patients developed NODAT (5% in the belatacept LI patients compared to 10% in the CsA patients).

The analysis of PLTD in the belatacept clinical trials was performed by the MO. Additional supplemental analyses of the rate of PLTD in previous NDA trials and transplant registries was performed by the Safety Statistical Team, in consultation with the MO.

The MO recommended that 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 patients receiving a kidney transplant in combination with basiliximab induction and mycophenolate mofetil and corticosteroid maintenance immunosuppression. Belatacept should be contraindicated among kidney transplant recipients who are EBV- at the time of transplantation due to the increased risk of PTLD observed in this population and that this information should be included in the Boxed Warning of the package insert. Finally, the MO agrees that a REMS in necessary to ensure safe use of the drug (as discussed in Section 9).

(b) (4)

See complete review by Patrick Archdeacon, M.D.

The following is a more detailed discussion of the more serious adverse events noted in the clinical trials, including deaths, PTLD, and PML.

Deaths

Due to the differences in the LI regimen between the Phase 2 and Phase 3 trials, only the deaths reported in the Phase 3 trials are shown in the table below.

The observed rates of death in both Phase 3 trials were similar across treatment groups and the causes of death appeared to be mainly due to cardiovascular or infectious causes, similar to what is expected in a kidney transplant population. The results support that kidney transplant patients maintained on either the belatacept MI or LI regimens had similar mortality outcomes at 24 months to the CsA control regimen, even among a patient population which included EBV- recipients and despite the impact of the imbalance in PTLD presentations across treatment groups (see **Table 17**).

Table 17: Deaths Occurring in the Phase 3 Trials

	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						
Up to Month 12	6 (2.7)	4 (1.8)	7 (3.2)	8 (4.3)	5 (2.9)	8 (4.3)
Up to Month 24	7* (3.2)	8† (3.5)	13 (5.9)	13 (7.1)	11‡ (6.3)	12 (6.5)
Through Safety Update Report	7* (3.2)	9† (4.0)	14 (6.3)	19 (10.3)	13‡ (7.4)	16 (8.7)

PTLD patient = patient diagnosed with PTLD at any time during trial
* = 3 PTLD patients alive at 24 months and at SUR
† = 2 PTLD patients alive at 24 months and at SUR
‡ = 3 PTLD patients alive at 24 months and at SUR; Note: Two of the three patients in the belatacept LI treatment group of Study IM103027 with PTLD diagnoses who were alive at 24 months of follow up and at SUR have since died (PID 27-10-10029 and PID 27-138-10593, both in June 2009). All other patients in the Phase 3 studies who were alive at 24 months of follow up with PTLD diagnoses are still alive.
Source: Table 24 in the Medical Officer review, BLA 125,288

PTLD

Post transplant lymphoproliferative disorder (PTLD) was found to be observed at an increased frequency in the belatacept groups in the 3 core belatacept trials (IM103008, IM103027, and IM103100). PTLD is a composite term encompassing the following MedDRA preferred terms: lymphoproliferative disorder, hematological malignancy, lymphoma, CNS lymphoma, hepatosplenic t-cell lymphoma, EBV-associated lymphoproloferative disorder, and b-cell lymphoma.

Up to 14-Dec-2009, there were 8 cases (1.7%) of PTLD in the belatacept MI group, 6 cases (1.3%) in the belatacept LI group, and 2 cases (0.4%) in the CsA group. Nine of the 16 cases presented with CNS involvement (6 belatacept MI, 3 belatacept LI and 0 CSA). The distribution of PTLD cases across the trials was as follows:

- IM103008: 3 belatacept MI, 2 belatacept LI, and 1 CsA
- IM103027: 2 belatacept MI, 4 belatacept LI, and 0 CsA
- IM103100: 3 belatacept MI, 0 belatacept LI, and 1 CsA.

An additional two patients out of 146 treated with belatacept in a Phase 2 study of liver transplant patients have also developed PTLD within the allograft compared to none out of 100 in the control groups.

EBV- serostatus of the recipient is a known and the most significant risk factor for the development of PTLD. **Table 18** summarizes the PLTD cases observed in the belatacept core trials by recipient EBV status and CNS or non-CNS involvement. While EBV- patients make up 12% of the trial population across the belatacept treatment groups, half of the PTLD cases were in EBV-negative patients.

Table 18: Summary of PTLD Cases IM103008, IM103027, and IM103100

Trial	Belatacept MI (N=477) EBV+ (n=404)	Belatacept MI (N=477) EBV- (n=45)	Belatacept MI (N=477) EBV Unknown (n=28)	Belatacept LI* (N=472) EBV+ (n=401)	Belatacept LI* (N=472) EBV- (n=51)	Belatacept LI* (N=472) EBV Unknown (n=20)	CsA (N=478) EBV+ (n=399)	CsA (N=478) EBV- (n=57)	CsA (N=478) EBV Unknown (n=22)
IM103100									
CNS PTLD		$2^{\Omega,\dagger}$							
Non-CNS PTLD			$1^{\dagger}$						$1^{\ddagger}$
IM103008									
CNS PTLD	1^{Ω}	1^{Ω}							
Non-CNS PTLD		1^{Ω}		$2^{\Omega,\Omega}$				$1^{\ddagger}$	
IM103027									
CNS PTLD	$1^{\dagger}$	$1^{\dagger}$		$2^{\Omega,\dagger}$	$1^{\ddagger}$				
Non-CNS PTLD					$1^{\ddagger}$				
Total	*2 (0.5)*	*5 (11.1)*	*1 (3.6)*	*4 (1.0)*	*2 (3.9)*	*0*	*0*	*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 24 months; ‡ = Patient died after first 24 months
Source: Table 33 in the Medical Officer review, BLA 125,288

Other than perhaps the overall incidence, the preponderance of CNS involvement among the kidney transplant recipients who received belatacept constitutes the most striking aspect of the PTLD presentations. Adverse events associated with CNS presentation included seizures, hemiparesis, aphasia, cognitive dysfunction, and behavioral changes. PTLD involving the CNS typically is a rare event among kidney transplant patients. For example, a retrospective analysis of 1,094 post- transplant lymphomas reported to the Collaborative Transplant Study registry, for instance, reported involvement of the CNS in only 11.7% of cases.[5] In contrast, nine out of fourteen (or 64.3%) of the PTLD cases observed in belatacept groups from the three kidney trials involved the CNS.

The unusual pattern of PTLD presentations provides additional context to other CNS-related signals detected in the belatacept clinical development program, such as the two isolated cases of PML and the seven CNS infections distributed across the belatacept MI groups in IM103100, IM103008, and IM103027 (including three cases of cryptococcal meningitis, one case of West Nile Virus, one case of cerebral aspergillosis, one case of neurological herpes zoster, and one of the PML cases) compared to only one event among the belatacept LI groups (cryptococcal meningitis) and one event among the CsA groups (also cryptococcal meningitis).

The incidence of PLTD in EBV+ patients in the belatacept clinical trials was calculated in person-years (PYs) in order to allow for comparison to registry data (as discussed further below). Given an incidence/PY of 0.0035 of the pooled data from the belatacept MI and LI regimens and of 0.0 in the CsA regimen from studies 008, 027 and 100, the estimated number needed to harm (NNTH) of 145 (95% CI: -532, 64) patients (see **Table 19**). This suggests that for every 145 EBV+ patients treated with a belatacept-based regimen instead of a CsA-based

[5] Opelz G. Döhler, B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Amer J of Transplantation 2003; 4: 222-30.

regimen for two years, one would expect at least one additional case of PTLD. The range for this NNTH suggests that as few as 63 belatacept patients to as many as 532 CsA patients need to be treated for two years to expect at least one case of PTLD. Similar results w when comparing belatacept LI alone vs. CsA and MI alone vs. CsA.

Table 19: Estimated Number Needed to Harm in EBV+ Patients Based on Incidence of PTLD: Belatacept Trials 008, 027 and 100

EBV+	Belatacept LI and MI	Belatacept LI	Belatacept MI	CsA
Incidence/PY	0.0035	0.0041	0.0028	0.0000
ARRI (vs CsA)	0.0069	0.0082	0.0056	NA
2-YR NNTH	144.7	122.0	178.8	NA
95% CI NNTH	-531.6, 63.7	-726.0, 56.3	-431.7, 74.1	NA

PY=person-year
AARI: annualized absolute risk increase (events $_{belatacept}$/(person-yrs $_{belatacept}$/2)-events $_{CsA}$ /(person-yrs $_{CsA}$ /2) (assumes constant risk)
NNTH: 1/AARI
Source: Table 35 in the Medical Officer review, BLA 125,288

Risk of PTLD – Analyses from Belatacept Clinical Trials, Transplant Registries and Other NDAs

The applicant acknowledged that the overall risk of PTLD appeared higher in the belatacept-treated patients compared to the CsA control patients in the clinical trials: 13 out of 949 patients (1.4%) receiving belatacept developed PTLD compared to 2 out of 478 patients (0.4%) receiving CsA. They also suggested that the increased risk is restricted to patients who are EBV- at baseline. However, in the EBV+ subpopulation in the clinical trials, there were 4 cases of PTLD in the belatacept-treated patients compared to no cases in the CsA-treated patietns. Finally, the applicant concluded that the risk of PTLD in EBV+ patients is similar to the incidence of PTLD in EBV+ patients derived using data from the United Network for Organ Sharing (UNOS) through the United States Renal Data System (USRDS). Therefore, a Safety Statistics analysis was conducted by Reviewers in the Division of Biometric VII in order to obtain a more accurate point estimate of the expected rate of PTLD, by EBV status, among *de novo* kidney transplant recipients using data from previously submitted New Drug Applications (NDAs) and kidney transplant registry data from the United Network for Organ Sharing (UNOS) through the United States Renal Data System (USRDS).

See complete review by Anita Abraham, MS, DrPH.

The Statistical Reviewer concludes that when considering all the evidence that has been analyzed from the CsA control arms, other similarly-designed randomized clinical trials that included a CsA-based immunosuppressant regimen, and kidney transplant registry data it is apparent that there is an increased risk of PTLD in belatacept treated patients and that this increase was found in both EBV negative and positive subgroups.

In the studies submitted by the applicant, to date, there have been eight (1.7%), six (1.3%) and two (0.4%) reported cases of PTLD in the belatacept MI, LI, and CsA groups respectively among the three belatacept trials. Among EBV+ patients, there were two (0.5%), four (1.0%) and zero (0%) PTLD cases in the belatacept MI, LI and CsA groups respectively. The

difference between the belatacept LI and CsA is 1%, exact 95% CI (0, 2.5). Among EBV- patients, there were five (11.1%), two (3.9%), and one (1.8%) PTLD cases in the belatacept MI, LI and CsA groups respectively. The difference between the belatacept LI and CsA is 2.1%, exact 95% CI (-5.9, 11.9). Note: At the time of the submission, complete follow-up data were available for all patients out to 24-months post-transplant. Of the PTLD cases reported above, 1 case in the belatacept LI (EBV+ serostatus) and 1 in the CsA (EBV status unknown) were reported after 24-months post-transplant.

When considering information from three previously submitted randomized clinical trials (RCTs) that contained an control regimen similar to the CsA regimen used in the belatacept trials, there were no cases of PTLD were reported (0%) among a total of 534 EBV+ kidney transplant recipients who received a CsA-based regimen. Among EBV- kidney transplant recipients, 1/158 (0.63%) experienced PTLD.

The analysis of OPTN/UNOS registry data found that the incidence of PTLD in EBV+ patients on a CNI-based regimen of either CsA or tacrolimus, found the 2-year incidence of PTLD in EBV+ patients to be 0.051/100 person years and 0.483/100 person years in EBV- patients. This incidence rate can be compared to the estimated incidence rates of 0.346/100 person years in EBV+ and 3.36/100 person-years in EBV- patients taking belatacept.

The greatest increase in risk of PTLD was present in patients who were EBV negative. When comparing the incidence from the pooled belatacept treatment groups to the incidence in pooled control arms of the belatacept trials, to the incidence in the control regimens from RCTs from previously submitted NDAs, and to incidence estimates using registry data, the risk of PTLD in the EBV- patients taking belatacept is unacceptably high vs. control estimates. These analyses also found that while the incidence of PTLD was lower among EBV+ patients compared to EBV- patients, the incidence in the belatacept regimens was higher compared to the control regimens among EBV+ patients.

Progressive Multifocal Leukoencephalopathy (PML)

A patient from the belatacept MI group in IM103027 was diagnosed with PML in Month 23; that patient died shortly after Month 24. A second case of PML was diagnosed in the belatacept liver transplant program (in Study IM103045) in October of 2009 and that patient has also died. The incidence of progressive multifocal leukoencephalopathy (PML) in the general kidney transplant population has been estimated at 14 cases per 100,000 patient-years.[6] Therefore, two occurrences of PML in the context of a drug development program constitute a safety signal. While the impact of an increased risk of PML on the overall risk-benefit profile of belatacept is potentially small, given that the outcome remains rare, the signal is important because it supports other data suggesting that belatacept may have specific effects on CNS immunity (e.g., the increased incidence of CNS PTLD, the increased rates of CNS infections seen in the belatacept MI treatment group).

[6] Neff RT, Hurst FP, Falta EM, et al. Progressive Multifocal Leukoencephalopathy and Use of Mycophenolate Mofetil after Kidney Transplantation. Transplantation 2008; 86(10): 1476-8.

9. Advisory Committee Meeting

The following is an internal report prepared by the Advisors and Consultants Staff of the Cardiovascular and Renal Drugs Advisory Committee meeting held on March 1, 2010.

The verbatim transcript is available at:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM209252.pdf

Quick Minutes
Meeting of the Cardiovascular and Renal Drugs Advisory Committee
March 1, 2010

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on March 1, 2010, at the Hilton Washington, DC/Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsor. The meeting was called to order by Emil Paganini, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Minh Doan, Pharm.D. (Acting Designated Federal Official). There were approximately 200 persons in attendance. There were no speakers for the Open Public Hearing session.

Issue: The committee discussed biologics license application (BLA) 125,288, from Bristol-Myers Squibb, for belatacept injectable, to be used in patients with kidney transplants to prevent rejection of the transplanted kidney.

Attendance:
Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
Sanjay Kaul, M.D., Mori Krantz, M.D., F.A.C.C., Darren McGuire, M.D., M.H.Sc., F.A.C.C., Emil Paganini, M.D., F.A.C.P., F.R.C.P. (Acting Chair)

Cardiovascular and Renal Drugs Advisory Committee Member Present (Non-Voting):
Jonathan C. Fox, M.D., Ph.D., F.A.C.C. (Industry Representative)

Special Government Employee Consultants Present (Voting):
Abdelmonem A. Afifi, Ph.D., Allan Coukell, BscPharm (Acting Consumer Representative), David Gjertson, Ph.D., James Gloor, M.D., Heather J. Johnson, Pharm.D., BCPS, Frederick J. Kaskel, M.D., Richard Mann, M.D., Elaine Morrato, Dr.P.H., M.P.H., C.P.H., , Parmjeet Randhawa, M.D., Allan R. Sampson, Ph.D., Malaysia Scott (Patient Representative), Jürgen Venitz, M.D., Ph.D.

Regular Government Employee Consultants Present (Voting):
Douglas A. Hale, M.D., Michael Proschan, Ph.D.

Guest Speaker Present (Non-Voting):

None

Cardiovascular and Renal Drugs Advisory Committee Members Not Present:
Henry R. Black, M.D., Jonathan L. Halperin, M.D., Robert A. Harrington, M.D., F.A.C.C., James D. Neaton, Ph.D.

FDA Participants (Non-Voting):
Edward Cox, M.D., M.P.H., Renata Albrecht, M.D., Patrick Archdeacon, M.D., Joette M. Meyer, Pharm.D., Cheryl Dixon, Ph.D.

Designated Federal Official:
Minh Doan, Pharm.D. (Acting)
Open Public Hearing Speakers:
None

The agenda was as follows:

Call to Order Introduction of Committee	Emil Paganini, M.D. Acting Chair, CRDAC
Conflict of Interest Statement	Minh Doan, Pharm.D. Acting, Designated Federal Official
FDA Introductory Remarks	Renata Albrecht, M.D. Director, Division of Special Pathogen and Transplant Products (DSPTP) Office of Antimicrobial Products (OAP), CDER
Sponsor Presentations	
Belatacept Introduction and Regulatory Background	Anthony Waclawski, Ph.D. Bristol-Myers Squibb Company
Unmet Need in Transplantation	Christian Larsen, M.D., DPhil Professor and Chairman, Department of Surgery, Surgeon-in-Chief, Associate Vice President and Executive Director, Emory Transplant Center, Emory University School of Medicine, Atlanta, GA
Belatacept Registrational Program • Design and Efficacy	Pushkal Garg, M.D. Bristol-Myers Squibb Company

APPEARS THIS WAY ON ORIGINAL

Charge to the Committee — Edward Cox, M.D., M.P.H., Director, OAP, CDER

Committee Discussion of Questions/Vote

BREAK

Continuation of Committee Discussion of Questions/Vote

Adjourn

Questions to the committee:

Based on the information presented from Studies IM103008, IM103027, and IM103100, please comment on the following questions regarding belatacept, in the context of the proposed Less Intensive (LI) regimen in combination with an interleukin-2 (IL-2) receptor antagonist (basiliximab), a mycophenolic acid (MPA) product (mycophenolate mofetil), and corticosteroids:

1. Discuss whether or not efficacy has been demonstrated for belatacept for the prophylaxis of acute rejection in *de novo* renal transplant recipients. If you do not believe efficacy has been demonstrated, what additional information is needed or what additional studies should be conducted? **(non-voting question)**

   While several Committee members expressed that efficacy was demonstrated, others felt that more data was 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.

2. Discuss whether or not safety has been demonstrated for belatacept for the prophylaxis of acute rejection in *de novo* renal transplant recipients. If you do not believe safety has been demonstrated, what additional information is needed or what additional studies should be conducted? **(non-voting question)**

   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 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.

3. Given the overall benefits and risks, do you recommend that belatacept be approved for the prophylaxis of acute rejection in *de novo* renal transplant recipients?
   a. Please discuss your rationale for your vote and comment on the following (as appropriate):
      - If you have concerns about the risks, please provide recommendations on how those risks can be managed.
      - If the answer is no, what additional studies would be needed to demonstrate that belatacept is safe and effective?
      - If the answer is yes, please discuss whether additional information or studies should be requested post-marketing.

   Vote: Yes 13 No 5 Abstain 0

   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.

Please see the transcript for detailed discussion.

The session adjourned @ approximately 4:30 p.m.

10. Pediatrics

BMS granted (November 19, 2007) 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)

11. Other Relevant Regulatory Issues

Manufacturing Facilities Inspections
See **Section 3** (CMC) for a summary of results and recommendations arising from manufacturing facilities' inspections.

DSI Inspections
Belatacept is a NME and therefore inspections were requested. There were no data integrity issues identified which would have prompted for-cause inspections. The two Phase 3 trials (IM103008 and IM103027) were conducted at 105 and 79 sites, respectively. In Study 008, 74% of the patients were enrolled at 71 non-US sites. Six sites in Mexico and 7 sites in France enrolled approximately 13% of the total subjects each. In Study 027, a total of 77% of the patients were enrolled at 53 non-US sites. Nine sites in France and six sites in Brazil enrolled about 17% of the total subjects.

The following sites were selected for inspection and the overall results of the inspections are discussed below the table.

Name of CI or Sponsor Location	Protocol #: and # of Subjects:	Inspection Dates	Interim Classification	Final Classification
Lionel Rostaing, MD/PhD Hoptial de Rangueil C H U De Toulouse (Office) Chu De Toulouse Hopital Rangueil Nephrologie-Hemodialyse-Transplantation 1 Avenue Du Pr Jean Poulhes Toulouse Cedex 31054 France	IM103008 Site 076 41 subjects IM 103027 Site 0035 24 subjects	12/07/09 – 12/18/09	Pending	Pending
Guillermo Mondragon-Ramirez, M.D. Instituto Mexicano De Transplantes, SC (Office and Patient Treatment) Av. Alta Tension 580-2 Colonia Cantarranas Cuernavaca, Morelos 62448 Mexico	IM103008 Site 0116 24 subjects	12/14/09 – 12/17/09	NAI	NAI
Rafael Reyes-Acevedo, MD Centenario Hospital Miguel Hidalgo (Office) Galeana Sur 465, Col. Obraje Aguascalientes, Aguascalientes 20230 Mexico	IM103008 Site 0123 25 subjects	12/7/09 – 12/11/09	NAI	NAI
Jose Medina Osmar Pestana, MD Hospital Do Rim E Hipertensao Rua Borges Lagoa 960 Vila Clementino Sao Paolo 04028-002 Brazil	IM103027 Site 0091 36 subjects	11/30/09 – 12/4/09	NAI	NAI
Valter Duro Garcia, PhD Hosp. Dom Vicente Scherer (Office) Avenue Independencia, 155 6° Andar Porto Alegre, Rio Grands Do Sul 90020-090 Brazil	IM103027 Site 0093; 21 subjects	12/7/09 – 12/11/09	NAI	NAI
Flavio Vincenti, MD University of California San Francisco Medical Center Transplant Service 505 Parnassus Avenue, Room 884M San Francisco, CA 94143-0780	IM103008 Site 0010 25 subjects IM103027 Site 010 7 subjects	10/21/09 – 11/04/09	VAI	Pending
Barbara Bresnahan, MD Froedtert Memorial Hospital 9200 Wisconsin Ave. FMCLB 216 Milwaukee, WI 53226	IM103008 Site 006 15 subjects	11/12/09 – 12/3/09	VAI	VAI
Sander Scott Florman, MD (Replaced by Rubin Zhang, MD) Tulane University Hospital and Clinic	IM103027 Site 0002 26 subjects	12/2/09 – 12/8/09	NAI	NAI

Name of CI or Sponsor Location	Protocol #: and # of Subjects:	Inspection Dates	Interim Classification	Final Classification
1415 Tulane Avenue TW-35 New Orleans, LA 70112				
Bristol-Myers Squibb 10 Waterview Blvd., 3rd Floor Parsippany, NJ 07054	IM103008 IM103027	11/09/09 – 11/25/09	VAI	Pending

According to the final Clinical Inspection Summary (CIS) from DSI dated March 9, 2010, in general, inspection of the sites of Drs. Mondragon-Ramirez, Reyes-Acevedo, Pestana, Garcia, Vincenti, Bresnahan, and Florman/Zhang revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspections documented minor regulatory violations at the sites of Drs. Vincenti, Bresnahan, and Florman/Zhang regarding protocol, adverse event reporting, and informed consent violations. In general, the studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

There were numerous protocol violations cited by the inspector at Dr. Rostaing's site, in addition to drug dispensation and informed consent violations. However, from DSI's review of Dr. Rostaing's written response, it appeared that the majority of the protocol violations were cited in error.

Concern about data integrity arose from the inspection of Bristol Myers Squibb (BMS). The applicant was not able to document the time of belatacept reconstitution prior to intravenous administration. Stability data in the BLA only goes out to 24 hours. The applicant's written response stated that at most sites, other site records (e.g., Pharmacy records) would allow precise determination of time of belatacept reconstitution. Sample documents from each site inspected were requested and provided in a written submission dated February 25, 2010 (with the exception of Dr. Florman/Zhang; at the time the CIS was written, BMS had yet to provide Dr. Vincente's records). The sample documents (with the exception of those from Drs. Vincenti Florman/Zhang) confirmed the applicant's claim that reconstitution date and time could be verified in 11 of the 12 examples requested. DSI concluded that although this is a small sample, it appears that in most cases verification of time of reconstitution and infusion is available at the trial sites.

Another issue raised during the inspection of BMS was the ability of the applicant to ensure compliance with trial procedures and requirements, in particular at Dr. Rostaing's site. Study monitoring appeared to have been effective at detecting issues requiring resolution, but achievement of resolution of these issues was not always documented. Additionally, resolution was not always accomplished in a timely manner. DSI concluded that the issues identified as unresolved do not appear to affect data integrity.

In conclusion, DSI stated that the data collected and maintained at the applicant's site and the eight clinical sites audited appear consistent with that submitted to the agency as part of and in support of BLA 125,288 and may be used to support the BLA.

Follow-Up Actions Noted in the CIS: The observations for Drs. Rostaing are based on

preliminary communications with the FDA Field investigators and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

QT-IRT Consult

A consult request was sent August 21, 2009 to the QT Intradisciplinary Review Team (QT-IRT). The following question was posed by the Division in the consult:

> Based on nonclinical and clinical findings, the sponsor concluded that belatacept does not prolong the QT interval. In Phase 3 trials, the proportion of subjects with a prolonged QTc interval >30 ms or > 60 ms compared with baseline and> 450 ms was similar across the 3 treatment groups (belatacept MI, belatacept LI, and cyclosporine). Do you agree with the sponsor's conclusion?

In their completed consult (dated November 23, 2009), the QT-IRT concluded:

> Based on review of the ECG data and narratives for AEs associated with QT prolongation, i.e. sudden death, cardiac arrest, significant ventricular arrhythmias, in clinical trials IM103008 and IM103027, it seems reasonable to conclude that there are no large effects on the QT interval due to belatacept based on the following:
>
> - The number of subjects with an absolute QTcB over 500 ms or with a 60 ms change from baseline was similar across the cyclosporine and belatacept treatment arms.
>
> - SAEs related to QT prolongation occurred in all treatment arms. On review of the narratives it seems reasonable to conclude that they were related to underlying comorbidities (HTN, DM, CAD) and complications (hypotension, sepsis, pulmonary embolism, renal vein thrombosis, acute MI etc.) expected in this population of renal transplant recipients. There were no reports of QT prolongation associated with these events.

Division of Pharmacovigilance II/Office of Surveillance and Epidemiology

Given the concern with potential autoimmunity with belatacept (as discussed above in **Section 4**), a consult was requested on February 2, 2010 from DPV II to search the Adverse Event Reporting System (AERS) database for post-marketing reports of abatacept (Orencia®) in association with autoimmune events. Abatacept was approved on December 23, 2005 for rheumatoid arthritis (with other drugs and as monotherapy) and on April 7, 2008 for polyarticular juvenile idiopathic arthritis (JIA).

Although there was no evidence of autoimmunity developing in rats and monkeys studies in toxicology studies in the belatacept BLA, nonclinical studies of a related product, abatacept, showed evidence of inflammation and autoimmunity in rats, one of three animal species tested. Abatacept differs from belatacept by two amino acid substitutions and, in rodents, has greater *in vitro* binding affinity and *in vivo* inhibition of a T-cell dependent antibody response than belatacept. In humans, belatacept has greater potency than abatacept. Toxicology studies of abatacept are therefore considered to be relevant to the belatacept safety assessment.

The consult requested a search for the following specific terms:

- Autoimmune thyroid disease
- Hashimoto's thyroiditis

- Graves' disease
- Hemolytic anemia
- Idiopathic thrombocytopenic purpura (ITP)
- Lupus (SLE)
- Insulin-dependent diabetes (type 1)

The consult also requested a comparison of autoimmune events between abatacept and another treatment modality (to be determined by DPV II) that is used in rheumatoid arthritis, as a positive control.

The completed consult was dated February 18, 2010. The reviewer (Peter Diak, Pharm.D., MPH) identified 19 AERS reports for autoimmune events between approval (12/23/05) and February 4, 2010. The majority (n=17, 90%) of the identified cases had one or more of the following: lacked clinical information, contained confounding factors such as additional suspect medications, or reported an exacerbation of an existing autoimmune disorder (e.g. lupus). In addition to searching AERS, the reviewer also searched the Empirica data mining application on February 4, 2010 for abatacept. The resulting data mining scores were uniformly low and did not meet the conventional threshold for disproportionate reporting suggestive of a potential safety signal. The reviewer also noted that since patients receiving abatacept have underlying autoimmune disorders, it is difficult to make an assessment of the relationship between the event(s) and the product. Finally, a comparison of abatacept to another rheumatoid arthritis medication was not performed by the reviewer due to the absence of any safety signals for abatacept and due to the limitations in using spontaneous AERS data to compare the safety of one drug(s) to another.

It was also noted in the consult response that a comprehensive review of the pediatric post-marketing safety for abatacept was recently completed by DPV II for the December 8, 2009 Pediatric Advisory Committee meeting, which also did not identify any safety signals among the pediatric population.[7]

In summary, DPV II did not identify any safety signal with abatacept and autoimmune events based upon 19 AERS reports of limited clinical information and confounding factors and low data mining scores.

12. Labeling

Proprietary name
The Division of Medication Errors and Prevention Analysis (DMEPA) found the proposed proprietary name "Nulojix" conditionally acceptable for the product on October 5, 2009. In the consult, DMEPA stated they would re-review the proposed proprietary name 90 days before approval of the BLA. However, given the CR action, the re-review will not be performed in this review cycle.

[7] Diak, P. Abatacept Pediatric Postmarketing Adverse Events Review. September 21, 2009.

Physician (Package Insert) and Patient (Medication Guide) Labeling
Final labeling revisions were not proposed during this review cycle, due to the recommended CR action. Therefore, OSE and DDMAC consults were not completed.

Carton and Immediate Container Labels
A review for the carton and container labels was drafted by the Office of Biotechnology Products, but was not finalized give the CR action. It is noted that the Reviewers had several deficiencies and recommendations for revisions. However, DMEPA did not complete a review; and therefore there are no plans to communicate any deficiencies/recommendations regarding the proposed carton/container labels with the applicant in this review cycle.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
From a clinical perspective this application is Approvable, pending finalization of labeling and the REMS. However, a Complete Response (CR) action is recommended, based on the CMC deficiencies noted in **Section 3**. Given the CR action, labeling and REMS will not be finalized in this review cycle.

CDTL Comment: Although not cited as a deficiency by the Clinical Review team, the Division and Office added a requirement to the CR letter for the 3-year data to be submitted from Studies IM103008 and IM103027 prior to approval:

> 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, and cardiovascular events from this 36-month study, including graft loss 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.

Overall Risk Benefit
Belatacept has been developed as a therapeutic agent for immunosuppression in *de novo* kidney transplant recipients; in the Phase 2 and Phase 3 trials, it was compared to CsA as the control, in an immunosuppression regimen that included basiliximab, MMF and steroids in both the belatacept and the CsA arms. The belatacept development program was designed to evaluate efficacy endpoints related to its effects on immunosuppression, namely patient graft loss and death and AR. However, the trials also evaluated other endpoints related to renal function (GFR), blood pressure, lipids, diabetes, and CAN; which are known toxicities associated with other immunuosuppressants, specifically the CNIs.

The differential effect of CsA and belatacept on renal hemodynamics (due to vasoconstrictive effects of CsA) complicates the interpretation of the GFR results from the Phase 3 trials for the evaluation of the efficacy of belatacept. While the composite renal impairment endpoint as defined in the Phase 3 trials was not adequate to establish efficacy, the belatacept treated groups also had significantly higher Month 12 GFRs. Other CNI-free regimens have not consistently been shown to result in higher GFRs. In other published randomized controlled

clinical trials (RCTs), CNI-free immunosuppressive regimens have been compared to CNI-based regimens and despite the renal hemodynamic advantage, the results in terms of GFR have not been consistent.[8,9,10,11] The literature also suggests that a higher GFR at Month 1 and Month 12 is associated with decreased cardiovascular death and improved graft survival; however, these data were derived largely from analyses of groups of patients with more comparable renal hemodynamics.[12,13,14]

Given the uncertainties that exist about the importance of therapies that result in a direct increase in GFR with an absent or unclear effect on kidney architecture, further insight into the potential clinical impact of the GFR differences observed in the belatacept clinical trials may be offered by a comparison of numbers of patients alive and with a functioning graft at Month 24 in the Phase 3 studies combined. The results numerically favor belatacept: 355 out of 403 (88.1%) belatacept MI-treated patients and 358 out of 401 (89.3%) belatacept LI patients versus 346 out of 405 (85.4%) CsA-treated patients. However, it should also be noted, that these studies lack the power to make statistical conclusions regarding outcomes of death and graft loss. Study IM103008 drives the observed difference in numbers of patients alive with a functioning graft and also is the trial where the greatest difference in GFR between belatacept and CsA patients was seen, strengthening the association between a higher GFR and an improved outcome.

Several other clinically important safety endpoints favor the belatacept regimen, including those pertaining to cardiovascular risk factors (hypertension, dyslipidemias, and NODAT). Of these, the differences in blood pressure detected between the belatacept groups and the CsA groups appears the most likely to result in a clinical benefit. A very low (4.6%) incidence of NODAT was observed among belatacept patients in the clinical trials, though the implication of that observation is somewhat mitigated by the low rate of NODAT observed in the CsA control group (9.6%). The difference in lipids observed between the belatacept patients and the CsA patients was driven by triglycerides. While the triglyceride profile associated with the belatacept patients seems more favorable, the literature correlating outcomes with cholesterol largely relates to LDL and HDL.

---

[8] Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Eng J Med 2007; 357: 2562-75.

[9] Larson TS, Dean PG, Stegall MD, et al. Complete avoidance of calcineurin inhibitors in renal transplantation: a randomized trial comparing sirolimus and tacrolimus. Am J Transplant 2006; 6(3): 514-22.

[10] Hamdy AF, El-Agroudy AE, Bakr MA, et al. Comparison of sirolimus with low-dose tacrolimus versus sirolimus-based calcineurin inhibitor-free regimen in live donor renal transplantation. Am J Transplant 2005; 5(10): 2531-8.

[11] Flechner SM, Goldfarb D, Solez, et al. Kidney transplantation with sirolimus and mycophenolate mofetil-based immunosuppression: 5-year results of a randomized prospective trial compared to calcineurin drugs. Transplantation 2007; 83(7): 883-92.

[12] Hariharan S, McBride MA, Cherikh WS, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int 2002; 62: 311-8.

[13] Meier-Kriesche HU, Baliga, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. Transplantation 2003; 75: 1291.

[14] Pilmore H, Dent H, Chang S. Reduction in Cardiovascular Death after Kidney Transplantation. Transplantation 2010; epublished ahead of print.

In terms of safety outcomes, the greatest risks associated with the use of belatacept in the clinical trials were related to increased rates of AR (including higher grades of AR), PTLD (predominantly CNS PTLD), PML, and CNS infection (only in the belatacept MI regimen).

An increase in overall rates of AR was observed in Study IM103008 among patients in the belatacept groups compared to the CsA control. In both IM103008 and IM103027, a trend towards higher grade rejections was noted among the belatacept patients. Many of the AR episodes in the belatacept arm were treated with lymphocyte depleting agents (e.g., thymoglobulin) and the contribution of the agents to the subsequent development of PTLD is unknown, but should be considered.

An imbalance in rates of PTLD was detected between the belatacept and CsA groups in both Phase 3 studies as well as the Phase 2 trial and a similar signal appears to be present in a preliminary Phase 2 liver trial. The finding that most of these cases presented with CNS involvement was also a distinguishing characteristic of these events.

The imbalance was greatest among EBV- patients, but was also detected among EBV+ patients. The applicant has concluded that the risk-benefit profile of belatacept justifies its use among EBV+ kidney transplant recipients but not EBV- kidney transplant recipients. The data support a point estimate that the use of a belatacept-based regimen that also includes IL-2 induction, MMF, and corticosteroids instead of a CsA-based regimen that also includes IL-2 induction, MMF, and corticosteroids will result in an additional case of PTLD for every 150 EBV+ kidney transplant recipients treated. It is expected that many of these additional cases would present in the CNS. The confidence intervals around this point estimate, however, are rather wide. Although the applicant suggested that the incidence of PTLD rates observed within the belatacept arms of the trial was consistent with rates of PTLD seen in registry and claims data of patients maintained on CNI-based regimens. However, this interpretation was not supported by a FDA review of previous NDA clinical trials or of registry data from UNOS, CTS, and CMS.

The report of one case of PML in the belatacept MI treatment group of IM103027 and of another PML case in a liver transplant patient exposed to a different belatacept MI regimen is noteworthy. Together with the high rate of CNS PTLD observed among recipients of both belatacept regimens and an elevated rate of other CNS infections observed among recipients of the belatacept MI regimen, the observation of two cases of PML in a clinical trial setting underline that CNS immunity is affected differently by exposure to belatacept than by exposure to CsA. While concerning, the rate of PML observed in the belatacept kidney program is unlikely to significantly change the estimate of the NNTH based on the primary safety signal related to PTLD.

The risks and benefits of belatacept were discussed at an Advisory Committee meeting on March 1, 2010 (as discussed in **Section 9**). The committed voted 13 to 5 that given the overall benefits and risks, belatacept should be approved for the prophylaxis of organ rejection in patients receiving kidney transplants.

The Review team agreed with the committee and also agreed with the applicant that belatacept should be contraindicated among kidney transplant recipients who are EBV- at the time of transplantation due to the increased risk of PTLD observed in this population and that this information should be included in the Boxed Warning of the package insert. The team also agreed that a REMS, consisting of a Medication Guide and Communication Plan, was necessary to ensure safe use of the drug (as discussed above).

(b) (4)

Recommendation for Postmarketing Risk Evaluation and Management Strategies

The applicant proposed a Risk Evaluation and Mitigation Strategies (REMS) for belatacept in the June 30, 2009 submission. In addition, the applicant submitted a response on February 17, 2010 to questions from DRISK about the proposed REMS. An additional submission from the applicant on April 1, 2010 which included updated information on the REMS materials was not reviewed during this review cycle by DRISK.

The stated goals for the proposed REMS are:

(b) (4)

The DRISK review team, Carolyn Yancy, M.D. (Medical Reviewer) and Suzanne Robottom Pharm.D. (Team Leader), were consulted on the proposed REMS. Also, in DSPTP the Deputy for Safety (Ozlem Belen, M.D.) was involved with the REMS discussions, liaisoned with DRISK and other consultants to facilitate the review, and concurs with the recommendations and the final comments to the applicant regarding the REMS.

The proposed REMS elements include a (b) (4)

The proposed REMS for belatacept (b) (4)

The primary modifiable safety issue associated with belatacept is PTLD, particularly CNS PTLD. While the observed incidence of PTLD was higher among both EBV+ and EBV- groups of patients maintained with belatacept rather than CsA in the pivotal kidney transplant trials, the absolute risk of PTLD among EBV- patients was sufficiently high to prompt the applicant to propose contraindicating the use of belatacept among EBV- kidney transplant recipients. In addition, the relative safety of belatacept among EBV+ kidney transplant recipients remains one of the most important areas requiring further study.

Labeling, including a Boxed Warning and Contraindication against the use of belatacept among EBV- kidney transplant recipients due to an elevated risk of PTLD and CNS PTLD, should limit such exposures to belatacept. However, the Review Team and DRISK feel that labeling alone, is not sufficient (b) (4)

(b) (4)

In addition a REMS designed to inform the patients of the serious risks including the risk of PTLD and PML, and a well-designed communication plan targeted at healthcare providers (HCP) should suffice to inform transplant physicians about the contraindication not to use belatacept among EBV- kidney transplant patients. The communication plan materials will be expected to be in line with the information in the approved package insert regarding the risks of PTLD and PML.

CDTL Comment: The members of the Cardiovascular and Renal Drug Advisory Committee emphasized the need for a "tight registry" to monitor the outcomes of belatacept patients, particularly with respect to PTLD. The DSPTP Review Team and DRISK feel that while monitoring the use of belatacept among EBV- patients should represent a component of the data collection, proper physician labeling and a well-designed communication plan should suffice to inform transplant physicians about the contraindication to use among EBV- kidney transplant patients. EBV testing is almost universal prior to renal transplantation and healthcare providers managing renal transplant recipients are highly specialized and acutely aware of the necessity of EBV testing as apart of initial work-up leading to surgery.
In the absence of a specific belatacept patient registry as component of REMS, UNOS captures EBV serostatus, post-transplant malignancies including PTLD at 6 months, one year and annually, thereafter up to 5 years. These data provide a basis for monitoring the use and serious risks associated with belatacept. The DSPTP Clinical Review Team and Deputy Director of Safety, as well as DRISK, believe the collection of these data should be a postmarketing requirement (PMR).

If, in the future, the data collected through the registry suggest otherwise, ETASUs restricting drug distribution to EBV+ patients should be considered subsequently. ETASUs are not recommended by the Division or DRISK at this time. See ***Appendix I*** *for the excerpts from the CR letter containing REMS language and the specific components of the Communication Plan that is needed at a minimum.*

In addition, the DSPTP Clinical Review Team believes the Communication Plan should also include elements which will encourage compliance with UNOS registry data collection.

Recommendations for other Postmarketing Requirements and Commitments

CMC

The CMC (drug product) team recommends one post-marketing commitment:

> Provide information and summary data on the container closure integrity test developed in support of finished product on stability in a Prior Approval Supplement

Clinical

The applicant has proposed the following postmarketing studies:

- IM103074 – Pattern of Use of Belatacept in US Transplant Recipients
- IM103075 – Belatacept and Risk of PLTD in US Renal Transplant Recipients
- IM103076 – (b) (4) (b) (4) (b) (4)

Since the recommended action is a CR, the adequacy of these proposed PMRs, has not been discussed. However, below is a summary of the proposed studies and a few comments on design and objectives. Additional comments on these protocols will be requested in the future from the Maternal Health Team (MHT) and Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology.

The protocol for Study IM103074 proposes to (b) (4) (b) (4) s

CDTL Comment: While missing data represents a limitation of the UNOS/OPTN database, the proposed study would provide significant insight into patterns of belatacept use among EBV+ and EBV- as an initial immunosuppressant regimen. The results of the study may be less reliable, however, as a means to measure belatacept use among EBV+ and EBV- patients who are converted to belatacept-based immunosuppression some time after transplantation.

The protocol for Study IM103075 proposes to (b) (4) (b) (4)

(b) (4)

CDTL Comment: While data submission regarding PTLD is a required component of OPTN/UNOS reporting, the reliability of such data is unclear. Educating transplant centers about the importance of these data should represent an important component of the Communication Plan of the REMS (see above).

Study IM103076 is a (b) (4)

(b) (4)

CDTL Comment: As a prospective study, IM103076 will have greater ability to collect in-depth data and verify outcomes than study IM103075. The study may, therefore, provide some additional insight into the risk-benefit profile of belatacept, particularly with regards to incidence rates of PTLD and CNS PTLD in an EBV+ patient population beyond that provided by IM103075.

(b) (4)

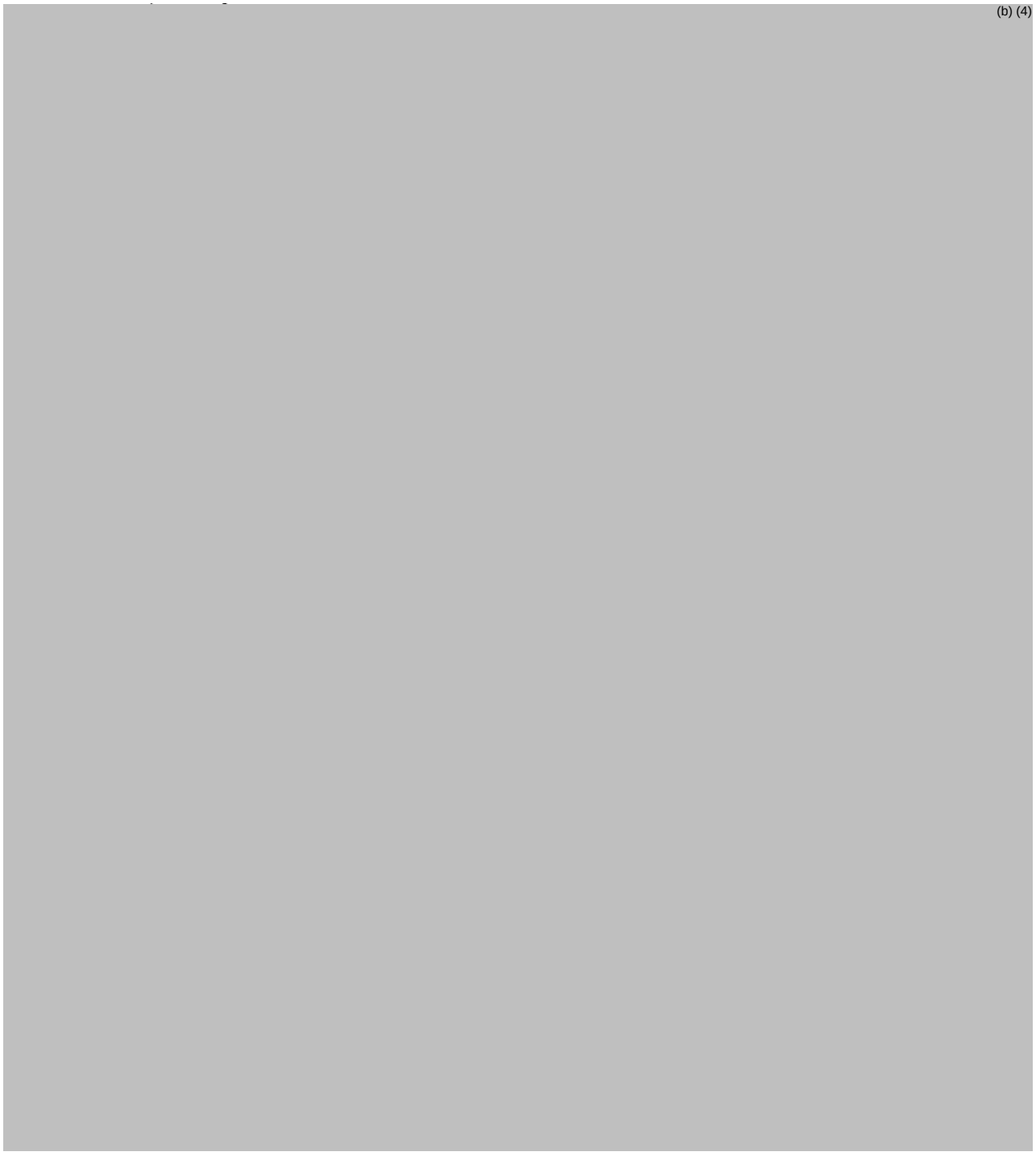
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Appendix II – Drug Substance Deficiencies

Inspection deficiencies identified during the November 2009 inspection of the BMS East Syracuse, NY facility, requiring adequate resolution prior to CDER/OC recommendation of BLA approval:

1) Regarding drug substance manufacturing:

(b) (4)



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Appendix III – Drug Product Deficiencies

Drug product process and sterility deficiencies, based on review of the BLA.

1. Readjust the [redacted]. The current [redacted] is not in line with your process capability.

2. The sensitivity (leak volume and the corresponding leak size) of the dye ingress test used to validate the integrity of the drug product container closure was not correlated to a microbial challenge test (using the same vacuum and pressure challenge conditions as the dye ingress test) and evaluated. Correlate the sensitivity of the two tests. In addition, provide information and summary data of the microbial challenge test.

[redacted]

4. With regard to the validation study for shipping of belatacept from the BMS distribution center to consumers, justify the [redacted] profile selected. It is not clear the selected profile represents the worst case [redacted] temperature conditions [redacted].

5. Because the updated drug product endotoxin specification [redacted]) does not provide a safety margin over the specified limit for parental drugs (5 EU/kg) at the lowest belatacept infusion solution concentration (2 mg/mL), you should lower the endotoxin specification to include a safety margin.

6. No microbiology data was provided to support the following [redacted] Alternatively, you can revise the product labeling to recommend that the constituted and diluted product may be stored for a maximum of 4 hours at 2° to 8°C or room temperature.

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125,288
Priority or Standard	Standard
Submit Date(s)	June 30, 2009
Received Date(s)	July 1, 2009
PDUFA Goal Date	May 1, 2010
Division / Office	DSPTP/OAP/OND
Reviewer Name(s)	Patrick Archdeacon, M.D.
Review Completion Date	March 26, 2010
Established Name	Belatacept
(Proposed) Trade Name	Nulojix
Therapeutic Class	Immunosuppressant
Applicant	Bristol-Myers Squibb Company
Formulation(s)	Lyophilized powder for IV infusion
Dosing Regimen	10 mg/kg on Day 1, 5, 14, 28,56, and 84; then 5 mg/kg every 4 weeks thereafter
Indication(s)	Prophylaxis of organ rejection
Intended Population(s)	Adult kidney transplant recipients

Clinical Reviewer 4/30/10

Clinical Team Leader 4/30/10

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 8

1.1 Recommendation on Regulatory Action 8
1.2 Risk Benefit Assessment 10
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .. 18
1.4 Recommendations for Postmarket Requirements and Commitments 21

2 INTRODUCTION AND REGULATORY BACKGROUND 23

2.1 Product Information 23
2.2 Tables of Currently Available Treatments for Proposed Indications 24
2.3 Availability of Proposed Active Ingredient in the United States 26
2.4 Important Safety Issues With Consideration to Related Drugs 26
2.5 Summary of Presubmission Regulatory Activity Related to Submission 27

3 ETHICS AND GOOD CLINICAL PRACTICES 28

3.1 Submission Quality and Integrity 28
3.2 Compliance with Good Clinical Practices 29
3.3 Financial Disclosures 32

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 32

4.1 Chemistry Manufacturing and Controls 32
4.2 Clinical Microbiology 33
4.3 Preclinical Pharmacology/Toxicology 34
4.4 Clinical Pharmacology 35
4.4.1 Mechanism of Action 37
4.4.2 Pharmacodynamics 38
4.4.3 Pharmacokinetics 40

5 SOURCES OF CLINICAL DATA 41

5.1 Tables of Studies/Clinical Trials 41
5.2 Review Strategy 43
5.3 Discussion of Individual Studies/Clinical Trials 43

6 REVIEW OF EFFICACY 45

Efficacy Summary 45
6.1 Indication 47
6.1.1 Methods 47
6.1.2 Demographics 52
6.1.3 Subject Disposition 53

6.1.4 Analysis of Primary Endpoint(s) 55
6.1.5 Analysis of Secondary Endpoints(s) 60
6.1.6 Other Endpoints 61
6.1.7 Subpopulations 62
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations 66
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects 69
6.1.10 Additional Efficacy Issues/Analyses 69

7 REVIEW OF SAFETY 70

Safety Summary 70
7.1 Methods 71
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 71
7.1.2 Categorization of Adverse Events 71
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 72
7.2 Adequacy of Safety Assessments 72
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 72
7.2.2 Explorations for Dose Response 73
7.2.3 Special Animal and/or In Vitro Testing 73
7.2.4 Routine Clinical Testing 73
7.2.5 Metabolic, Clearance, and Interaction Workup 73
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class 74
7.3 Major Safety Results 75
7.3.1 Deaths (and Graft Loss) 75
7.3.2 Serious Adverse Events 81
7.3.3 Dropouts and/or Discontinuations 98
7.3.4 Significant Adverse Events 100
7.3.5 Submission Specific Primary Safety Concerns 112
7.4 Supportive Safety Results 115
7.4.1 Common Adverse Events 115
7.4.2 Laboratory Findings 116
7.4.3 Vital Signs 117
7.4.4 Electrocardiograms (ECGs) 117
7.4.5 Special Safety Studies/Clinical Trials 117
7.4.6 Immunogenicity 118
7.5 Other Safety Explorations 118
7.5.1 Dose Dependency for Adverse Events 118
7.5.2 Time Dependency for Adverse Events 119
7.5.3 Drug-Demographic Interactions 119
7.5.4 Drug-Disease Interactions 119
7.5.5 Drug-Drug Interactions 120
7.6 Additional Safety Evaluations 121
7.6.1 Human Carcinogenicity 121
7.6.2 Human Reproduction and Pregnancy Data 121

7.6.3 Pediatrics and Assessment of Effects on Growth 121
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound 121
7.7 Additional Submissions / Safety Issues 122

8 POSTMARKET EXPERIENCE 122

9 APPENDICES 123

9.1 Literature Review/References 123
9.2 Labeling Recommendations 123
9.3 Advisory Committee Meeting 123

QUICK MINUTES 123

MEETING OF THE CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE 123

MARCH 1, 2010 123

Table of Tables

Table 1: Maintenance Immunosuppressants in Kidney Transplantation....25
Table 2: Clinical Sites Inspected....30
Table 3: Studies and Trials with Key Information on the Clinical Pharmacology of Belatacept (Intravenous)....36
Table 4: Relationship between belatacept C_{trough} and percentage of patients with a decrease in mGFR ≥ 10 ml/min from Month 3 to Month 12 in the Phase 3 belatacept kidney transplant trials (data from LI and MI regimens were combined)....39
Table 5: Belatacept Pharmacokinetics in Healthy Subjects and Kidney Transplant Patients....40
Table 6: Core clinical trials supporting the Belatacept BLA....42
Table 7: Demographics in the Phase 3 Kidney Transplant Trials....53
Table 8: Reasons for Treatment Discontinuations at 12 Months in IM103008....54
Table 9: Reasons for Treatment Discontinuations at 12 Months in IM103027....54
Table 10: Patient and Graft Survival at 12 Months....55
Table 11: Composite Renal Impairment Endpoint....56
Table 12: Acute Rejection (as Defined by the Applicant) at 12 Months....57
Table 13: Additional Patients Included in FDA's Definition of BPAR in Study 008....58
Table 14: Additional Patients Included in FDA's Definition of BPAR in Study 027....59
Table 15: FDA's Analysis of Biopsy Proven Acute Rejection, Graft Loss, and Death at 12 Months....60
Table 16: Measured GFR at Month 12 in the Phase 3 Kidney Trials....60
Table 17: Prevalence of Chronic Allograft Nephropathy (CAN) at 12 Months....61
Table 18: Patient and Graft Survival at 12 Months by EBV serostatus....62
Table 19: Composite Renal Function at Month 12 by EBV serostatus....63
Table 20: Acute Rejection (as Defined by the Applicant) at 12 Months by EBV serostatus....64
Table 21: FDA's Analysis of Biopsy Proven Acute Rejection, Graft Loss, and Death at 12 Months by EBV Serostatus....65
Table 22: Measured GFR at Month 12 by EBV Serostatus....65
Table 23: Safety Population from Pooled Studies....72
Table 24: Deaths Occurring in the Phase 3 Trials....76
Table 25: Narratives of Deaths among CsA Patients in IM103008 at 24 Months....77
Table 26: Narratives of Deaths among Belatacept LI Patients in IM103008 at 24 Months....77
Table 27: Narratives of Deaths among Belatacept MI Patients in IM103008 at 24 Months....78
Table 28: Narratives of Deaths among CsA Patients in IM103027 at 24 Months....78
Table 29: Narratives of Deaths among Belatacept LI Patients in IM103027 at 24 Months....79
Table 30: Narratives of Deaths among Belatacept MI Patients in IM103027 at 24 Months....79
Table 31: Patient and Graft Status in the Phase 3 Trials....80

Table 32: Death and/or Graft Loss at 12 and 24 Months and Safety Update 81
Table 33: All PTLD Cases for Belatacept Trials 008, 027 and 100.....82
Table 34: Summary of PTLD Cases Observed in Belatacept Trials 008, 027 and 100 .83
Table 35: Estimated Number Needed to Harm in EBV+ Patients based on Incidence of PTLD: Belatacept Trials 008, 027 and 100.....91
Table 36: 2-year PTLD incidence rates/100 Person-Years among EBV+ Belatacept Patients in IM103100, IM103008, and IM103027 compared to EBV+ Patients Maintained on CNI-based Regimens Followed in the UNOS and CTS Registries 92
Table 37: Estimated Number Needed to Harm (NNTH) based on registry data 93
Table 38: Serious Adverse Events in at least 2% of Patients at Month 12 98
Table 39: Adverse Events Leading to Treatment Discontinuation in ≥1% of Patients Up to Month 12 (Pooled Trials 008, 027, and 100) 99
Table 40: Acute Rejection (as Defined by the Applicant) at 12 Months 100
Table 41: Calculated GFR at 12 months by Rejection Status at 12 months 102
Table 42: Use of Lymphocyte Depleting Therapy Through Month 24.....103
Table 43: Slope for Calculated GFR from Month 3 to 24.....105
Table 44: Mean Blood Pressure at Month 12 107
Table 45: Incidence of New Onset Diabetes After Transplantation at Month 12.....108
Table 46: Serum Lipids at Month 12.....109
Table 47: Infections Reported as Adverse Events up to 12 Months in Trials 008, 027, and 100 110
Table 48: Cases of CNS Infections in Trials 008, 027, and 100 up to Database Lock.111
Table 49: Cases of Tuberculosis in the Phase 3 Trials at Database Lock.....111
Table 50: Selected Adverse Events Associated with Class Effects Up to Month 12....116
Table 51: PTLD events among EBV+ patients maintained on belatacept in Phase 2 and Phase 3 kidney transplant trials 120

Table of Figures

Figure 1: Acute Rejections within the First Year Post-Transplant According to OPTN Registry Data 12
Figure 2: Steroid Use among Adult First Kidney Alone Transplant Recipients 13
Figure 3: Overall Incidence of PTLD by EBV Serostatus and Treatment Groups in the Belatacept Kidney Trials 14
Figure 4: Most Common Maintenance Immunosuppresion Regimens among US Kidney Transplant Recipients at Time of Transplant: 2005-07 25
Figure 5: Most Common Immunosuppression Induction Agents Used in US Kidney Transplant Recipients: 2005-07 26
Figure 6: Percent of patients with AR occurring within first month post-transplant as a function of median belatacept C_{trough} on Day 5 in the Phase 3 kidney transplant trials (Quartile analysis) 39
Figure 7: Trials in the Belatacept Developmental Program 41
Figure 8: Belatacept C_{trough} in *de novo* kidney transplant patients receiving the LI regimen (left panel) and the MI regimen (right panel). Data from Phase 3 trials IM103008 and 103027 were combined. The bottom and top of each box represent the inter quartile range (i.e., 25th and 75th percentiles, respectively). The bar inside each box represents the median C_{trough}. The whiskers represent 5th and 95th percentiles, respectively. The horizontal reference lines represent the targeted C_{trough} for each regimen. 67
Figure 9: Whole Blood Trough Concentrations of CsA in Patients Randomized to CsA in the Phase 3 Studies IM103008 (red, left-side bars at each day) and IM103027 (blue, right-side bars at each day) 68
Figure 10: Overall Incidence of PTLD by EBV Serostatus and Treatment Groups in the Belatacept Kidney Trials 89
Figure 11: NNTH Estimate from Belatacept Trials 90
Figure 12: Cumulative incidence of non-Hodgkin's Lymphoma according to EBV status in kidney, heart, and liver transplant recipients in the Collaborative Transplant Study registry data 96
Figure 13: Mean Calculated GFR (mL/min) in Trial IM103008 104
Figure 14: Mean Calculated GFR (mL/min) in Trial IM103027 105
Figure 15: Distribution of belatacept average concentrations (C_{avg}) up to 6 months after transplantation (C_{avg} = cumulative AUC divided by time) in subjects treated with belatacept who did and did not develop CNS events in the belatacept kidney transplant trials 118

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

On June 30, 2009, Bristol Myers Squibb Company (BMS) submitted a BLA requesting the approval of belatacept IV for the indication of "prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants." While BMS had studied both a more intensive (MI) belatacept regimen and a less intensive (LI) belatacept regimen in two Phase 3 kidney transplant trials, the applicant requested approval of the belatacept LI regimen only.

(b) (4)

Substantial evidence of the effectiveness of belatacept was demonstrated through an examination of an endpoint based on AR (the same endpoint which has supported approvals for newer immunosuppressive agents for transplant indications since the advent of CsA) in two randomized Phase 3 trials. For the endpoint based on the outcome of AR, the trials used a noninferiority (NI) design. The results of the two trials suggested that while belatacept has efficacy as an immunosuppressant, it may not be as effective as the comparator drug, CsA, for the prevention of AR episodes at the doses tested: while the belatacept groups met a scientifically justified NI margin of 20%, patients receiving belatacept experienced both numerically more events of AR and higher grades of AR. Although some concerns exist regarding the consequences of a potential loss of efficacy, the regulatory standard of demonstrating efficacy was met. From a clinical point-of-view, the potential loss of efficacy is an important consideration, but not necessarily a contraindication to approval: 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.

Supportive evidence of the efficacy of belatacept was provided from additional endpoints from the pivotal Phase 3 kidney transplant trials. Those endpoints were based on patient and graft survival and on measured GFR. While the applicant and the FDA held discussions regarding these endpoints in 2004 and a Special Protocol Assessment (SPA) was reviewed in 2005 for one of the pivotal Phase 3 trials, the endpoints were not relied on as primary evidence of the efficacy of belatacept in this review. A NI margin of 10% had been discussed for the co-primary endpoint of patient and graft survival, but data to support this margin was not available. In the absence of scientific justification for the NI margin, the endpoint could not constitute substantial evidence of efficacy. Belatacept appeared to be superior to CsA in the Phase 3 trials according to the Glomerular Filtration Rate (GFR)-based co-primary endpoint. The use of that endpoint to establish the efficacy of belatacept, however, was confounded by the well-characterized effect of CsA on renal hemodynamics (and, thereby, GFR). The data showed, however, that more patients on belatacept regimens than CsA regimens were alive with a functioning graft at 12 and 24 months. The data also showed that patients on belatacept regimens had higher mean GFRs and similar preservation of GFR at 12 and 24 months. Those findings are consistent with the substantial evidence of the effectiveness of belatacept provided by analysis of the endpoint based on AR.

The relative safety of belatacept, compared to that of CsA, was established through an exhaustive analysis of both pre-specified endpoints and observed safety signals. As discussed briefly in Section 1.2 and exhaustively in Section 7, belatacept was associated with higher rates and grades of AR, with a higher incidence of post-transplant lymphoproliferative disorder (PTLD) – particularly among Epstein Barr Virus seronegative (EBV-) patients and with a preponderance of central nervous system (CNS) presentations, and with the development of progressive multifocal leukoencephalopathy (PML). On the other hand, patients maintained on belatacept avoided the toxic effects of CsA on GFR, blood pressure, blood sugar, and lipids.

According to my review of the clinical data, 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 patients receiving a kidney transplant in combination with basiliximab induction and mycophenolate mofetil and corticosteroid maintenance immunosuppression.

(b) (4)

I agree with the applicant that the use of belatacept should be contraindicated among kidney transplant recipients who are EBV- at the time of transplantation due to the increased risk of PTLD observed in this population and that this information should be included in the Boxed Warning of the package insert. I also agree that a REMS in necessary to ensure safe use of the drug (as discussed in Section 1.3).

1.2 Risk Benefit Assessment

The pivotal Phase 3 kidney transplant trials demonstrated that belatacept has efficacy as an immunosuppressant in the context of an adult kidney transplant recipient. All immunosuppressive regimens used in this setting are associated with significant risks and benefits; in the clinical practice of transplant medicine, the patient and healthcare providers must work together to identify a regimen which optimizes a range of inter-related outcomes. The selection of a regimen inherently requires balancing various risks and adverse effects. The approval of belatacept, then, hinges on the finding that the risk benefit profile associated with belatacept is potentially favorable for some identifiable population of kidney transplant recipients.

The finding that belatacept may have less efficacy than CsA for the prophylaxis of AR at the exposures tested is an important consideration. AR episodes, especially high grade rejections, may lead to decreased renal function and shortened graft life. An endpoint based on AR has supported the approval of several agents for indications in solid organ transplant, speaking to the clinical relevance of such events (please see Section 6 for a full discussion of endpoints based on AR). On the other hand, however, one must also examine the marginal benefit of immunosuppressive approaches which result in ever lower AR rates. Improved graft survival was observed in the period from 1988 to 1996 corresponding with the introduction of modern immunosuppression agents; an analysis of registry data during that period showed that AR events during the first year of transplantation had a detrimental effect on long-term graft survival.[1] Despite additional incremental decreases in AR rates in the period from 1995 to 2000, however, no further improvement in graft survival resulted.[2] The data suggest, then, that while effective prophylaxis of AR is critical to patient and graft survival; the correlation between AR rates and improved outcomes becomes less clear as AR rates approach those observed in the modern era. The implication is that, with the tools currently available, the marginal benefit of avoiding additional AR events is offset by accompanying toxicities. In evaluating the overall benefit of an immunosuppressive regimen within a given population, then, the rate of rejection represents only one of many factors which must receive consideration.

[1] Hariharan S, Johnson CP, Bresnahan BA, et al. Improved graft survival after renal transplantation in the United States, 1988-96. N Engl J Med 2000; 342: 605-12.
[2] Meier-Kriesche H-U, Schold JD, Srinivas TR, et al. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004; 378-83.

A proper risk benefit assessment would most easily be accomplished through the conduct of clinical trials with adequate power and length of follow up to definitively determine whether the proposed belatacept-based immunosuppressive regimen results in increased patient and graft survival. In the modern transplant era, however, the conduct of such trials is not feasible. Instead, one must attempt a calculus of a variety of disparate surrogate measures to determine whether an approach is a success or failure.

In the context of the current review, the most important factors across treatment groups which require consideration include:

- Rates of AR
- Incidence of PTLD and CNS PTLD
- Incidence and implications of events of PML
- Mean GFR
- Cardiovascular risk profiles
- Patient preferences

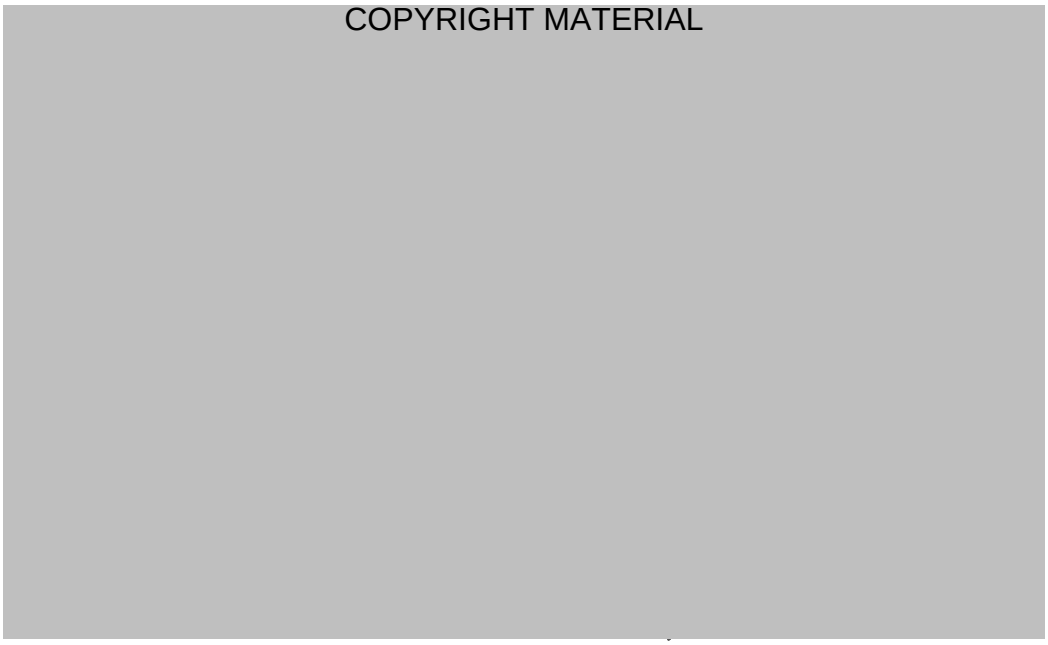
Acute Rejection (AR)

As previously discussed above and exhaustively reviewed in Sections 6 and 7, AR events were numerically more frequent among recipients of the proposed belatacept-based regimen than the CsA control. The point estimate of the rejection rate was significantly higher in the belatacept LI arm: 17.3% compared to 7.2% in the CsA arm [10.1% difference; 97.3% CI (2.9, 17.3)] according to the applicant's analysis. In the trial of extended criteria donor recipients, the point estimates of the rejection rates were higher, but not statistically significant: 17.7% and 14.1%, respectively [3.6% difference; 97.3% CI (-5.5, 12.7)]. The grades of the rejection events also appeared higher, particularly in the trial of recipients of standard criteria kidney transplants.

Given that the patient populations in the trials did not include patients at the highest risk of rejection (e.g., highly sensitized patients or patients undergoing repeat transplantation), the absolute rates of rejection observed in the belatacept control groups appear somewhat high compared to those observed in the general transplant population, as shown in Figure 1below. In 2006, for example, 10-12% of US kidney transplant recipients experienced AR in the first year after transplantation.[3] Those data are consistent with an observation of the clinical trials that belatacept may be associated with higher rates of AR than CsA. The data also suggest, however, that the rates observed in the trial roughly approximate those observed since the introduction of mycophenolate mofetil (MMF) in 1995 (see Figure 1).

[3] United States Renal Data System 2009 Annual Data Report, Chapter 7, p. 292.

Figure 1: Acute Rejections within the First Year Post-Transplant According to OPTN Registry Data

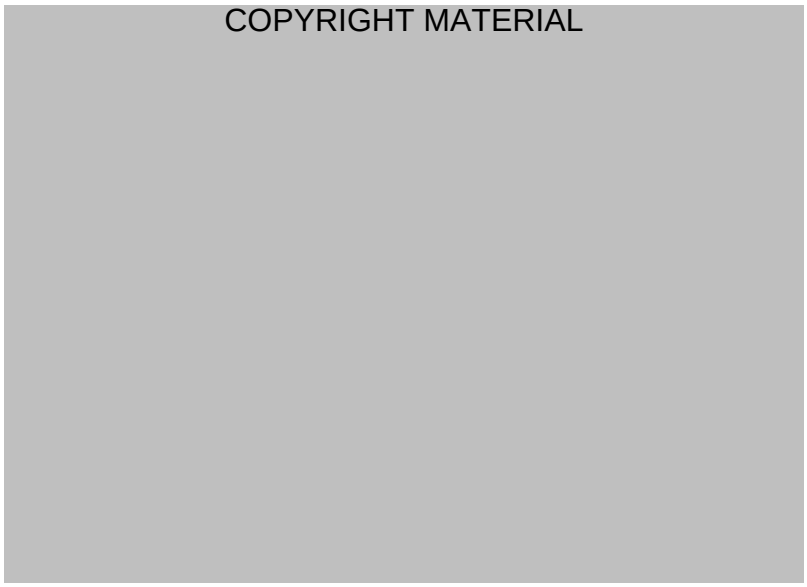


Source: United States Renal Data System 2009 Annual Data Report

While any avoidable AR episode must certainly factor against belatacept in the consideration of the overall risk-benefit analysis, then, most transplant physicians would not judge the higher rates of rejection seen in the pivotal Phase 3 trials as unacceptably high. In fact, many transplant centers and physicians routinely modify immunosuppressive regimens in an attempt to limit the associated toxicities. While preserving low rates of rejection is desirable, slight increases in rates of rejection are often considered justifiable if the modified regimen reduced or eliminates a toxic agent. Steroid withdrawal or avoidance is perhaps the most popular of these approaches, typically resulting in rates of AR greater than 20%: in 2007, almost 40% of first kidney-alone transplants recipients were performed without corticosteroids (see Figure 2).[4,5] Reduced dosing of CNIs represents another maneuver employed to limit toxicities despite awareness that it also results in higher rates of rejection. Such practices remain common and have been deemed successful despite the higher rates of rejection observed.

[4] Kramer BK, Kruger B, Mack M et al. Steroid withdrawal or steroid avoidance in renal transplant recipients: focus on tacrolimus-based immunosuppressive regimens. Transplant Proc. 2005; 37(4): 1789-91.
[5] United States Renal Data System 20009 Annual Data Report, Chapter 7, p. 290.

Figure 2: Steroid Use among Adult First Kidney Alone Transplant Recipients



Source: United States Renal Data System 2009 Annual Data Report

PTLD and CNS PTLD

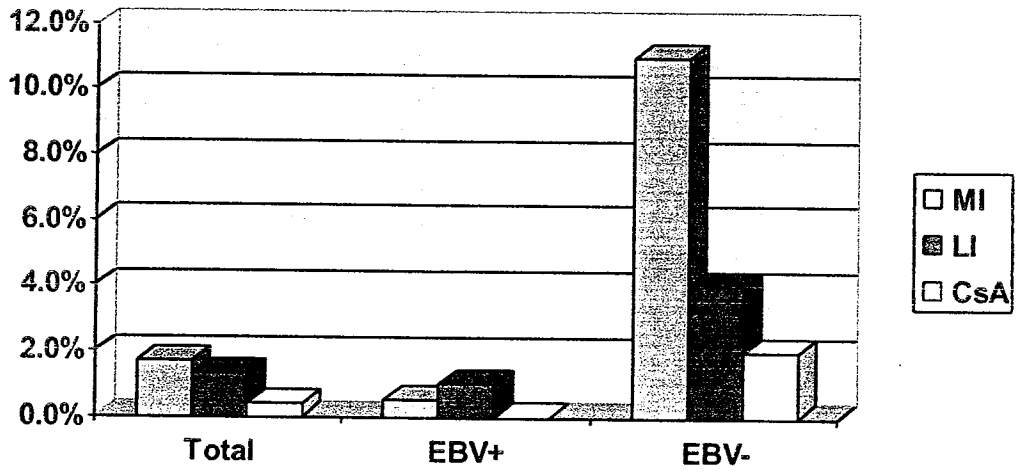
In conjunction with the higher rates of AR, a signal related to increased risk of PTLD (and particularly of CNS PTLD) represented the most significant safety finding of the review (see Section 7.3.2 for more details): eight patients maintained on the belatacept MI regimen and six patients maintained on the belatacept LI regimen developed PTLD compared to only two patients maintained on the CsA regimen. The events of PTLD which occurred in the context of exposure to belatacept were in some ways distinct from the range of presentations of PTLD typically seen among kidney transplant recipients. CNS involvement is generally rare – the literature suggests that such presentation include only 10-15% of kidney transplant recipients who develop PTLD.[6] In contrast, nine out of the fourteen belatacept patients who developed PTLD had CNS involvement. PTLD with CNS involvement is associated with a higher degree of morbidity and mortality. Clinical presentations included instances of hemiparesis, seizures, aphasia, and behavioral changes. Beyond any additional morbidity and mortality associated with a CNS presentation, the unusual pattern of presentation is also relevant because it constitutes additional evidence that the events are causally related to exposure to belatacept. While the general diagnostic term of PTLD has a wide-ranging clinical significance depending on the specific nature of the event, the majority of the PTLD events observed among the belatacept-treated patients in the clinical trials represented more serious presentations: eleven of the fourteen events

[6] Opelz G. Döhler, B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Amer J of Transplantation 2003; 4: 222-30.

were sufficiently severe to either result in death or require treatment with traditional chemotherapeutic agents and/or radiation therapy. In addition to those eleven patients, two additional patients received treatment with rituximab. To date, eight of the fourteen patients have died.

A known risk factor for the development of PTLD is an EBV- serostatus at time of transplantation. Most PTLD events are driven by the EBV virus; those patients without prior immunity have difficulty mounting an effective immune response to EBV virus encountered during or after transplantation. The data from the belatacept clinical trials are consistent with that established correlation: the highest incidences of PTLD were observed among the EBV- patients across treatment groups. Exposure to belatacept appeared to be an independent risk factor for the development of PTLD. Although the increased risk of PTLD was most easily detected among the EBV- patients, the incidence of PTLD among EBV seropositive (EBV+) patients treated with belatacept was also higher than that observed among the EBV+ patients treated with CsA (see Figure 3).

Figure 3: Overall Incidence of PTLD by EBV Serostatus and Treatment Groups in the Belatacept Kidney Trials



Source data: Created by the Clinical Reviewer based on narratives of PTLD events in BLA 125,288

The rate of PTLD among EBV- patients with exposure to belatacept was sufficiently high to prompt the applicant to suggest contraindicating the use of belatacept among EBV- kidney transplant recipients. The data suggest, however, that even among an EBV+ population, use of belatacept-based immunosuppression may result in additional cases of PTLD. As detailed in Section 7.1, an analysis of the clinical trial data suggests that one might expect an additional case of PTLD for approximately every 150 EBV+ kidney transplant patients treated with belatacept rather than CsA and that the majority

of these additional cases would have a CNS presentation. The confidence interval around this estimate is rather large.

The conclusion that a new treatment is associated with an increased risk of frequently fatal malignancy is certainly a significant finding. In the context of kidney transplant recipients, however, it does not necessarily preclude the conclusion that the treatment could still have an overall positive risk-benefit ratio. It may be worth noting that other treatments commonly used in kidney transplantation have been associated with higher rates of PTLD, most notably thymoglobulin. Despite the awareness that such lymphocyte depleting agents have been associated with increased risk of PTLD, transplant physicians continue to rely on them (both as induction agents and for the treatment of some high grade rejection events) due to a belief that the benefits of their use outweigh their risks. In 2007, approximately 40% of first kidney alone transplant recipients received thymoglobulin induction at time of transplant.[7] At present, thymoglobulin is FDA approved only for the treatment of AR.

Progressive Multifocal Leukoencephalopathy (PML)

PML represented another primary safety signal which emerged during the review of the belatacept BLA. A single event of PML was observed in the belatacept kidney transplant program. PML represents a known but extremely rare outcome in renal transplant patients: the best estimate from the literature suggests an incidence rate around one event every 14,000 patient years. The presentation of even one event in the context of a clinical transplant trial, then, represents a safety signal – albeit a signal that is difficult to evaluate with additional context. The presentation of another case of PML in the belatacept liver transplant program provides some such context. PML is associated with significant mortality; both patients have died. It is likely, however, that the incidence of PML in the context of exposure to belatacept remains sufficiently rare such that overall mortality rates would not be significantly impacted. Together with the safety signal of excess CNS PTLD, however, the data suggests that belatacept may have a particular effect on CNS immunity that has not been elucidated.

Glomerular Filtration Rate (GFR)

The applicant prospectively declared the intent to study differences in GFR across treatment groups and discussed approaches with the FDA to using a GFR based endpoint to demonstrate efficacy. For reasons discussed both in the previous section and exhaustively in Section 6, differences in renal hemodynamics confounded the analyses of that efficacy endpoint. While use of the GFR data to provide substantial evidence of the effectiveness of belatacept as a maintenance immunosuppressant was therefore inappropriate, the data clearly showed that patients maintained on the belatacept based regimens exhibited a markedly higher GFR throughout the course of the pivotal trials. Mean GFRs were approximately 15 mL/min higher in the trial of

[7] United States Renal Data System 20009 Annual Data Report, Chapter 7, p. 290.

standard criteria donor (SCD) kidneys and approximately 8 mL/min higher in the trial of extended criteria donor (ECD) kidneys among patients assigned to either of the belatacept groups. Decreased GFR, in both the general population and the kidney transplant population, has been established as a strong independent cardiovascular risk factor and cardiovascular deaths are the leading cause of death in among kidney transplant patients.[8] Epidemiologic studies of kidney transplant recipients have also shown that superior GFRs at one year post transplant correlate with improved graft life.[9,10,11] Such studies are largely based on data from transplant registries comparing outcomes of patients almost universally managed with CNIs (and who therefore had more comparable renal hemodynamics). While it is not entirely clear how applicable those data are to a context where clear differences in GFR exist but renal hemodynamics are also difference, the higher GFRs observed among the belatacept patients in the Phase 3 trials likely translated to some clinical benefit regardless of whether they derived from structural or hemodynamic differences.

Cardiovascular Risk Profiles

Cardiovascular deaths are the leading cause of death among kidney transplant patients.[12] The toxicities associated with CNIs directly contribute to the risk of cardiovascular death. The associated impairment in renal function could arguably constitute the most important toxicity related to the unfavorable cardiovascular outcomes of patients managed with CNIs, but it is not the only one. CNIs cause increases in blood pressure and may lead to diabetes and lipid abnormalities. In the Phase 3 studies, mean systolic blood pressures were approximately 6-8 mmHg and mean diastolic blood pressures were approximately 2-4 mmHg lower among belatacept treated patients compared to CsA-treated patients. The incidence of new onset diabetes after transplantation was also lower among patients who received a belatacept regimen (approximately 5% of those patients versus 10% of patients who received the CsA regimen). Despite the differences in cardiovascular risk profiles, no differences in rates of cardiovascular death were detected within the first two years of follow-up.

Patient Preferences

In comparing the risks associated with belatacept (higher rates of AR, PTLD, PML) with the risks associated with CsA (lower GFR, higher blood pressure, unfavorable impact on metabolic profile), one notes that adverse effects associated with belatacept are

[8] Aakhus S, Dahl K, Wideroe TE. Cardiovascular morbidity and risk factors in renal transplant patients. Nephrol Dial Transplant 1999; 14: 648-54.
[9] Pilmore H, Dent H, Chang S. Reduction in Cardiovascular Death after Kidney Transplantation. Transplantation 2010; epublished ahead of print.
[10] Meier-Kriesche HU, Baliga, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. Transplantation 2003; 75: 1291.
[11] Hariharan S, McBride MA, Cherikh WS, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int 2002; 62: 311-8.
[12] Aakhus S, Dahl K, Wideroe TE. Cardiovascular morbidity and risk factors in renal transplant patients. Nephrol Dial Transplant 1999; 14: 648-54

perhaps more significant when they occur but they manifest in a minority of patients while those associated with CsA are perhaps less dramatic but they affect every patient to a greater or lesser degree. While the evidence remains largely circumstantial, a consensus exists among most transplant experts that exposure to CNIs is nephrotoxic and contributes to the suboptimal long term graft survival presently achieved with the current standard of care.

Patients, like all human beings, exhibit a range of appetites for risk. The data from the trial suggest that for, perhaps, every ten to thirty patients treated with a belatacept regimen rather than a CsA regimen, one additional patient will experience an AR episode. The data further imply that for somewhere around every 150 EBV+ kidney transplant recipients managed with belatacept rather than CsA, one additional patient will develop PTLD. Very rarely patients managed with belatacept may even develop PML. On the other hand, the majority of patients who receive belatacept instead of CsA will not experience any of these events but may anticipate the benefiting from a significantly higher GFR, better blood pressure control, and an improved metabolic profile. In addition, those patients may also potentially benefit from avoiding direct nephrotoxicities inherent to exposure to CNIs. It is likely that, presented with the data, some patients would prefer management with CNIs despite their blanket toxicities while other patients would prefer management with belatacept despite their association with more uncommon (but sometimes catastrophic) outcomes.

Risk-Benefit Summary

In theory, it might be possible to perform a calculus that could determine whether a population of patients managed with belatacept or CsA should, on average, experience better outcomes. In practice, however, limitations of the currently available data prevent a clear determination of overall risk-benefit. Belatacept patients demonstrated a predilection for developing CNS PTLD which led to several instances of death and, despite improved cardiovascular risk profiles, did not experience fewer cardiovascular deaths. On the other hand, a numerically more belatacept patients than CsA patients were alive and with a functioning graft at 24 months in the SCD kidney trial (93.5% vs. 89.6%) though the observation was not convincingly replicated in the ECD kidney trial (82.7% vs. 80.5%) – perhaps a reflection of the benefits accrued from avoidance of the toxicities associated with CsA.

The trials, in the view of this reviewer, provide substantial evidence of the efficacy of belatacept. Certainly, the safety signals appear adequate to justify a contraindication to use among EBV- recipients of kidney transplants. The present data are insufficient to predict whether differences in population outcomes will ultimately emerge between belatacept-based treatments and CsA-based treatments among EBV+ kidney transplant recipients. In the view of this reviewer, however, the data are sufficient to support a positive risk-benefit assessment for well-informed EBV+ adult kidney recipients who are willing to accept a higher risk of relatively uncommon but potentially fatal events in order to avoid well-characterized toxic effects associated with the standard of care.

Reviewer comment: As noted in the discussion above, around 40% of kidney transplant patients are maintained on steroid-free regimens. The vast majority of these patients received induction with thymoglobulin and maintenance with tacrolimus and MMF (as common wisdom holds that use of an IL-2 antagonist for induction or CsA as the CNI would lack sufficient potency). Such practices, while common, represent off-label use of these products as data supporting the safety and efficacy of such approaches have never been submitted to the FDA. Given the higher rates of AR observed with belatacept in comparison to CsA and given the relative contraindication to use of thymoglobulin in conjunction with belatacept due to increased risk of PTLD, it is likely that regimens using belatacept will continue to require use of corticosteroids (which are associated with their own well-known toxicities). The risk-benefit analysis above relied on a comparison of the proposed belatacept regimen to a CsA-based regimen whose relative safety and efficacy has been established in multiple trials reviewed by FDA, but whose popularity with US transplant physicians has waned markedly over the last decade. A meaningful risk-benefit analysis of the proposed belatacept regimen in comparison to some more novel regimens (including steroid-free regimens) currently favored by the US transplant community is not possible based on available data. In the event that belatacept is approved, however, market forces will likely ensure that trials making such direct comparisons will be performed.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The applicant has proposed a Risk Evaluation and Mitigation Strategies (REMS) for belatacept. The stated goals are:

(b) (4)

The proposed REMS elements include a (b) (4)

(b) (4)

(b) (4)

The term REMS refers to a set of strategies beyond labeling and routine safety reporting designed to ensure that the benefits of a drug outweigh its risks. REMS should reflect specific goals and should be associated with related objectives. Typical components of REMS include Medication Guides which help achieve goals through patient education, Communication Plans which help achieve goals through education and enlistment of health care providers, and ETASUs which help assure that goals are achieved by linking access to the drug with compliance with adherence to REMS objectives. For REMS to have an optimal impact they must not only reduce the risk associated with the product but they must also preserve the benefit associated with the product. Restricting access to drug will necessarily have some impact on the benefit of the product; such REMS, then, should have particularly clear benefits to justify their implementation.

The primary modifiable safety issue associated with belatacept is PTLD, particularly CNS PTLD. While the observed incidence of PTLD was higher among both EBV+ and EBV- groups of patients maintained with belatacept rather than CsA in the pivotal kidney transplant trials, the absolute risk of PTLD among EBV- patients was sufficiently high to prompt the applicant to propose contraindicating the use of belatacept among EBV- kidney transplant recipients. In addition, the relative safety of belatacept among EBV+ kidney transplant recipients remains one of the most important areas requiring further study.

Labeling, including a Boxed Warning and Contraindication against the use of belatacept among EBV- kidney transplant recipients due to an elevated risk of PTLD and CNS PTLD, should limit such exposures to belatacept. Labeling alone, however, is not sufficient. REMS designed with the goals of both further reducing use of belatacept in that population and also collecting additional data regarding the safety of belatacept among EBV+ kidney transplant recipients could help ensure that the benefits associated with belatacept outweigh its risks.

The decision to prescribe belatacept is one that will be undertaken by a limited number of physicians with specific training in transplant medicine. Fewer than 300 centers in the United States have the capacity to perform a kidney transplant. Targeting materials to this group of physicians to communicate the risks of PTLD associated with belatacept and to encourage compliance with related data collection, then, represents an achievable goal.

I agree with the recommendation of the Cardiovascular and Renal Drug Advisory Committee which emphasized the need for a "tight registry" to monitor the outcomes of

belatacept patients, particularly with respect to PTLD (see also Section 9.3).[13] In my estimation, the primary goal of the registry should be the collection of additional outcomes data, not the enforcement of the contraindication against the use of belatacept among EBV- kidney transplant patients. While monitoring the use of belatacept among EBV- patients should represent a component of the data collection, proper labeling and a well-designed communication plan should suffice to inform the small cadre of transplant physicians about the contraindication to use among EBV- kidney transplant patients. While a small number of physicians may consciously choose to ignore the Boxed Warning under rare circumstances (e.g., a patient unable to tolerate CNIs), it is unlikely that any prescribing physicians will be unaware of the contraindication. If the data collected through the registry suggest otherwise, ETASUs restricting drug distribution to EBV+ patients could be added subsequently.

As the intent of the registry is to monitor safety issues and not to restrict the distribution of belatacept, ETASUs may not be required and are not recommended by this reviewer. Without the use of ETASUs, one cannot assure 100% compliance with a registry. On the other hand, by law, UNOS/OPTN already collect data on 100% of US transplant patients. While the data collection conducted by UNOS/OPTN is imperfect in some regards, the data regarding initial immunosuppression regimens are generally reliable. In addition, UNOS/OPTN requires collection of EBV serostatus at time of transplant. Whether the belatacept registry is attached to the existing UNOS/OPTN registry or whether a separate belatacept registry is established, use of UNOS/OPTN data should allow the identification of essentially every patient whose initial regimen includes belatacept. Assuring the identification of all patients who are converted to belatacept from another immunosuppression regimen would be more difficult in the absence of ETASUs. As the primary intent of the registry is to monitor safety issues associated with belatacept, however, a registry which captures the vast majority of belatacept patients may be sufficient. While ETASUs could provide added assurance that a belatacept registry would capture data for every patient with exposure to belatacept, the added value may be offset by the harm incurred by restricting access (including, potentially, the harm associated with missing or delaying an infusion of belatacept).

Another important safety concern associated with belatacept related to its impact on CNS immunity. In addition to the increased incidence of PTLD, two events of PML were observed in the belatacept developmental program (one in a kidney transplant patient, one in a liver transplant patient). In addition, a higher rate of CNS infections were observed among recipients belatacept MI regimen than among recipients of either the belatacept LI regimen or the CsA control regimen in the pivotal kidney transplant trials. Unlike the risk of PTLD, which is associated with pre-transplant EBV status, no clear strategy presently exists to modify the potential of belatacept with regards to CNS infection. I recommend, however, monitoring a registry of belatacept patients for signals

[13] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm192863.htm

related to CNS immunity (including PML). As the intent of the registry is to monitor a safety issue rather than restrict the distribution of belatacept to an identifiable patient population, a registry either attached to or validated against UNOS/OPTN data (rather than one attached to an ETASU) may be sufficient.

Reviewer comment: I recommend that belatacept should be approved with a REMS that includes a Medication Guide and a Communication Plan. Goals of the Communication Plan should include increased awareness of the risk of PTLD, CNS PTLD, and PML with belatacept and of the contraindication of its use among EBV- kidney transplant recipients. The Communication Plan should also include elements which will encourage compliance with belatacept registry data collection.

In order to formulate more detailed recommendations regarding the structure of the REMS, additional input from DRISK is required. The DRISK review of the applicant's proposed REMS is ongoing at the time of this writing.

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant has proposed the following postmarketing studies which may, in part, address outstanding concerns related to belatacept:

- IM103074 – Pattern of Use of Belatacept in US Transplant Recipients
- IM103075 – Belatacept and Risk of PLTD in US Renal Transplant Recipients
- IM103076 (b) (4)

(b) (4)

The protocol for Study IM103074 proposes (b) (4)

Reviewer comment: While the submission of data to the registry is mandatory, transplant center compliance with UNOS/OPTN data collection is imperfect. Data collected at time of transplant (including those related to recipient EBV and CMV serostatus and initial immunosuppression regimen) tend to be more reliable than data collected at follow up (including those related to current immunosuppression regimen). While missing data represents a limitation of the UNOS/OPTN database, the proposed

study would provide significant insight into patterns of belatacept use among EBV+ and EBV- as an initial immunosuppressant regimen. The results of the study may be less reliable, however, as a means to measure belatacept use among EBV+ and EBV- patients who are converted to belatacept-based immunosuppression some time after transplantation.

The protocol for Study IM103075 proposes to (b) (4)

Reviewer comment: While data submission regarding PTLD is a required component of OPTN/UNOS reporting, the reliability of such data is unclear. Educating transplant centers about the importance of these data should represent an important component of the Communication Plan of the REMS (see Section 1.3).

The Clinical Pharmacology review team has suggested a requirement for additional study of a potential link between CMV serostatus and development of PTLD in the EBV+ kidney transplant population (see Section 7.5.4). Minor modifications to IM103075 may enable this study to meet such a requirement.

Study IM103076 (b) (4)

Reviewer comment: As a prospective study, IM103076 will have greater ability to collect in-depth data and verify outcomes than study IM103075. In addition, enrollment of a large number of patients into a prospective observational study may be easier than enrollment of a similar number of patients (b) (4) *The study may, therefore, provide some additional insight into the risk-benefit profile of belatacept, particularly with regards to incidence rates of PTLD and CNS PTLD in an EBV+ patient population beyond that provided by IM103075.* (b) (4)

(b) (4)

(b) (4)

The Maternal Health Team (MHT) and Division of Epidemiology in the Office of Surveillance and Epidemiology have been consulted regarding the applicant's proposed postmarketing studies and their reviews are ongoing at the time of this writing. In order to formulate more detailed recommendations regarding the (b) (4) *additional input from DRISK will also be required.*

2 Introduction and Regulatory Background

2.1 Product Information

Belatacept (proposed trade name: Nulojix found acceptable by DMEPA on October 5, 2009) is a new molecular entity (NME) developed as a new therapeutic agent for immunosuppression in kidney transplant recipients; it was studied as a replacement for CsA in an immunosuppressive regimen that also included an IL-2 antagonist, MMF and corticosteroids.

The applicant has proposed that belatacept receive an indication for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving kidney transplants. Immunosuppressants used as components of maintenance regimens among recipients of solid organ transplants have previously been granted an indication for prophylaxis of rejection; the indication of "preservation of a functioning allograft", however, represents a novel indication not previously granted. The applicant has proposed that belatacept should be contraindicated among patients who are EBV seronegative due to an elevated risk of post-transplant lymphoproliferative disorder (PTLD). The proposed dosing regimen is:

Dosing for Initial Phase	Dose
Day of transplantation, prior to implantation (Day 1)	10 mg/kg
Day 5, Day 14, and Day 28 (1 month after transplantation)	10 mg/kg
Month 2 and 3 after transplantation	10 mg/kg
Dosing for Maintenance Phase	**Dose**
Monthly, starting at Month 4 after transplantation	5 mg/kg

Belatacept is a recombinant soluble fusion protein consisting of the extracellular domain of human CTLA-4 and a fragment (hinge–CH2–CH3 domains) of a modified Fc domain of human IgG1. CTLA-4 is a member of the immunoglobulin superfamily with structural similarities to CD28. While both CTLA-4 and CD28 bind CD80/86 on antigen presenting cells, CTLA-4 inhibits activation of T cells whereas CD28 augments activation of T cells. As a soluble fusion protein, belatacept does not transmit inhibitory signals like CTLA-4, but it interferes with CD28:CD80/CD86 interactions, key costimulatory signals required for T cell activation. T cells require at least 2 signals for full activation. The first signal is delivered by the T cell receptor and the second via costimulatory molecules like CD28. By preventing signaling through CD28, belatacept modulates immune responses and acts as an immunosuppressant.

The pharmacologic class for belatacept is still under discussion at the time of this writing. However, it is structurally related to abatacept (Orencia®) which is designated as a "selective T cell costimulation modulator." Belatacept has greater binding affinity and inhibition of T-cell proliferation and activation than abatacept in human *in vitro* studies. Abatacept is not used as an immunosuppressant in transplantation and is indicated for the treatment of rheumatoid arthritis and polyarticular juvenile idiopathic arthritis. However, toxicology studies of abatacept in rodents are considered to be more relevant than nonclinical rodent studies of belatacept due to a greater *in vitro* binding affinity and *in vivo* inhibition of T-cell dependent antibody response than belatacept (see Sections 4.3 and 7.3.5).

2.2 Tables of Currently Available Treatments for Proposed Indications

Several products are currently labeled for use as components of a maintenance immunosuppressive regimen for the indication of prophylaxis of organ rejection in recipients of kidney transplants, including CsA, tacrolimus, sirolimus, azathioprine, mycophenolate mofetil, mycophenolate sodium, and corticosteroids, as shown in Table 1. Both mycophenolate mofetil and mycophenolate sodium are metabolized to produce the active moiety, mycophenolic acid (MPA). The products are used in a variety of combinations to form immunosuppressive regimens. The labeling across products is inconsistent: as newer products have been approved and labeled in the context of various regimens, labeling of the other components of those regimens has not always been updated. In addition, off-label use of these products is common. According to all

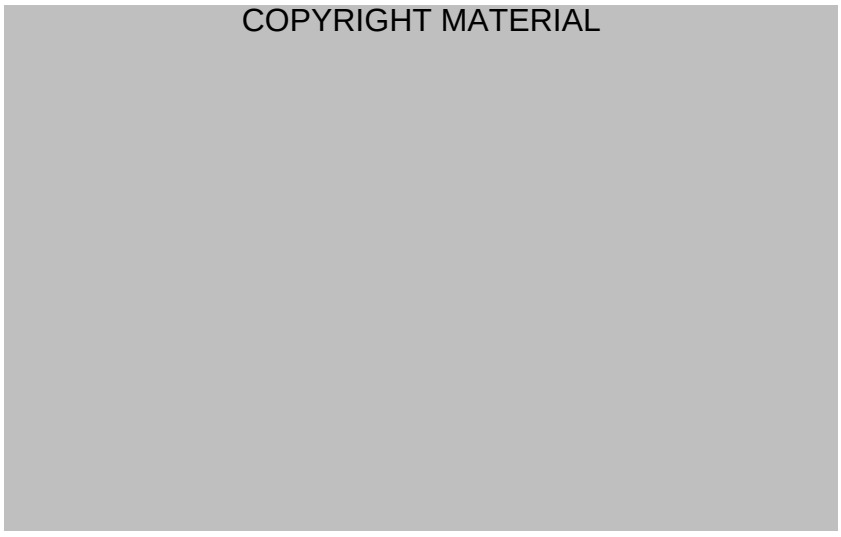
labeling, however, immunosuppression regimens used in kidney transplant patients should include a CNI (either CsA or tacrolimus).

Table 1: Maintenance Immunosuppressants in Kidney Transplantation

Immunosuppressant	**Trade Name**
Cyclosporine	Neoral, SandImmune, and generics
Tacrolimus	Prograf
Sirolimus	Rapamune
Mycophenolate Mofetil (MMF)	CellCept
Mycophenolate Sodium (MPS)	Myfortic
Azathioprine	Imuran
Corticosteroids	Various

Belatacept was studied as a replacement for CsA in an immunosuppressive regimen that also included an IL-2 antagonist, MMF, and corticosteroids. CsA is a member of a class of immunosuppressives known as CNIs; tacrolimus is another CNI which has received approval for indications in solid organ transplantation. CNIs are the cornerstone of immunosuppressive regimens in kidney transplantation: more than 80% of patients receive either tacrolimus or CsA as a component of their immunosuppressive regimen (see Figure 4).

Figure 4: Most Common Maintenance Immunosuppresion Regimens among US Kidney Transplant Recipients at Time of Transplant: 2005-07

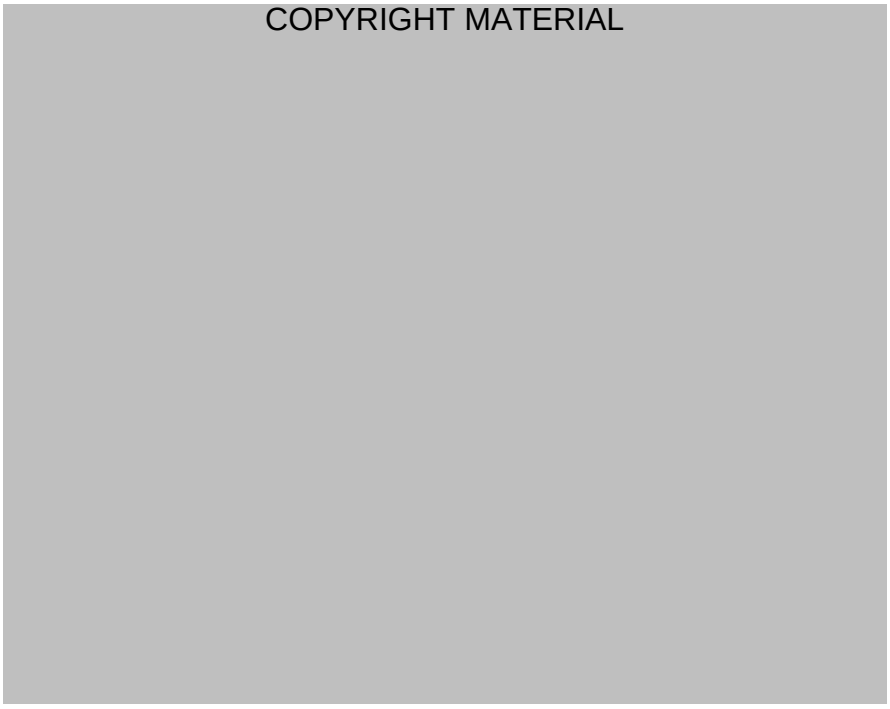


Source: United States Renal Data System 2009 Annual Data
(Tac=tacrolimus; MPA=mycophenolic acid; cyclo=cyclosporine; mTOR=sirolimus)

In the pivotal Phase 3 kidney transplant trials, the induction immunosuppressant used across treatment groups was basiliximab. Currently available products frequently used as induction immunosuppression agents in kidney transplantation include basiliximab

(Simulect), daclizumab (Zenapax), antithymocyte globulin (Thymoglobulin), muronomab-CD3 (OKT3), and alemtuzumab (Campath). Of these, only basiliximab and daclizumab – both IL-2 receptor antagonists – have been approved for this indication. The use of IL-2 receptor antagonists as induction agents peaked around 2003; currently, thymoglobulin (a lymphocyte depleting agent) is the most commonly used induction agent (see Figure 5). Thymoglobulin is considered a more potent induction agent than basiliximab by the transplant community, though its use has been associated with higher rates of some adverse events including PTLD.

Figure 5: Most Common Immunosuppression Induction Agents Used in US Kidney Transplant Recipients: 2005-07



Source: United States Renal Data System 2009 Annual Data Report

2.3 Availability of Proposed Active Ingredient in the United States

Belatacept is a new molecular entity not currently marketed in this or any other country.

(b) (4)

2.4 Important Safety Issues With Consideration to Related Drugs

As belatacept was studied as a replacement to CsA, a calcineurin-inhibitor in the core studies of the BLA application, the safety issues associated with CsA and tacrolimus

(the most commonly used CNI among U.S. kidney transplant patients) are most relevant.

Calcineurin-inhibitors are associated with increased frequency and/or worsening of a variety of cardiovascular risk factors, including new onset diabetes after transplantation, hypertension, and dyslipidemia. Calcineurin-inhibitors may also lead to decreased renal function, both through a physiologic effect on renal blood flow and also through a cumulative nephrotoxicity whose mechanisms have not been well-characterized. Avoidance of this CNI nephrotoxicity represents a primary goal of efforts to identify effective CNI-free immunosuppression regimens.

In addition to these common adverse events, CNIs have also been associated with a variety of serious but rare adverse events. These events include lymphomas and other malignancies, opportunistic infections (including polyoma viruses and CMV infections), and progressive multifocal leukoencephalopathy.

At the time of the conduct of the trials, tacrolimus and MMF were not labeled for use with one another in kidney transplantation as data supporting their safe and effective use together had not been submitted to FDA for review. For that reason, the applicant was advised to use CsA rather than tacrolimus as the comparator agent in the control group. As demonstrated by Figure 4 above in Section 2.3, tacrolimus has superseded CsA as the most commonly used CNI in the US due to a perception among transplant practitioners that tacrolimus has greater efficacy than CsA.

Belatacept was studied in the context of a regimen which included induction with basiliximab (an IL-2 receptor antagonist) rather than thymoglobulin (a lymphocyte depleting agent and the most common induction agent used among US kidney transplant recipients – see Figure 5 above in Section 2.3). While the use of thymoglobulin rather than basiliximab in conjunction with belatacept might be expected to result in lower rates of AR, it might also potentiate the risk of PTLD associated with belatacept. (b) (4)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Belatacept has been developed under IND 9,418 for indications in solid organ transplantation since October 2000. During its development, belatacept has fallen under the purview of different centers and divisions (including CBER, ODEVI at CDER, and, most recently, DSPTP at CDER). In September of 2004, at an End-of Phase-2 Meeting, endpoints for Phase 3 studies were discussed, including the co-primary endpoints of death and graft loss and of the composite renal impairment endpoint. In August of 2005, a SPA of Study IM103008 was submitted to the FDA. While discussions were held regarding non-inferiority margins for the composite of death and graft loss and regarding the relevance of the composite renal impairment endpoint, the understanding of the science supporting both non-inferiority studies and transplant renal function have

evolved at FDA since 2005. While the FDA acknowledges that certain agreements were reached which may have seem reasonable in 2005, it must also recognize that emerging science must take precedence over formal agreements.

Other important regulatory actions:

- Fast track designation granted on January 26, 2005
- Orphan Drug designation granted on February 20, 2008
- Pre-BLA meetings occurred in April 2008 and May 2009

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

For the most part, the BLA submission was well-organized and complete. The clinical study reports presented the data from the clinical trials in a clear fashion, both in the body of the report and the in the appendices. The datasets were not formatted in such a fashion to allow the optimal use of the jREVIEW application: better formatting would have allowed manipulation of the datasets without the need for reference to codes. Due to the formatting, some delays were encountered as the information technology group at FDA declined to load the datasets onto the jREVIEW server until updated datasets were formatted. The applicant should not, however, be held primarily responsible for those delays. The original datasets provided were immediately amenable to manipulation with SAS and JMP.

The submission did, however, include critical defects regarding studies referenced in support of the applicant's original interpretation of the PTLD safety signal. The applicant initially asserted that the risk of PTLD among the EBV- patient population was elevated, but appeared similar in the EBV+ patient population based on analyses of registry data. In support of those claims, the applicant referenced an epidemiologic study of Centers for Medicare and Medicaid Services (CMS) claims data commissioned by BMS and a personal communication from Dr. Gerhard Opelz (the director of the Collaborative Transplant Study). When asked to produce datasets and computer code substantiating the epidemiologic study, the applicant reported that such material would only be available through the group subcontracted to perform the study. In part due to the delays in responding to the request, the Division ultimately obtained CMS claims datasets and UNOS transplant patient datasets directly from the USRDS and the SRTR. The Division's analysis of those datasets did not support the findings submitted by the applicant. In addition, review of the literature generated by the Collaborative Transplant

Study appeared inconsistent with the personal communication cited by the applicant.[14] Direct communication with Dr. Opelz confirmed that the personal communication was erroneous.

Reviewer comment: The use of registry data by the applicant appeared focused on mitigating concerns regarding the PTLD safety signal rather than on elucidating the signal further. In addition to the defects in the original BLA submission and in the response to Division requests describe above, one additional event suggests the possibility that the applicant examined PTLD data from outside of the clinical trials selectively. During discussions with the applicant regarding their use of data provided by USRDS around November 2009, it became evident to BMS that the Division had obtained OPTN/UNOS datasets (see Section 7.3.2 and the Statistical Safety Review for further details regarding these datasets). Almost immediately afterwards, BMS provided an analysis of the OPTN/UNOS data, not previously submitted, which (consistent with the FDA and SRTR analysis of those data) supported the findings of the clinical trials linking exposure to belatacept with higher rates of PTLD. It is unclear why that analysis of OPTN/UNOS data had not been included in the original BLA submission nor in the Investigator's Brochure discussion of the risk of PTLD.

3.2 Compliance with Good Clinical Practices

DSI inspections are routinely performed for New Molecular Entities (NMEs). While no data integrity issues prompted for-cause inspections, DSI inspections were therefore performed at several centers where the belatacept Phase 3 kidney trials were conducted. The two Phase 3 trials (IM103008 and IM103027) were conducted at 105 and 79 sites, respectively.

The following sites were selected for inspection and the overall results of the inspections are discussed below in Table 2.

[14] Opelz G, Daniel V, Naujokat C, et al. Epidemiology of Pretransplant EBV and CMV Serostatus in Relation to Posttransplant Non-Hodgkin Lymphoma. Transplantation 2009; 88: 962-7.

Table 2: Clinical Sites Inspected

Name of CI or Sponsor Location	Protocol #: and # of Subjects:	Inspection Dates	Interim Classification	Final Classification
Lionel Rostaing, MD/PhD Hoptial de Rangueil C H U De Toulouse (Office) Chu De Toulouse Hopital Rangueil Nephrologie-Hemodialyse-Transplantation 1 Avenue Du Pr Jean Poulhes Toulouse Cedex 31054 France	IM103008 Site 076 41 subjects IM 103027 Site 0035 24 subjects	12/07/09 – 12/18/09	Pending	Pending
Guillermo Mondragon-Ramirez, M.D. Instituto Mexicano De Transplantes, SC (Office and Patient Treatment) Av. Alta Tension 580-2 Colonia Cantarranas Cuernavaca, Morelos 62448 Mexico	IM103008 Site 0116 24 subjects	12/14/09 – 12/17/09	NAI	NAI
Rafael Reyes-Acevedo, MD Centenario Hospital Miguel Hidalgo (Office) Galeana Sur 465, Col. Obraje Aguascalientes, Aguascalientes 20230 Mexico	IM103008 Site 0123 25 subjects	12/7/09 – 12/11/09	NAI	NAI
Jose Medina Osmar Pestana, MD Hospital Do Rim E Hipertensao Rua Borges Lagoa 960 Vila Clementino Sao Paolo 04028-002 Brazil	IM103027 Site 0091 36 subjects	11/30/09 – 12/4/09	NAI	NAI
Valter Duro Garcia, PhD Hosp. Dom Vicente Scherer (Office) Avenue Independencia, 155 6o Andar Porto Alegre, Rio Grands Do Sul 90020-090 Brazil	IM103027 Site 0093; 21 subjects	12/7/09 – 12/11/09	NAI	NAI
Flavio Vincenti, MD University of California San Francisco Medical Center Transplant Service 505 Parnassus Avenue, Room 884M San Francisco, CA 94143-0780	IM103008 Site 0010 25 subjects IM103027 Site 010 7 subjects	10/21/09 – 11/04/09	VAI	Pending
Barbara Bresnahan, MD Froedtert Memorial Hospital 9200 Wisconsin Ave. FMCLB 216 Milwaukee, WI 53226	IM103008 Site 006 15 subjects	11/12/09 – 12/3/09	VAI	VAI

Name of CI or Sponsor Location	Protocol #: and # of Subjects:	Inspection Dates	Interim Classification	Final Classification
Sander Scott Florman, MD (Replaced by Rubin Zhang, MD) Tulane University Hospital and Clinic 1415 Tulane Avenue TW-35 New Orleans, LA 70112	IM103027 Site 0002 26 subjects	12/2/09 – 12/8/09	NAI	NAI
Bristol-Myers Squibb 10 Waterview Blvd., 3rd Floor Parsippany, NJ 07054	IM103008 IM103027	11/09/09 – 11/25/09	VAI	Pending

Key: NAI = No deviation from regulations, VAI = Deviation(s) from regulations, Pending = Preliminary classification based on information in 483 or preliminary communication with the field
Source: Clinical Inspection Summary, Division of Scientific Investigations

According to the final Clinical Inspection Summary (CIS) from DSI dated March 9, 2010, the site inspections of Drs. Mondragon-Ramirez, Reyes-Acevedo, Pestana, Garcia, Vincenti, Bresnahan, and Florman/Zhang concluded that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspections documented minor regulatory violations at the sites of Drs. Vincenti, Bresnahan, and Florman/Zhang regarding protocol, adverse event reporting, and informed consent violations. In general, the studies at these sites appear to have been conducted adequately: the CIS report concluded that the data generated by these sites may be used in support of the indication.

There were numerous protocol violations cited by the inspector at Dr. Rostaing's site, resulting in the issuance of a Form FDA 483. However, from DSI's review of Dr. Rostaing's written response, it appeared that the majority of the protocol violations were cited in error. The CIS report states that "At present, the data derive from this site appear acceptable for use in support of the NDA. If conclusions change upon receipt of the EIR, the review division will be notified expeditiously."

Concern about data integrity arose from the inspection of BMS. The applicant was not able to document the time of belatacept reconstitution prior to intravenous administration. Stability data in the BLA only goes out to 24 hours. The applicant's written response stated that at most sites, other site records (e.g., Pharmacy records) would allow precise determination of time of belatacept reconstitution. Sample documents from each site inspected were requested and provided in a written submission dated February 25, 2010 (with the exception of Dr. Florman/Zhang; at the time the CIS was written, BMS had yet to provide Dr. Vincente's records). The sample documents (with the exception of those from Drs. Vincenti Florman/Zhang) confirmed the applicant's claim that reconstitution date and time could be verified in 11 of the 12 examples requested. DSI concluded that although this is a small sample, it appears that in most cases verification of time of reconstitution and infusion is available at the trial sites.

Another issue raised during the inspection of BMS was the ability of the applicant to ensure compliance with trial procedures and requirements, in particular at Dr. Rostaing's site. Study monitoring appeared to have been effective at detecting issues requiring resolution, but achievement of resolution of these issues was not always documented. Additionally, resolution was not always accomplished in a timely manner. DSI concluded that the issues identified as unresolved do not appear to affect data integrity.

In conclusion, DSI stated that the data collected and maintained at the applicant's site and the eight clinical sites audited appear consistent with that submitted to the agency as part of and in support of BLA 125,288 and may be used to support the BLA.

3.3 Financial Disclosures

Information regarding financial disclosures was included in the BLA submission; in the view of the clinical reviewer, the disclosures did not materially affect the apparent integrity of the submitted trial data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC product quality team (Jack Ragheb, M.D., PhD. And Susan Kirshner, Ph.D.) has not provided a review at the time of this writing.

Reviewer comment: During the review cycle, a CMC reviewer expressed concerns about the immunogenicity of belatacept. The reviewer also expressed concerns about its potential for autoimmunity, both in patients maintained on belatacept and in individuals with incidental exposure to belatacept in utero. The concerns did not relate to specific findings of the CMC review but rather derived from the CMC reviewer's familiarity with abatacept, a related molecule with properties and concerns similar to those of belatacept. Please see Section 4.3 (Preclinical Pharmacology/Toxicology) and Section 4.4 (Clinical Pharmacology) and Section 7 (Safety) for further discussion of these issues.

The CMC drug substance team (Michelle Clark-Stuart, MGA, MT (ASCP) and Patricia Hughes, Ph.D.) recommends BLA approval from a product quality/ microbiology perspective.

The CMC Micro team (Bo Chi, Ph.D. and Patricia Hughes, Ph.D.) *do not* recommend approval of the BLA from a sterility assurance and product quality microbiology perspective. A request for information was sent to the applicant on January 29, 2010 and the applicant responded with a 486-page amendment on February 12, 2010. This submission is considered to be a major amendment. Therefore, the BLA will be given a Complete Response (CR) based on CMC deficiencies and the applicant will be asked to address these deficiencies in a subsequent review cycle.

According to Dr Chi's review, the BLA is not recommended for approval from a sterility assurance and product quality microbiology perspective because information on a container closure integrity (CCI) test is required for a successful stability program. Information on the CCI test was not available during the CMC drug product sterility review. In addition, the review states that the pre-license inspection of the drug product manufacture site was performed the week of March 15, 2010. Results of that inspection were not available prior to the completion of this review.

Reviewer comment: Prior to approval of the belatacept BLA, the applicant must satisfy the concerns raised during the review of drug product sterility.

4.2 Clinical Microbiology

Please refer to the Microbiology/Immunology Review by Aaron Ruhland, Ph.D. for details.

The Microbiology/Immunology team states that the BLA is approvable pending an acceptable version of the labeling. Labeling should specify the increased risk of developing PTLD in EBV negative patients, and certain standards should be maintained for the testing EBV serostatus. The EBV tests used should be highly specific for IgG antibodies against VCA and EBNA antigens. These clarifications should be made in appropriate sections of the labeling so that the message goes to the prescribing physicians and the clinical microbiology laboratories responsible for EBV testing.

In proof-of-concept studies, belatacept demonstrated binding activity with CD80 and CD86 (its putative targets), suppression of human T-cell proliferation induced by antigen presenting cells, and suppression of IL-2, IL-4, IFN-γ in mixed lymphocyte reaction cultures. Additional studies suggested that the saturation level of CD86 on antigen presenting cells in a mixed lymphocyte reaction culture correlated with the activity of belatacept. In a primate orthotopic transplant model, belatacept showed efficacy in prolonging graft survival and inhibiting the development of anti-donor antibodies.

Belatacept is a second generation variant of the related fusion protein abatacept (Orencia); belatacept was generated from abatacept by changing two amino acids in the CTLA-4 binding domain in order to increase the binding affinity to human CD80 and CD86. Whereas belatacept has greater potency in humans and non-human primates than abatacept, abatacept has greater potency than belatacept in rodents. For that

reason, some non-clinical studies in rodents were performed with abatacept. Administration of abatacept in rats was associated with an increased absolute number of T-cells, CD4+ T cells, and CD8+ T cells in the peripheral blood but with a decrease in the number of regulatory T-cells (CD25+, FOX3+, CD3+). After discontinuation of abatacept, the T-cell subsets recovered towards normal levels (see also Section 4.3).

Flow cytometry analysis of samples obtained from a small number of patients enrolled in the Phase 2 and Phase 3 clinical trials showed a transient decrease in regulatory T-cells. The decrease was similar among patients in both the belatacept and CsA groups.

Based on observations in the clinical trials of kidney transplantation, the applicant has recommended contraindicating the use of belatacept in EBV- kidney transplant recipients due to an increased risk of PTLD. As outlined in the Clinical Microbiology review, all diagnostic tests may occasionally return false positive and false negative results. In the As a false positive EBV serology result may result in an EBV- kidney transplant patient receiving belatacept, the Clinical Microbiology review recommends the use of a panel of test with high specificity that can detect IgG antibodies against both VCA and EBNA to minimize the likelihood of a false positive EBV serostatus.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the nonclinical Pharmacology and Pharmacokinetic Review by Janice Lansita, PhD and the Toxicology Review by Ying Mu, PhD/MD for details.

The Pharmacology/Toxicology team supports the proposed use of belatacept in the prophylaxis of organ rejection in kidney transplant patients and has no post-marketing requirements or post-marketing commitments for the applicant.

In a peri-, post-natal study of rats with exposure to belatacept, infections in the dams led to mortality and loss of litters. Infections leading to mortality were also observed in studies of juvenile rats with exposure to abatacept.

An anti-drug antibody (ADA) response to belatacept was observed in mice, rats, rabbits, and cynomolgus monkeys. The incidence and onset of immunogenicity directed against belatacept varied inversely with belatacept dosing: as drug concentrations decreased, the appearance of ADAs increased. ADAs directed against belatacept have a theoretical potential to result in decreased efficacy and also in autoimmune disease (through modulation of endogenous CD80/86 and CTLA-4 signaling pathways).

Autoimmunity was observed in adult and juvenile rats exposed to abatacept, including thyroiditis and insulitis. The findings increased in severity after the withdrawal of abatacept. In addition, one out of twenty rat offspring exposed to abatacept *in utero* and during lactation developed autoimmune thyroiditis. Evidence of autoimmunity was not detected in nonclinical studies of belatacept. However, belatacept is less potent in rats than abatacept.

Carcinogenicity studies with belatacept were not conducted. Given that abatacept is more potent than belatacept in rodents (and that belatacept is more potent than abatacept in humans and non-human primates), carcinogenicity studies with abatacept were submitted instead. Those studies had been previously reviewed as part of the abatacept application (BLA 125,118). In a carcinogenicity study of abatacept in mice, an increased incidence of lymphomas and mammary gland tumors were observed.

4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology Review by Gerlie Gieser, PhD, Seong Jang, PhD, Jiang Liu, PhD, Shashi Amur, PhD, and Li Zhang, PhD for details.

The Clinical Pharmacology review team agrees that the clinical pharmacology information presented in the BLA is acceptable to support the approval of belatacept for the proposed indication of prophylaxis of organ rejection (b) (4) Based on the efficacy and safety findings observed in the pivotal clinical trials, the reviewers agree with the sponsor's proposal to recommend the less intensive (LI) belatacept regimen for the prophylaxis of kidney transplant rejection.

The following studies and trials informed the clinical pharmacology review (see Table 3).

Table 3: Studies and Trials with Key Information on the Clinical Pharmacology of Belatacept (Intravenous)

Study Number/ Manufacturing Process of Drug Substance	Objectives	Study Design/ Treatment Duration	Type of Subjects	Dosage, Route	Number of Treated Subjects
Phase 1 Studies of IV Belatacept in Healthy Subjects					
IM103001[3] (b) (4)	Safety, tolerability, PK, immunogenicity	Phase 1, randomized, double-blind, placebo-controlled/ Single dose	Healthy	Belatacept 0.1, 1, 5, 10, 20 mg/kg or placebo; IV	Belatacept,30 Placebo, 10
IM103024[4] (b) (4)	PK, safety, immunogenicity	Phase 1, randomized, open-label, parallel group/ Single dose	Healthy	Belatacept 10 mg/kg, (b) (4) IV	15 (b) (4) 15 (b) (4)
Phase 2 Studies of IV Belatacept in Renal Transplant Recipients					
IM103047[6] Interim PK (b) (4)	PK, PD, safety	Phase 2, open-label/ 3 years	De novo renal transplant subjects	**Belatacept LI regimen:** same as IM103008	12
IM103100[7] (12-month phase) (b) (4)	Efficacy, safety, immunogenicity, PK	Phase 2, randomized, open-label, partially-blinded, active-controlled, parallel-group/ Ongoing until drug is marketed	De novo renal transplant subjects	**Belatacept MI regimen:** same as IM103008 **Belatacept LI regimen:** 10 mg/kg Days 1, 15, 29, 57, 85, then 5 mg/kg every 4 or 8 weeks; **CsA**: same as IM103008 **Background meds (all subjects)**: same as IM103008	MI, 74 LI, 71 CsA, 73

Study Number/ Manufacturing Process of Drug Substance	Objectives	Study Design	Type of Subjects	Dosage, Route	Number of Treated Subjects
Phase 3 Studies of IV Belatacept in Renal Transplant Recipients					
IM103008 (b) (4)	Efficacy, safety, immunogenicity, PK	Phase 3, randomized, open-label, partially-blinded, active-controlled, parallel group/ 3 years	De novo renal transplant subjects	**Belatacept MI regimen**: 10 mg/kg Days 1 and 5 then every 2 weeks through Month 3, then every 4 weeks through Month 6, then 5 mg/kg every 4 weeks through Month 36; IV **Belatacept LI regimen**: 10 mg/kg Days 1 and 5, then every 2 weeks through Month 1, then every 4 weeks through Month 3, then 5 mg/kg every 4 weeks through Month 36; IV **CsA**: twice daily for trough serum 150 -300 ng/mL during Month 1 and 100-250 ng/mL thereafter **Background meds (all subjects)**: basiliximab induction, MMF + corticosteroids	MI, 219 LI, 226 CsA, 215
IM103027 (b) (4)	Efficacy, safety, immunogenicity, PK	Phase 3, randomized, open-label, partially-blinded, active-controlled, parallel group/ 3 years	De novo renal transplant subjects who received grafts from extended criteria donors	**Belatacept MI regimen**: same as IM103008 **Belatacept LI regimen**: same as IM103008 **CsA**: same as IM103008 **Background meds (all subjects)**: same as IM103008	MI, 183 LI, 174 CsA, 179

Source: Corresponds to Table 8, Clinical Pharmacology Review, BLA 125,288

4.4.1 Mechanism of Action

Belatacept is a recombinant soluble fusion protein consisting of the extracellular domain of human CTLA-4 and a fragment (hinge–CH2–CH3 domains) of a modified Fc domain of human IgG1. CTLA-4 is a member of the immunoglobulin superfamily with structural

similarities to CD28. While both CTLA-4 and CD28 bind CD80/86 on antigen presenting cells, CTLA-4 inhibits activation of T cells whereas CD28 augments activation of T cells. As a soluble fusion protein, belatacept does not transmit inhibitory signals like CTLA-4, but it interferes with CD28:CD80/CD86 interactions, key costimulatory signals required for T cell activation. T cells require at least 2 signals for full activation. The first signal is delivered by the T cell receptor and the second via costimulatory molecules like CD28. By preventing signaling through CD28, belatacept modulates immune responses and acts as an immunosuppressant.

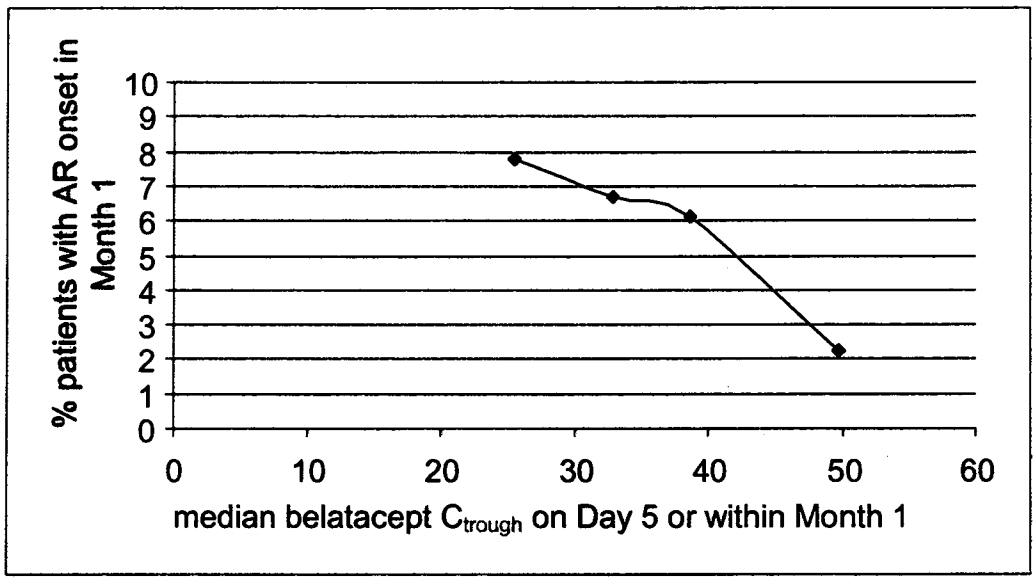
In the nonclinical studies and the clinical trials, exposure with belatacept was associated with decreases in the number of peripheral Treg cells and decreases in total serum immunoglobulin levels. Patients in the CsA control arm also experienced decreases in Treg cells and immunoglobulin levels. It is unclear whether these changes are intrinsically linked to the efficacy of belatacept or whether they represent off-target effects.

4.4.2 Pharmacodynamics

The Clinical Pharmacology Review suggested that the data from the Phase 3 clinical trials provided some evidence of exposure-response relationships with belatacept.

Higher belatacept trough concentrations (C_{trough}) on Day 5 were associated with a lower incidence of AR during the first month after transplantation (see Figure 6). The significance of the observation is unclear, however, as two-thirds of all AR events occurred after the first month, but no correlation between C_{trough} levels and the incidence of those episodes was elucidated.

Figure 6: Percent of patients with AR occurring within first month post-transplant as a function of median belatacept C_{trough} on Day 5 in the Phase 3 kidney transplant trials (Quartile analysis)



Source: Corresponds to Figure 4, Clinical Pharmacology Review, BLA 125,288

Higher mean belatacept $C_{troughs}$ were also associated with a lower incidence of a decrease in measured GFR ≥ 10ml/min between Month 3 and Month 12. The observation was most evident in the trials of SCD kidneys, but the trend was repeated across both trials and in both belatacept regimens (see Clinical Pharmacology Review for complete tables and analyses at various time points and by trial and belatacept regimen).

Table 4: Relationship between belatacept C_{trough} and percentage of patients with a decrease in mGFR ≥ 10 ml/min from Month 3 to Month 12 in the Phase 3 belatacept kidney transplant trials (data from LI and MI regimens were combined)

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
		All Months		
Median (10-90th percentile) belatacept C_{trough} (µg/mL)	7.5 (5.1 – 9.3)	11.3 (9.9 – 12.8)	15.6 (13.9 – 18.7)	27 (20.9 – 42.7)
Percentage of patients with mGFR10 (%; n/N)	31.4 (61/194)	21.7 (42/194)	22.7 (44/194)	14.1 (27/192)

Source: Adapted from Table 4, Clinical Pharmacology Review, BLA 125,288

Reviewer Comment: As reported above and detailed further in the Clinical Pharmacology Review, the Clinical Pharmacology review team noted some evidence of

exposure-response relationships in the belatacept clinical trials. I would note, however, that AR rates were, in fact, slightly numerically higher in the belatacept MI arms of both Phase 3 trials and that the mean GFRs of the belatacept LI and MI regimens were essentially identical over time in both Phase 3 trials, despite the higher exposure to belatacept among recipients of the MI regimen.

4.4.3 Pharmacokinetics

As described in the Clinical Pharmacology Review, the pharmacokinetic parameters of belatacept were linear over a range of escalating IV doses form 1 to 20 mg/kg among healthy subjects and the mean estimate of systemic clearance (CL) and volume of distribution (Vss) following IV doses of 5 mg/kg and 10 mg/kg in renal transplant patients were comparable. Similarly, the mean estimates of belatacept half-life (T1/2) were similar between healthy subjects and kidney transplant patients – approximately 8 to 10 days. The between subject variability in the PK estimates was 18-28% in healthy subjects and 27-35% in kidney transplant patients.

Table 5: Belatacept Pharmacokinetics in Healthy Subjects and Kidney Transplant Patients

Pharmacokinetic Parameters	Healthy Subjects (After 10 mg/kg Single IV Infusions) N=15	Kidney Transplant Patients during the Maintenance Phase (After 5 mg/kg Multiple IV Infusions) N=14	Kidney Transplant Patients during the Initial Phase (After 10 mg/kg Multiple IV Infusions) N=10
Peak concentration (C_{max}) [µg/mL]	300 ± 77 (190-492)	139 ± 28 (80-176)	247 ± 68 (161-340)
AUC[a] [µg•h/mL]	26398 ± 5175 (18964-40684)	14090 ± 3860 (7906-20510)	22252 ± 7868 (13575-42144)
Terminal half-life (T½) [days]	9.8 ± 2.8 (6.4-15.6)	8.2 ± 2.4[b] (3.1-11.9)	9.8 ± 3.2 (6.1-15.1)
Systemic clearance (CL) [mL/h/kg]	0.39 ± 0.07 (0.25-0.53)	0.51[b] (0.33-0.75)	0.49 ± 0.13 (0.23-0.70)
Volume of distribution (Vss) [L/kg]	0.09 ± 0.02 (0.07-0.15)	0.12[b] (0.09-0.17)	0.11 ± 0.03 (0.07-0.17)

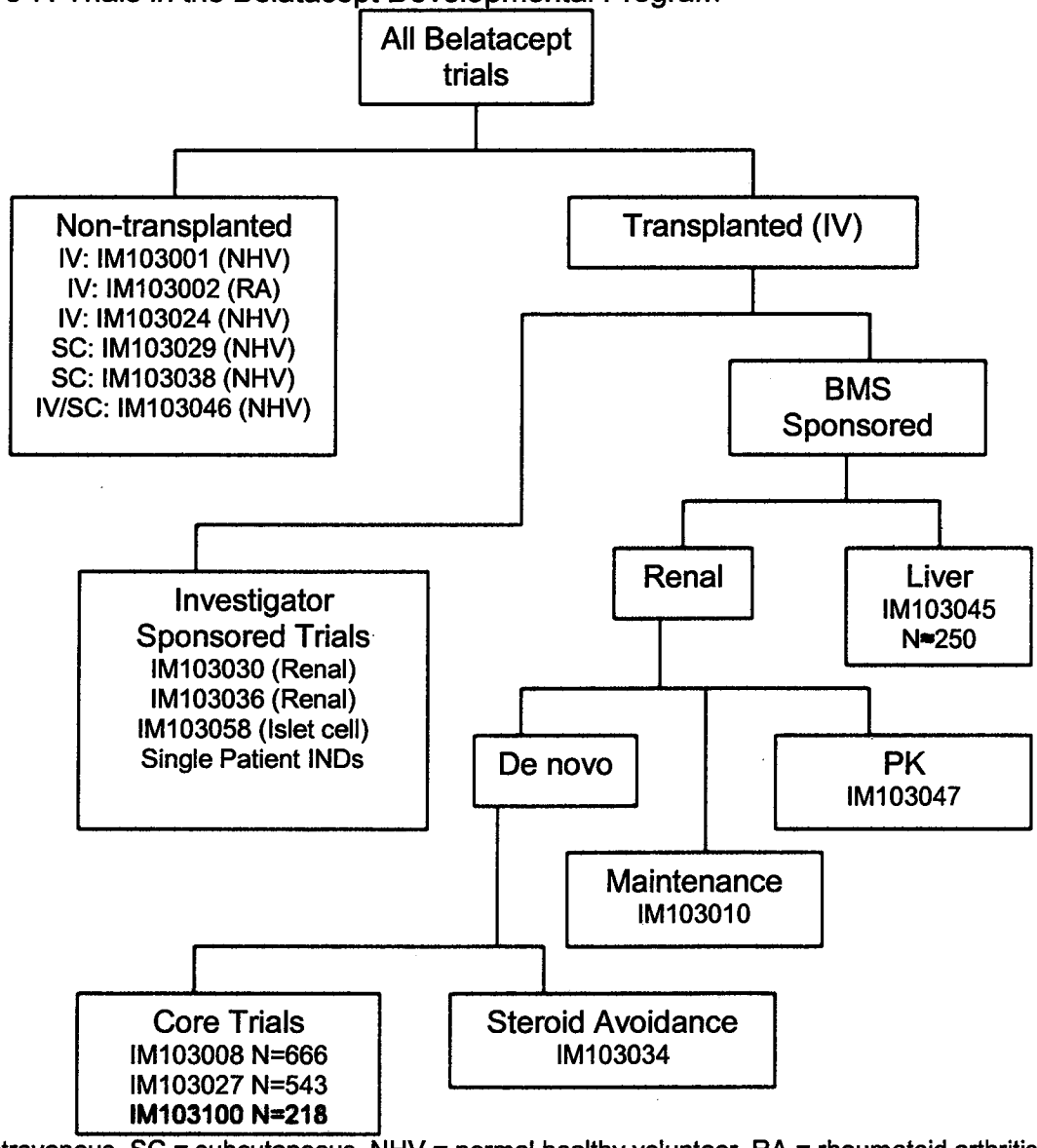
[a] AUC=AUC (INF) after single dose and AUC (TAU) after multiple dose, where TAU=4 weeks
[b] TAU=8 weeks
Source: Corresponds to Table 1, Clinical Pharmacology Review, BLA 125,288

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program for belatacept is shown in Figure 7 below, as adapted from the applicant's submission.

Figure 7: Trials in the Belatacept Developmental Program



IV = intravenous, SC = subcutaneous, NHV = normal healthy volunteer, RA = rheumatoid arthritis
Source: Figure adapted from Figure 3 of BMS Advisory Committee Briefing Document

The core clinical trials in support of the BLA application are IM103008, IM103027, and IM103100, as shown in Table 6. The focus of the review, then, is on the efficacy and safety data contained in those trials. In addition, however, data from the Organ Procurement Transplant Network (OPTN) registry – also known as the UNOS registry -- was obtained through the United States Renal Data System (USRDS). Those additional data were obtained to evaluate statements made by the applicant with regards to observed rates of PTLD in the general kidney transplant population. Finally, the clinical review of safety also considered two events of PTLD (including one case of CNS PTLD) and an additional event of PML which occurred in a Phase 2 trial in *de novo* liver transplant patients, IM103045.

Table 6: Core clinical trials supporting the 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

[a] Belatacept MI = 10 mg/kg on Day 1 and Day 5, then every 2 weeks through Month 3, then every 4 weeks through Month 6, then 5 mg/kg every 4 weeks; Belatacept LI = 10 mg/kg on Day 1 and Day 5, then every 2 weeks through Month 1, then every 4 weeks through Month 3, then 5 mg/kg every 4 weeks
[b] Belatacept MI = 10 mg/kg on Day 1, Day 5, and Day 15, then every 2 weeks through Month 3, then every 4 weeks through Month 6, then 5 mg/kg every 4 or 8 weeks; Belatacept LI = 10 mg/kg on Day 1, Day 5, Day 15, Day 29, Day 57, and Day 85, then 5 mg/kg every 4 or 8 weeks
Source: Adapted from Applicant's AC Briefing Document

The IM103008 and IM103027 12 month study reports and datasets provided in the electronic submission were reviewed. These can be found in the electronic submission located at: \\cbsap58\m\eCTD_Submissions\STN125288\0000. Additional analysis datasets were provided in the electronic submission located at \\cbsap58\m\eCTD_Submissions\STN125288\0006. Datasets for the 120-day safety update (2 year data) were provided in the electronic submission at \\cbsap58\m\eCTD_Submissions\STN125288\0013.

5.2 Review Strategy

The core clinical trials in support of the BLA application are IM103008, IM103027, and IM103100. The focus of the review, then, is on the efficacy and safety data contained in those trials. The efficacy review (See Section 6) was conducted by the Statistical Reviewer (Cheryl Dixon, Ph.D.) with input from the Clinical Reviewer on clinical interpretation of the results. For the purposes of the efficacy review, the 12 month data was used from the Phase 3 trials (IM103008 and IM103027). Results from the studies were not pooled.

The Clinical Reviewer performed the safety review, focusing on the clinical trial data from the three core trials. For most analyses 12 month data was utilized. Deaths are reported through 24 months or "Through Safety Update Report" (covering events occurring between the March 2009 BLA database lock and June/July 2009). Follow-up on patients with PLTD and PML were provided through database lock and in real time by the applicant as information became available. More specific information regarding the pooling of trials and timeframe analyzed is provided in Section 7 for each type of adverse event discussed.

In addition, however, data from the Organ Procurement Transplant Network (OPTN) registry – also known as the UNOS registry -- was obtained through the United States Renal Data System (USRDS). Those additional data were obtained to evaluate statements made by the applicant with regards to observed rates of PTLD in the general kidney transplant population. A dedicated Statistical Safety team (Anita Abraham Ph.D. and LaRee Tracy, Ph.D.) evaluated the rates of PTLD observed in the core clinical trials in comparison to those captured in the registry databases. The Clinical Reviewer provided direction and clinical perspective for this review, as well.

Finally, the Clinical Pharmacology team evaluated exposure response for both efficacy and safety. The Pharmacogenomics group within Clinical Pharmacology team evaluated patient risk factors for PTLD. The Clinical Reviewer also worked with both of these groups.

5.3 Discussion of Individual Studies/Clinical Trials

The Phase 3 kidney transplant trials (IM103008 and IM103027) were designed as three year studies, with the primary analysis of efficacy at Month 12. They are still ongoing and all patients have completed at least 2 years of follow-up. The Phase 3 trials declared co-primary endpoints based on patient and graft survival, a composite measure of renal impairment created specifically for these trials, and (for IM103008 only) AR. Mean GFR at 12 months and incidence of chronic allograft nephropathy (CAN) were also secondary endpoints in both trials. The protocols have recently been amended to collect long-term safety information out to 7 years.

A Phase 2 kidney transplant trial (IM103100) was designed as a one year study; while a long term extension (LTE) of the trial was implemented, only a third of the 73 patients in the CsA control group part participated. In effect, then, IM103100 lacked a control group after the first year of follow-up. IM103100 also used different endpoints than the Phase 3 trials. Its primary efficacy endpoint was the incidence of clinically-suspected and biopsy-proven acute rejection (CSBPAR) at six months after transplant. Secondary endpoints included a combined endpoint of CSBPAR, death, or graft loss at 6 months. The concomitant immunosuppression was identical to that used in the Phase 3 trials (induction with basiliximab and maintenance with MMF and corticosteroids). The belatacept MI and LI regimens were similar but non-identical to those used in the Phase 3 trials. The belatacept LI regimens, in particular, differed in the Phase 2 and Phase 3 trials due to the addition of an extra 10 mg/kg dose on Day 5 to the Phase 3 regimen. Due both to the significant difference in the belatacept LI regimens studied in Phase 2 and Phase 3 and also to the effective lack of a control group after the first year in the Phase 2 trial, the clinical efficacy and safety reviews concentrated on the Phase 3 trials.

The patient populations studied in the three kidney transplant trials also differed. IM103008 enrolled recipients of SCD kidneys, IM103027 enrolled recipients of ECD kidneys, and IM103100 enrolled both. All the trials limited enrollment of patients who were judged as high immunologic risk. The inclusion and exclusion criteria used in each trial are described more fully below.

IM103008

IM103008 studied a population of kidney transplant recipients receiving higher quality donor kidneys. All patients enrolled into IM103008 received either a living donor kidney or a deceased donor kidney with an anticipated cold ischemia time less than 24 hours. In addition, recipients of a kidney whose donor was ≥ 60 years old or was 50-59 years old and had a history of stroke, hypertension, and/or serum creatinine > 1.5 mg/dL were excluded. Patients who received kidneys from donors who had a non-beating heart at time of donation were also excluded. Patients enrolled into IM103008 also represented a population of patients with relatively low immunologic risk: the trial excluded first-time recipients with a PRA ≥ 50%, recipients undergoing repeat transplantation with PRA ≥ 30%. The trial also excluded patients with evidence of hepatitis C, hepatitis B, and/or HIV infection.

IM103027

IM103027 studied a population of kidney transplant recipients receiving lower quality donor kidneys. All patients enrolled into IM103027 received deceased donor kidneys with an anticipated cold ischemia time greater than 24 hours or whose donor was ≥ 60 years old or was 50-59 years old and had a history of stroke, hypertension, and/or serum creatinine > 1.5 mg/dL or had a non-beating heart at time of donation. Patients enrolled into IM103027 represented a population of patients with relatively low

immunologic risk: the trial excluded first-time recipients with a PRA ≥ 30%. The trial also excluded patients with evidence of hepatitis C, hepatitis B, and/or HIV infection.

IM103100

Enrollment into IM103100 occurred in two phases. During the enrollment of the first 54 patients, patients with history of a previous kidney transplant or a panel of reactive antibodies (PRA) > 20%, or otherwise considered by trial investigators to be at relatively high risk for AR were excluded. During the enrollment of the remaining 102 patients, the number of such higher risk subjects was limited to 10% of the total number of subjects in the trial. While some higher risk patients were allowed during the second phase of enrollment, the exclusion criteria still prohibited the enrollment of recipients of kidneys with greater than 36 hours of cold ischemia time, or whose donor were older than 60, or whose donor's heart was not beating. The trial excluded recipients of a related donor kidney with a zero antigen mismatch due to their good long-term prognosis on standard-of-care regimens. Patients under age 18 were also excluded. The trial also excluded patients with evidence of hepatitis C, hepatitis B, and/or HIV infection.

Reviewer Comment: Given that the trials excluded some higher immunologic risk patients, the applicability of the findings of those trials to that population of patients is uncertain. As AR rates and grades were higher among patients maintained on belatacept regimens than CsA regimens in both Phase 3 trials (see Section 6 and Section 7 for further details), a particular concern exists that the belatacept regimens studied may not provide sufficient prophylaxis against AR in those higher risk patient populations.

Reviewer Comment: As described above, the two Phase 3 trials studied identical belatacept regimens in rather different contexts (higher quality donor kidneys and lower quality donor kidneys). As described in Section 6 and Section 7 below, some trends detected in each Phase 3 trial were not convincingly reproduced in the other (e.g., numerically more belatacept patients than CsA patients alive with a functioning graft; higher rates of rejection among belatacept patients than CsA patients). It is difficult to know whether differences in patient populations contributed to the lack of reproducibility of those observations.

6 Review of Efficacy

Efficacy Summary

The two Phase 3 kidney transplant trials, IM103008 and IM103027, were the key trials for demonstrating the efficacy of belatacept. In both trials, the control groups used a CsA-based immunosuppressive regimen. The Phase 2 trial, IM103100, did not study a regimen identical to that proposed by the applicant for approval. In addition, the Phase 2 trial lacked the statistical power to draw scientifically sound conclusions regarding

efficacy. The efficacy results of IM103100, however, were noted to be consistent with the FDA analysis of efficacy based of the Phase 3 belatacept trial data.

The co-primary efficacy endpoints as pre-specified in the Phase 3 protocols were:

- The composite of patient and graft survival at 12 months, and
- The composite of renal impairment as assessed by measured glomerular filtration rate (GFR) < 60 mL/min/1.73m^2 at Month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73m^2 from Month 3 to Month 12, as measured by the cold-iothalamate method, and
- The incidence of AR, defined as a biopsy confirmed histological evidence of rejection along with clinical evidence, at 12 months (IM103008 only)

The incidence of AR was a secondary endpoint in IM103027. Mean GFR at 12 months and incidence of chronic allograft nephropathy (CAN) were also secondary endpoints in both trials.

The protocols specified that the endpoints of patient and graft survival and of AR were to be assessed for noninferiority (NI), whereas the endpoint of composite renal impairment was to be assessed for superiority. The endpoints were to be examined sequentially in the order of hierarchy stated above. The Type I error rate was set at 2.7% using Dunnett's adjustment for each belatacept regimen versus CsA. Thus treatment differences between each belatacept treatment groups and CsA were tested at the 0.027 significance level and 97.3% confidence intervals about differences between the treatment groups are reported.

Of the efficacy endpoints declared by the protocols, the only endpoint which was not confounded and whose NI margin could be scientifically justified was the incidence of AR. In both trials, numerically more patients maintained on belatacept were alive with a functioning graft at 12 months. That observation was consistent with a conclusion that belatacept had efficacy, however, insufficient historical data exist to determine a NI margin for this endpoint in the context of the CsA-based control group and concomitant immunosuppression with basiliximab, MMF, and corticosteroids. In the absence of a scientifically justified NI margin, the patient and graft survival data cannot provide primary evidence of efficacy. While the trials demonstrated that patients maintained on belatacept exhibited superior GFRs to those maintained on CsA, the effect of CsA on renal hemodynamics confounded the use of endpoints based on GFR to establish the efficacy of belatacept as an immunosuppressant in the context of kidney transplantation. Due to the off-target effects of CsA on GFR, differences across treatment groups were detectable from the first measurable time point. One cannot, therefore, rely on the continued presence of those differences at 12 months as primary evidence of the efficacy of belatacept. Sufficient historical data exist to justify a NI margin for the endpoint of AR. In keeping with the trial protocols, the applicant analyzed the endpoint of AR without imputing missing data as treatment failures. The FDA analyzed the endpoint of AR both according to the approach specified in the trial

protocols and according to the approach it has traditionally employed when examining this endpoint in previous reviews (imputing missing data as treatment failures and defining AR as any event of biopsy proven acute rejection). In all analyses of AR, belatacept met the 20% NI margin. While belatacept met the NI margin in both trials, however, numerically more patients on belatacept than CsA experienced AR.

Reviewer Comment: Based on the analysis of the AR endpoint, an endpoint which has traditionally been used to determine efficacy for the indication of prophylaxis of AR in kidney transplant recipients, one can conclude that belatacept has efficacy for that indication. The data suggest, however, that belatacept may have less efficacy than CsA for the prevention of AR at the doses of each used in the trials.

6.1 Indication

The applicant proposed that belatacept receive an indication for "the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants." Other products used as components of maintenance immunosuppression regimens have received wording similar to "prophylaxis of organ rejection", but the wording "preservation of a functioning allograft" would represent a novel indication. Previously (b) (4)

6.1.1 Methods

The strengths and limitation of the endpoints of patient and graft survival, composite renal impairment, mean GFR, AR, and CAN will each be discussed. Of particular importance are the underlying limitations in the comparisons of GFR between the belatacept and CsA groups due to the differential effects of the treatment regimens on renal hemodynamics. However, because of the identified limitations with the evaluation and interpretation of these endpoints, including the limitation in the ability to justify the proposed NI margin for the patient and graft survival endpoint; the FDA also conducted an additional analysis of AR in the study populations. This analysis of AR by FDA has been used by FDA in the analysis of other kidney transplantation trials, and the proposed NI margin for this analysis can be supported from previous kidney transplantation studies (see Statistical Efficacy Review by Cheryl Dixon, Ph.D. for details) and is described below. The results of these endpoints are presented in Section 6.1.4.

Patient and Graft Survival at 12 Months

The impact of CsA on patient outcomes, when compared to the conventional immunosuppression of the era (azathioprine and steroids), was readily measureable by evaluating patient and graft survival. The graft loss and death rate in the trials of Sandimmune® were in the range of 10% to 20% in the Sandimmune arms compared to approximately 35% to 45% in the control arms of azathioprine and corticosteroids (p-value < 0.05).[15] In the modern transplant era, one can no longer depend on patient and graft survival to demonstrate the efficacy of newer regimens by comparison to a regimen reflecting standard of care, since the high rate of short-term (1 year) patient and graft survival obtained using these regimens does not allow one to power a trial to demonstrate the superiority of the newer regimen for an endpoint based on patient and graft survival at 12 months. In theory, a NI approach could be used to demonstrate that a newer regimen had some efficacy for the indication of preventing patient death and graft loss, but the size of the effect of CsA on patient and graft survival given the current standard regimen including induction, corticosteroids, and MMF cannot be easily estimated and therefore we cannot define a NI margin. However, given that the endpoint of patient and graft survival is an important endpoint, we make sure there this is not an unacceptable loss of efficacy.

For these reasons, the endpoint of patient and graft survival in the belatacept trials is not viewed as a primary endpoint for the demonstration of efficacy; however, it is an important endpoint for assessing safety, i.e., whether or not the trials merit further review.

Composite Renal Impairment and mean Glomerular Filtration Rate (GFR)

CsA causes vasoconstriction of the afferent renal artery leading to a physiologic decrease in GFR.[16] Such a physiologic effect on GFR could conceivably have deleterious consequences, especially among renal transplant patients. However, the reliance on GFR in the context of the Phase 3 trials as a measure of prophylaxis of organ rejection or preservation of a functioning allograft in adult patients receiving renal transplants is confounded by the hemodynamic effects of CsA, which was used only in the control group. The difference in the hemodynamic effect between the belatacept groups and the CsA groups manifested immediately in the trial: the data show that the belatacept groups and the CsA groups had significantly different GFRs from the first measurable time points (see Figure 13 and Figure 14 in Section 7.3.4). While the GFR for the belatacept groups remained consistently higher than those in the CSA groups through 24 months, the differences may simply reflect the hemodynamic differences rather than any structural differences in the allografts between treatment groups. As GFR is an important measure of renal function, the higher GFRs exhibited by patients

[15] Sandimmune Summary Basis for Approval
[16] Bobadilla NA, Gamba G. New insights into the pathophysiology of cyclosporine nephrotoxicity: a role of aldosterone. Am J Physiol Renal Physiol. 2007; 293(1): F2-9.

maintained on belatacept regimens may translate into important clinical benefits. However, one cannot rely on an improvement in observed GFR to prove the efficacy of belatacept for preserving GFR if the comparison is to CsA, which is known to decrease GFR through a direct physiologic mechanism.

For purposes of assessing efficacy based on the renal composite endpoint, patients were classified as successes or failures based on whether GFR was less than 60 mL/min at Month 12 or whether GFR had declined more than 10 mL/min between Month 3 and Month 12 (defined as failure). In the belatacept Phase 3 trials, most patients who met the endpoint were classified as efficacy failures due to a GFR less than 60 mL/min, not due to a decline more than 10 mL/min between Month 3 and Month 12. The selection of a Month 12 GFR of 60 mL/min was based on a retrospective study of registry data which suggested better outcomes among renal transplant patient whose serum creatinine at 1 year was less than 1.5 mg/dL.[21] That literature analyzed populations of patients who were almost universally maintained on CNI containing regimens and, therefore, had comparable renal hemodynamics allowing meaningful comparisons of GFR as a surrogate of kidney allograft function and structure. It is less clear; however, what a comparison of GFRs between the belatacept groups and the CsA groups in the belatacept Phase 3 trials implies about expected outcomes for the two groups. The imbalance, then, in starting GFRs (post-transplantation once therapy was started) between the investigational arms and the control arms confounds the analysis and interpretation of these findings.

Study IM103008 exclusively enrolled recipients of LD and SCD kidneys and some of these maintained GFRs greater than 60 mL/min, Study IM103027 enrolled patients with ECD kidneys, and almost all patients in this trial (both in the belatacept and the CsA groups) were treated as efficacy failures due to a Month 12 GFR less than 60 mL/min. In retrospect, these results are not surprising, because the recipients of extended criteria donor kidneys rarely achieve a GFR greater than 60 mL/min. In fact the majority of patients in all arms in IM103027 started out with GFRs less than 60 mL/min. As a result, the composite renal endpoint did not detect a significant difference between the belatacept and the CsA treatment groups despite a considerable difference in mean GFRs observed between these same groups.

Given the limitations of the composite renal endpoint in the setting of incomparable renal hemodynamics across treatment groups and given the limitations of the composite renal endpoint in the setting of a trial of ECD kidneys, it is difficult to understand the significance or relevance of these analyses as an efficacy endpoint. However, because GFR remains an important measure of renal function, differences in mean GFR at Month 12 were given consideration both as a secondary efficacy endpoint and a safety endpoint.

Acute Rejection (AR)

Study IM103008 specified the incidence of AR (defined as central biopsy proven rejection that was either "clinically suspected by protocol defined reasons or clinically suspected by other reasons and treated") as one of its three co-primary endpoints while Study IM103027 specified the incidence of AR as a secondary endpoint. However, given the limitations of the patient and graft loss endpoint and the combined renal impairment endpoint as described in the above paragraphs, it may be reasonable to examine the outcome of AR in both trials as a primary efficacy endpoint. AR as an endpoint has traditionally been used by the FDA to assess efficacy of other products for the indication of prophylaxis of rejection in kidney transplant recipients.

In the modern transplant era, rates of AR are low. Most transplant trials rely on a non-inferiority approach to evaluate the efficacy of a new product for maintenance immunosuppression. The belatacept trials also relied on a non-inferiority margin to evaluate the efficacy of belatacept for the prophylaxis of AR. In order to be able to interpret a non-inferiority trial, a scientific justification of the non-inferiority margin is needed. On the basis of data from a trial of an IL-2 receptor antagonist plus MMF plus corticosteroids and an estimate that CsA-based regimens are expected to result in a 15% rate of AR, the Division concluded that the data support a 20% non-inferiority margin as the effect that CsA adds to this regimen on AR. Use of this margin then allows for the conclusion of whether or not belatacept adds some contribution to the regimen with respect to prevention of AR (see Statistical Efficacy Review for a complete discussion with regards to the derivation of the NI margin).[11,12] However, while a 20% margin is sufficient to demonstrates an effect over placebo, it does not demonstrate that the potential loss of efficacy compared to the standard of care is clinically acceptable. Improved graft survival was observed in the period from 1988 to 1996 corresponding with the introduction of modern immunosuppression agents; an analysis of registry data during that period showed that AR events during the first year of transplantation had a detrimental effect on long-term graft survival.[17] Despite additional incremental decreases in AR rates in the period from 1995 to 2000, however, no further improvement in graft survival resulted.[18] The data suggest, then, that while effective prophylaxis of AR is critical to patient and graft survival; the correlation between AR rates and improved outcomes becomes less clear as AR rates approach those observed in the modern era.

Therefore, the endpoint of AR as defined by the applicant and as analyzed by Statistical/Clinical Reviewers in the belatacept trials was viewed as the primary endpoint for the demonstration of efficacy.

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[17] Hariharan S, Johnson CP, Bresnahan BA, et al. Improved graft survival after renal transplantation in the United States, 1988-96. N Engl J Med 2000; 342: 605-12.

[18] Meier-Kriesche H-U, Schold JD, Srinivas TR, et al. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004; 378-83.

In the FDA analyses of AR, patients who experience death, graft loss, or loss to follow up are not considered as having a positive outcome (i.e., no rejection). Instead, these patients' outcomes are imputed as efficacy failures from the point-of-view of the AR endpoint. Patients with death, graft loss, or loss to follow up do not have complete data at 12 months. Additionally, considering them as having a positive outcome for this analysis does not seem appropriate given that the subjects who have obtained an endpoint of death or graft loss have obtained an endpoint of even more clinical importance than AR.[19] The FDA analysis of the AR endpoint has therefore often been described as the "combined endpoint" of biopsy-proven acute rejection (BPAR), graft loss, death, and loss to follow up. It is important that this endpoint be taken into consideration when assessing the efficacy results of the Phase 3 studies in this application. The FDA also considers that the definition of BPAR includes all events where the central review of the biopsy indicated AR, regardless of the reason for performing the biopsy. That definition of BPAR differs slightly from that used by the applicant, who defined BPAR to include only those events where central review of the biopsy indicated AR and AR was either clinically suspected by protocol defined reasons or clinically suspected by other reasons and treated. Sensitivity analyses, however, confirmed that the conclusions of the FDA analysis of BPAR remained unchanged regardless of which definition of BPAR was used.

The applicant also assessed the presence of chronic allograft nephropathy (CAN) at Month 12 as a secondary endpoint, using protocol biopsies in an attempt to assess differences in structural changes across the treatment groups. CAN was developed as a term to describe histopathologic findings on biopsy associated with progressive renal dysfunction not attributable to a more specific diagnosis. In practice, its use has come to encompass a heterogeneous group of findings that may develop from a variety of underlying processes.[20] Although the observation of CAN reflects structural findings, the understanding of its clinical relevance remains rather uncertain and continues to evolve, and recent publications suggest its prognostic value for long term graft survival is unclear. For example, the Long Term Deterioration of Kidney Allograft Function (DeKAF) multicenter consortium published data suggesting that CAN has no prognostic value for the outcome of graft loss.[21] Based on its study of 440 biopsies, the group reported:

> "the most important finding of our study, to date, is the observation that, in the cross-sectional cohort, the local diagnosis of CAN was of no prognostic significance... Those with and without CAN had identical patterns of postbiopsy graft failure. There was also no functional difference (for those with and without CAN) in the postbiopsy slope of 1/creatinine versus time. Clearly, for recipients with

[19] Lubsen J, Kirwan BA. Combined endpoints: can we use them? Statistics in Medicine 2002; 21:2959-70
20 Colvin, RB. Chronic Allograft Nephropathy. N Engl J Med 2003; 349: 2288-90.
21 Gourishankar S, Leduc R, Connett J, et al. Pathological and Clinical Characterization of the 'Troubled Transplant': Data from the DeKAF Study. Amer J of Transplantation 2010; 10: 324-330.

new onset late graft dysfunction, the nonspecific diagnosis of CAN does not define a group of patients with a different outcome."[22]

6.1.2 Demographics

Reflective of the kidney transplant recipient population, approximately two-thirds of the kidney transplant recipients enrolled in the Phase 3 trials were male (see Table 7). Most patients in both trials were enrolled outside of the US: around 40% of the patients in IM103008 and 25% of the patients in IM103027 were from North America. Compared to their prevalence in the US kidney transplant recipient population, Black patients (whether enrolled in or outside the US) were under-represented in the trials: in 2009, Black patients represented 25% of the kidney transplant recipients in the US, as opposed to 10% of the patients in the belatacept Phase 3 trials.[23]

Baseline disease characteristics of transplant donors were consistent with each study's inclusion/exclusion criteria. In IM103008, 58% of donors were living (42% related, 16% unrelated) and 42% were deceased. In IM103027, nearly all (99%) of the donors met the ECD criteria defined in the protocol. Among these, 70% to 72% of donors met the UNOS ECD criteria.[24]

The proportion of donors and recipients with mismatched human leukocyte antigen (HLA) serologies was balanced between treatment groups.

Subject EBV status was determined locally at the site and was reported on the case report form. For 11 and 44 patients in Studies IM103008 and IM103027, respectively, whose EBV status was unknown at baseline, retrospective blood sample analysis was performed by the central laboratory. Approximately 85-90% of the patients enrolled in the Phase 3 trials were EBV+ at baseline.

In general, the various demographic characteristics of the patients appeared to be evenly distributed across the treatment groups in both Phase 3 trials.

22 Gourishankar S, Leduc R, Connett J, et al. Pathological and Clinical Characterization of the 'Troubled Transplant': Data from the DeKAF Study. Amer J of Transplantation 2010; 10: 324-330.
23 http://optn.transplant.hrsa.gov/
24 Metzger RA, Delmonico FL, Feng S, et al. Expanded criteria donors for kidney transplantation. Am J Transplant 2003;3(Suppl 4):114-125.

Table 7: Demographics in the Phase 3 Kidney Transplant Trials

	IM103008			IM103027		
	MI N=219	LI N=226	CsA N=221	MI N=184	LI N=175	CsA N=184
Mean Age (years)	43.6	42.6	43.5	56.7	56.1	55.7
Gender, n (%)						
Male	151 (68.9)	146 (64.6)	165 (74.7)	119 (64.7)	129 (73.7)	116 (63.0)
Female	68 (31.1)	80 (35.4)	56 (25.3)	65 (35.3)	46 (26.3)	68 (37.0)
Race, n (%)						
White	132 (60.3)	133 (58.8)	139 (62.9)	137 (74.5)	134 (76.6)	137 (74.5)
Black	15 (6.8)	23 (10.2)	17 (7.7)	25 (13.6)	24 (13.7)	22 (12.0)
Asian	27 (12.3)	29 (12.8)	27 (12.2)	7 (3.8)	3 (1.7)	4 (2.2)
Other	45 (20.5)	41 (18.1)	38 (17.2)	15 (8.2)	14 (8.0)	21 (11.4)
Geographic region, n (%)						
North America	95 (43.4)	92 (40.7)	94 (42.5)	49 (26.6)	40 (22.9)	45 (24.5)
Rest of World	124 (56.6)	134 (59.2)	129 (57.4)	135 (73.4)	135 (73.1)	139 (75.5)
Recipient EBV serology						
Positive	194 (88.6)	199 (88.1)	184 (83.3)	169 (91.8)	156 (89.1)	168 (91.3)
Negative	25 (11.4)	27 (11.9)	37 (16.7)	14 (7.6)	19 (10.9)	16 (8.7)
Unknown	0	0	0	1 (0.5)	0	0

Source: Adapted from the Applicant's Summary of Clinical Safety; BLA 125,288

6.1.3 Subject Disposition

Clinical trials in transplantation, even randomized controlled trials intended to support the approval of a new therapy, are rarely conducted in a double blind fashion, primarily due to logistical issues and patient safety concerns regarding therapeutic drug monitoring. The belatacept Phase 3 trials were also conducted overall as open-label trials although the two belatacept regimens were blinded. Discontinuations were roughly evenly distributed across the treatment groups in both IM103008 and IM103027 at 12 months (see Table 8 and Table 9), but there were differences in the reasons for discontinuations between belatacept and CsA groups: more belatacept patients discontinued treatment due to lack of efficacy whereas more CsA patients discontinued treatment due to adverse events.

Table 8: Reasons for Treatment Discontinuations at 12 Months in IM103008

	IM103008		
Number randomized and transplanted	Belatacept MI N=219	Belatacept LI N=226	CsA N=221
Number randomized, transplanted, and treated	219	226	215
Number Discontinued Treatment, N (%)	46 (21.0)	45 (19.9)	42 (19.5)
Adverse Event	9 (4.1)	12 (5.3)	20 (9.3)
Lack of Efficacy	26 (11.9)	24 (10.6)	10 (4.7)
Death	4 (1.8)	2 (0.9)	3 (1.4)
Lost to Follow Up	0	0	1 (0.5)
Other	2 (0.9)	4 (1.8)	5 (2.3)
Non-Compliance	0	0	2 (0.9)
Withdrew Consent	5 (2.3)	3 (1.3)	1 (0.5)
Number Continuing Treatment	173 (79.0)	181 (80.1)	173 (80.5)

Source: Adapted from Table 5.1, Clinical Study Report IM103008, BLA 125,288

Table 9: Reasons for Treatment Discontinuations at 12 Months in IM103027

	IM103027		
Number randomized and transplanted	Belatacept MI N=184	Belatacept LI N=175	CsA N=184
Number randomized, transplanted, and treated	183	174	179
Number Discontinued Treatment, N (%)	50 (27.3)	45 (25.9)	54 (30.2)
Adverse Event	22 (12.0)	27 (15.5)	31 (17.3)
Lack of Efficacy	16 (8.7)	15 (8.6)	14 (7.8)
Death	5 (2.7)	2 (1.1)	2 (1.1)
Other	6 (3.3)	1 (0.6)	5 (2.8)
Withdrew Consent	1 (0.5)	0	2 (1.1)
Number Continuing Treatment	133 (72.7)	129 (74.1)	125 (69.8)

Source: Adapted from Table 5.1, Clinical Study Report IM103027, BLA 125,288

6.1.4 Analysis of Primary Endpoint(s)

Patient and Graft Survival

Patient and graft survival at 12 months is presented in Table 10. In Study IM103008, patient and graft survival at 12 months was 95%, 96.5%, and 93.2% in the belatacept MI, belatacept LI and CsA groups, respectively. The patient and graft survival rates were lower in Study IM103027 than those seen in IM103008; IM103027 evaluated recipients of ECD kidneys and rates are 85.9%, 88.6%, and 84.8% in the belatacept MI, belatacept LI and CsA groups, respectively. The lower bound of the 97.3% confidence interval about the difference between belatacept regimen and CsA was greater than -5% for all comparisons with the exception of the belatacept MI versus CsA comparison in Study IM103027 which was -7.6%. It should be noted that these results are slightly different than those presented by the Applicant since all patients with unknown survival status at Month 12 are treated as failures.

Table 10: Patient and Graft Survival at 12 Months

Study		Belatacept MI	Belatacept LI	CsA
008	Surviving with a functioning graft	208/219 (95.0)	218/226 (96.5)	206/221 (93.2)
	Graft Loss	4 (0 died)	5 (1 died)	8 (1 died)
	Death w/ functioning graft	6	3	6
	Unknown status	1	0	1
	Difference from CsA (97.3% CI)	1.8 (**-3.6**, 7.2)	3.3 (**-1.8**, 8.4)	
027	Surviving with a functioning graft	158/184 (85.9)	155/175 (88.6)	156/184 (84.8)
	Graft Loss	17 (2 died)	16 (1 died)	20 (3 died)
	Death w/ functioning graft	6	4	5
	Unknown status	3	0	3
	Difference from CsA (97.3% CI)	1.1 (**-7.6**, 9.8)	3.8 (**-4.7**, 12.3)	

Source: Adapted from Tables 3 and 13, Statistical Review, BLA 125,288

Composite Renal Endpoint

The proportions of subjects meeting the composite renal impairment endpoint as well as the reasons for meeting the composite endpoint are presented in Table 11. The difference in the proportion of subjects meeting the composite endpoint was statistically significantly better for a belatacept versus CsA comparisons with the exception of the belatacept LI versus CsA comparison in Study IM103027. It should be noted that the analyses presented here are slightly different from that presented by the applicant in that subjects with missing measured GFR data for reasons other than death or graft loss are also included as failures of the endpoint. The conclusions drawn, however, are not different.

Table 11: Composite Renal Impairment Endpoint

Study		Belatacept MI	Belatacept LI	CsA
008		(n=219)	(n=226)	(n=221)
	Composite endpoint	125 (57.1)	128 (56.6)	174 (78.7)
	Reason for meeting composite:			
	-M12 < 60 and Decrease ≥ 10 from M3 to 12	33	34	52
	-M12 < 60 only	58	58	92
	-Decrease ≥ 10 from M3 to M12 only	15	16	8
	-Imputed due to GL or death	9	8	14
	-Missing	10	12	8
	p-value	<0.0001	<0.0001	
027		(n=184)	(n=175)	(n=184)
	Composite endpoint	132 (71.7)	135 (77.1)	157 (85.3)
	Reason for meeting composite:			
	-M12 < 60 and Decrease ≥ 10 from M3 to 12	27	41	37
	-M12 < 60 only	71	64	83
	-Decrease ≥ 10 from M3 to M12 only	4	6	7
	-Imputed due to GL or death	22	19	24
	-Missing	8	5	6
	p-value	.0022	.0575	

Source: Adapted from Tables 4 and 14, Statistical Review, BLA 125,288

Acute Rejection (AR)

Acute rejection was defined in the Phase 3 protocols as a clinical/pathological event requiring clinical evidence; and biopsy confirmation of histological evidence of rejection, as determined by a blinded central pathologist. Clinical evidence of AR was defined by one or more of the following conditions:

- An unexplained rise of serum creatinine (SCr) ≥ 25% from baseline;
- Occurrence of one or more of the following: an unexplained decreased urine output; fever and graft tenderness; a SCr that remained elevated within 14 days after transplantation and clinical suspicion of AR;
- A reason other than those listed above and the subject was treated for this episode.

The three most common reasons for clinical suspicion of AR in the Phase 3 studies included an unexplained rise of SCr ≥ 25% from baseline, a SCr that remained elevated within 14 days post-transplantation, and other reasons (related to renal dysfunction and elevations of SCr that did not meet the protocol criteria).

Table 12 summarizes the incidence of AR, as defined by the applicant, at 12 months. Noninferiority of all belatacept regimens to CsA based on a NI margin of 20% was

shown, as demonstrated by an upper bound of the 97.3% confidence interval (CI) of less than 20%, with the exception of the belatacept MI regimen in Study IM103008.

However, it should also be noted that there were numerically more ARs in the belatacept-treated subjects than in the CsA-treated subjects. In Study IM103008 for both the belatacept regimens the lower bound of the 97.3% CI was above zero, indicating a significant increase in the number of ARs compared to CsA. In addition, the severity of rejection was greater in the belatacept groups, which will be discussed further in the safety discussion.

Table 12: Acute Rejection (as Defined by the Applicant) at 12 Months

Study		Belatacept MI	Belatacept LI	CsA
008	Acute Rejection	49/219 (22.4)	39/226 (17.3)	16/221 (7.2)
	Mild IA	7	4	3
	Mild IB	3	8	5
	Moderate IIA	17	16	6
	Moderate IIB	20	10	2
	Severe III	2	1	0
	Difference from CsA (97.3% CI)	15.2 (7.4, **23.0**)	10.1 (2.9, **17.3**)	
027	Acute Rejection	33/184 (17.9)	31/175 (17.7)	26/184 (14.1)
	Mild IA	0	4	2
	Mild IB	7	2	2
	Moderate IIA	10	17	17
	Moderate IIB	16	8	5
	Severe III	0	0	0
	Difference from CsA (97.3% CI)	3.8 (-5.2, **12.8**)	3.6 (-5.5, **12.7**)	

Source: Adapted from Tables 5 and 15, Statistical Review, BLA 125,288

As discussed previously in the discussion on efficacy endpoints (see Section 5), the Statistical/Clinical Reviewers felt there were limitations with the applicant's evaluation of AR, specifically that events of death, graft loss, or loss to follow up were imputed as successes. Therefore, another analysis of AR using the traditional combined endpoint of BPAR, graft loss, death or lost to follow-up was also conducted.

In the FDA's assessment, BPAR was also based upon central biopsy confirmed histological evidence, but also included additional rejections not necessarily accompanied by clinical signs and symptoms. Table 13 and Table 14 below describe the additional patients included in the FDA definition of BPAR for Studies IM103008 and IM103027, respectively.

Table 13: Additional Patients Included in FDA's Definition of BPAR in Study 008

	Patient	Biopsy Diagnosis	Date of Biopsy (Month)	Final Clinical Diagnosis	Treatment
Belatacept MI	70 M	Mild acute (IB)	12	None	None
	24 M	Mild acute (IB)	12	AR (non-steroid resistant)	Steroids
	47 M	Mild acute (IB)	12	AR (non-steroid resistant)	Steroids
Belatacept LI	52 M	Mild acute (IB)	6	none	None
	50 M	Mild acute (IA)	6	AR (non-steroid resistant)	None
	55 M	Moderate acute (IIB)	6	none	None
	18 M	Mild acute (IB)	12	none	None
	45 M	Moderate acute (IIB)	12	Active Chronic Rejection	Steroids and Lymphocyte depleting agent
	67 F	Moderate acute (IIB)	6	AR (non-steroid resistant)	Steroids
CsA	35 M	Mild acute (IB)	6	Focal involvement of graft by PTLD	None
	39 M	Mild acute (IB)	12	Histological rejection w/o clinical findings	None
	18 M	Moderate acute (IIB)	12	None	None
	56 F	Mild acute (IA)	12	AR (non-steroid resistant)	Other (?)
	55 M	Moderate acute (IIB)	6	None	None
	29 M	Mild acute (IB)	12	None	None
	26 M	Mild acute (IA)	12	AR (steroid resistant)	Steroids and OKT3

Source: Created by the Clinical Reviewer from the applicant's datasets

Table 14: Additional Patients Included in FDA's Definition of BPAR in Study 027

	Patient	Biopsy Diagnosis	Date of Biopsy (Month)	Final Clinical Diagnosis	Treatment
Belatacept MI	39 F	Moderate acute (IIA)	6	Tubulopathy	None
	59 M	Moderate acute (IIA)	12	None	None
	69 M	Moderate acute (IIB)	6	AR (steroid resistant)	None
	49 M	Moderate acute (IIA)	12	None	None
	36 M	Moderate acute (IIA)	6	Acute tubular necrosis	None
		Moderate acute (IIB)	6	AR (non-steroid resistant)	Steroids
	56 M	Mild acute (IB)	12	None	None
	68 M	Moderate acute (IIA)	6	Hydrop tubli nephrosclerosis	None
Belatacept LI	44 M	Moderate acute (IIA)	12	AR (non-steroid resistant)	Steroids
	60 F	Moderate acute (IIA)	6	Negative for cellular and humoral rejection	None
	62 M	Moderate acute (IIA)	12	None	None
	60 F	Moderate acute (IIA)	12	None	None
	53 F	Moderate acute (IIA)	6	Interstitial fibrosis and hyalinization	None
	50 M	Moderate acute (IIB)	6	None	None
CsA	52 M	Moderate acute (IIA)	12	None	None
	48 M	Moderate acute ((B)	6	Histological rejection w/o clinical findings	None
	51 F	Moderate acute (IIA)	6	Glomerulosclerosis lesions	None
	42 F	Mild acute (IB)	12	None	None
	73 M	Moderate acute (IIB)	6	None	None
	65 F	Moderate acute (IIA)	6	No clinical significant event	None
		Moderate acute (IIA)	6	Histological rejection w/o clinical findings	Steroids
	66 M	Mild acute (IB)	12	AR (non-steroid resistant)	Steroids
	72 M	Moderate acute (IIA)	6	nephrosclerosis	none

Source: Created by the Clinical Reviewer from the applicant's datasets

The results of the FDA's composite endpoint analysis using the FDA definition of BPAR are presented in Table 15. Of note, a similar analysis to that in Table 12 was also conducted using the applicant's definition of AR and similar results were obtained (data not shown). Using a margin of 20%, NI of all belatacept regimens to CsA for the FDA endpoint was shown. While the upper limit of the 97.3% CI for the LI arms is 13.7% and 11.9% for the two studies and thus each study meets the 20% margin, the upper bound of the CI for the belatacept MI arm in IM103008 is essentially 20%.

Table 15: FDA's Analysis of Biopsy Proven Acute Rejection, Graft Loss, and Death at 12 Months

Study		Belatacept MI	Belatacept LI	CsA
008	Met Endpoint	60/219 (27.4)	49/226 (21.7)	37/221 (16.7)
	Biopsy Proven Acute Rejection	52	45	23
	Graft Loss	3	3	7
	Death	4	1	6
	Unknown	1	0	1
	Difference from CsA (97.3% CI)	10.7 (1.6, **19.8**)	5.5 (-3.7, **13.7**)	
027	Met Endpoint	62/184 (33.7)	51/175 (29.1)	52/184 (28.3)
	Biopsy Proven Acute Rejection	40	37	34
	Graft Loss	14	11	12
	Death	6	3	5
	Unknown	2	0	1
	Difference from CsA (97.3% CI)	5.4 (-5.8, **16.6**)	0.8 (-10.3, **11.9**)	

* First occurrence of biopsy proven acute rejection, graft loss, or death. Refer to subject and graft survival table for total number of graft losses and deaths
Source: Adapted from Tables 6 and 16, Statistical Review, BLA 125,288

6.1.5 Analysis of Secondary Endpoints(s)

Measured GFR at Month 12

Measured GFR at Month 12 was significantly higher for both belatacept regimens compared to CsA in Study IM103008 (see Table 16). In the study of ECD kidneys, Study IM103027, measured GFR at Month 12 was higher for belatacept treated patients compared to CsA but the finding was statistically significant only for the belatacept MI versus CsA comparison.

Table 16: Measured GFR at Month 12 in the Phase 3 Kidney Trials

Study		Belatacept MI	Belatacept LI	CsA
008	Mean (sd) at Month 12	65.0 (30.0)	63.4 (27.7)	50.4 (18.7)
	# in analysis	200	206	199
	Difference from CsA (97.3% CI)	14.6 (8.9, 20.4)	13.0 (7.3, 18.7)	
	p-value	<0.0001	<0.0001	
027	Mean (sd) at Month 12	52.1 (21.9)	49.5 (25.8)	45.2 (21.1)
	# in analysis	154	151	154
	Difference from CsA (97.3% CI)	6.9 (1.1, 12.7)	4.3 (-1.5, 10.2)	
	p-value	0.0089	0.0995	

Source: Adapted from Tables 7 and 17, Statistical Review, BLA 125,288

As noted previously in the discussion of efficacy endpoints (see Section 5), similar differences were also detected as early as 1 month after transplantation. These early differences may reflect hemodynamic (rather than structural) differences due to the

vasoconstrictive effects of CsA on the renal artery. The CsA group likely received less renal blood flow, resulting in lower GFR.

Chronic Allograft Nephropathy at Month 12

In the Phase 3 trials, protocol biopsies were performed at Month 12 to assess structural changes in the renal allografts. Direct examination of a protocol biopsy may provide significant information to a local practitioner about the health of a transplant kidney. The most appropriate methodology for quantifying protocol biopsy results for use in transplant trials, however, remains undefined. In IM103008 and IM103027, biopsies were classified as meeting or not meeting criteria for chronic allograft nephropathy (CAN). A trend towards a higher prevalence of CAN was detected among the CsA groups (see Table 17). As a histopathologic diagnosis, however, CAN has fallen into disfavor specifically because it lacks a rigorous consensus definition and carries unclear prognostic implications.

Table 17: 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: Created by the Statistical Reviewer using the applicant's datasets, BLA 125,288

6.1.6 Other Endpoints

The applicant analyzed and presented in its BLA application a number of other endpoint as secondary endpoints. These include endpoints pertaining to the incidence of new onset diabetes after transplantation (NODAT), hypertension, and dyslipidemia. The rationale for presenting these as efficacy endpoints appeared to reflect both the fact that the applicant had elected to study them prospectively (b) (4) However, as with the data pertaining to GFR, the differences between treatment groups more likely reflect toxicities associated with CsA (b) (4). No mechanism has been proposed to suggest that belatacept should prevent diabetes, hypertension, or dyslipidemia and each of these is a well-known adverse event associated with CsA. While the differences remain clinically important when weighing the risks and benefits associated with CsA-based immunosuppression regimen and belatacept-based immunosuppression regimen, (b) (4) For that reason, these analyses have been presented in the Review of Safety (see Section 7).

6.1.7 Subpopulations

EBV Serostatus

As previously discussed, a higher rate of PTLD was observed among recipients of belatacept-based immunosuppression compared to CsA-based immunosuppression in the core clinical trials. This difference was particularly pronounced among recipients who were EBV seronegative at time of transplant. An EBV- serostatus has been established as an important independent risk factor for the development of PTLD in a non-belatacept context. It is not surprising, then, that any increased risk for PTLD associated with belatacept would be particularly evident among that subpopulation. The applicant has suggested that the overall risk-benefit profile of belatacept does not justify its use among EBV- kidney transplant recipients, but does justify its use among EBV+ kidney transplant recipients (where the absolute risk of PTLD is lower).

No biologic reason exists to believe that the efficacy of belatacept should be different among EBV+ and EBV- subpopulations. However, given that the applicant has suggested that its use should be restricted to the EBV+ subpopulation, an analysis of the data supporting the efficacy of belatacept in that subpopulation was performed, as shown in Table 18, Table 19, Table 20, Table 21, Table 22.

Table 18: Patient and Graft Survival at 12 Months by EBV serostatus

Study	EBV status recipient		Belatacept MI	Belatacept LI	CsA
008	Positive	Surviving with a functioning graft	184/194 (94.8)	195/199 (98.0)	170/184 (92.4)
		Graft Loss	3	1	7 (1 died)
		Death w/ functioning graft	6	3	6
		Unknown status	1	0	1
		Difference from CsA (97.3% CI)	2.4 (**-3.7**, 8.5)	5.6 (**0.2**, 11.0)	
	Negative	Surviving with a functioning graft	24/25 (96.0)	23/27 (85.2)	36/37 (97.3)
		Graft Loss	1	4 (1 died)	1
		Death w/ functioning graft	0	0	0
		Unknown status	0	0	0
027	Positive	Surviving with a functioning graft	144/169 (85.2)	139/156 (89.1)	143/168 (85.1)
		Graft Loss	17 (2 died)	14 (1 died)	19 (3 died)
		Death w/ functioning graft	5	3	4
		Unknown status	3	0	2
		Difference from CsA (97.3% CI)	0.1 (**-9.1**, 9.3)	0.4 (**-4.8**, 12.8)	
	Negative	Surviving with a functioning graft	13/14 (92.9)	15/19 (78.9)	13/16 (81.3)
		Graft Loss	0	2	1
		Death w/ functioning graft	1	1	1
		Unknown status	0	1	1

Source: Table 36, Statistical Review, BLA 125,288

Table 19: Composite Renal Function at Month 12 by EBV serostatus

Study	EBV status recipient		Belatacept MI	Belatacept LI	CsA
008	Positive		(n=194)	(n=199)	(n=184)
		Composite endpoint	105 (54.1)	108 (54.3)	143 (77.7)
		Reason for meeting composite:			
		-M12 < 60 and Decrease ≥ 10 from M3 to 12	28	31	43
		-M12 < 60 only	46	48	74
		-Decrease ≥ 10 from M3 to M12 only	14	13	7
		-Imputed due to GL or death	8	4	13
		-Missing	9	12	6
		p-value	<0.0001	<0.0001	
	Negative		(n=25)	(n=27)	(n=37)
		Composite endpoint	20 (80.0)	20 (74.1)	31 (83.8)
		Reason for meeting composite:			
		-M12 < 60 and Decrease ≥ 10 from M3 to 12	5	3	9
		-M12 < 60 only	12	10	18
		-Decrease ≥ 10 from M3 to M12 only	1	3	1
		-Imputed due to GL or death	1	4	1
		-Missing	1	0	2
027	Positive		(n=169)	(n=156)	(n=168)
		Composite endpoint	121 (71.6)	123 (78.8)	143 (85.1)
		Reason for meeting composite:			
		-M12 < 60 and Decrease ≥ 10 from M3 to 12	26	39	33
		-M12 < 60 only	63	58	76
		-Decrease ≥ 10 from M3 to M12 only	4	5	6
		-Imputed due to GL or death	21	17	23
		-Missing	7	4	5
		p-value	.0026	.1411	
	Negative		(n=14)	(n=19)	(n=16)
		Composite endpoint	10 (71.4)	12 (63.2)	14 (87.5)
		Reason for meeting composite:			
		-M12 < 60 and Decrease ≥ 10 from M3 to 12	1	2	4
		-M12 < 60 only	7	6	7
		-Decrease ≥ 10 from M3 to M12 only	0	1	1
		-Imputed due to GL or death	1	2	1
		-Missing	1	1	1

Source: Table 40, Statistical Review, BLA 125,288

Table 20: Acute Rejection (as Defined by the Applicant) at 12 Months by EBV serostatus

Study	EBV status recipient		Belatacept MI	Belatacept LI	CsA
008	Positive	Acute Rejection	46/194 (23.7)	35/199 (17.6)	13/184
		Mild IA	7	4	(7.1)
		Mild IB	3	8	1
		Moderate IIA	15	12	5
		Moderate IIB	20	10	5
		Severe III	1	1	2
					0
		Diff. from CsA (97.3% CI)	16.6 (8.1, **25.1**)	10.5 (2.7, **18.3**)	
	Negative	Acute Rejection	3/25 (12.0)	4/27 (14.8)	3/37 (8.1)
		Mild IA	0	0	2
		Mild IB	0	0	0
		Moderate IIA	2	4	1
		Moderate IIB	0	0	0
		Severe III	1	0	0
027	Positive	Acute Rejection	30/169 (17.8)	26/156 (16.7)	24/168
		Mild IA	0	3	(14.3)
		Mild IB	5	2	1
		Moderate IIA	10	16	2
		Moderate IIB	15	5	16
		Severe III	0	0	5
					0
		Diff. from CsA (97.3% CI)	3.5 (-5.9, **12.9**)	2.4 (-7.1, **11.9**)	
	Negative	Acute Rejection	3/14 (21.4)	5/19 (26.3)	2/16 (12.5)
		Mild IA	0	1	1
		Mild IB	2	0	0
		Moderate IIA	0	1	1
		Moderate IIB	1	3	0
		Severe III	0	0	0

Source: Table 41, Statistical Review, BLA 125,288

Table 21: FDA's Analysis of Biopsy Proven Acute Rejection, Graft Loss, and Death at 12 Months by EBV Serostatus

Study	EBV status recipient		Belatacept MI	Belatacept LI	CsA
008	Positive	Met Endpoint Biopsy Proven AR Graft Loss Death Unknown	57/194 (29.4) 49 3 4 1	42/199 (21.1) 40 1 1 0	31/184 (16.8) 18 6 6 1
		Diff from CsA (97.3% CI)	12.6 (2.6, **22.6**)	4.3 (-5.0, **13.7**)	
	Negative	Met Endpoint Biopsy Proven AR Graft Loss Death Unknown	3/25 (12.0) 3 0 0 0	7/27 (25.9) 5 2 0 0	6/37 (16.2) 5 1 0 0
027	Positive	Met Endpoint Biopsy Proven AR Graft Loss Death Unknown	57/169 (33.7) 36 14 5 2	45/156 (28.8) 32 10 3 0	47/168 (28.0) 31 11 4 1
		Diff from CsA (97.3% CI)	5.7 (-6.0, **17.4**)	0.8 (-10.9, **12.5**)	
	Negative	Met Endpoint Biopsy Proven AR Graft Loss Death Unknown	5/14 (33.7) 4 0 1 0	6/19 (31.6) 5 1 0 0	5/16 (31.3) 3 1 1 0

Source: Table 37, Statistical Review, BLA 125,288

Table 22: Measured GFR at Month 12 by EBV Serostatus

Study	EBV status recipient		Belatacept MI	Belatacept LI	CsA
008	Positive	Mean (sd) at Month 12 # in analysis Diff from CsA (97.3% CI) p-value	67.3 (30.0) 177 15.6 (9.3, 21.8) <0.0001	64.7 (27.9) 183 13.0 (6.8, 19.2) < 0.0001	51.7 (18.1) 165
	Negative	Mean (sd) at Month 12 # in analysis	47.5 (24.4) 23	52.8 (23.8) 23	43.9 (20.4) 34
027	Positive	Mean (sd) at Month 12 # in analysis Diff from CsA (97.3% CI) p-value	51.5 (20.7) 141 6.3 (0.4, 12.2) 0.0184	48.5 (25.5) 135 3.3 (-2.7, 9.3) 0.2250	45.2 (20.7) 140
	Negative	Mean (sd) at Month 12 # in analysis	59.3 (33.9) 12	56.7 (27.5) 16	45.4 (25.2) 14

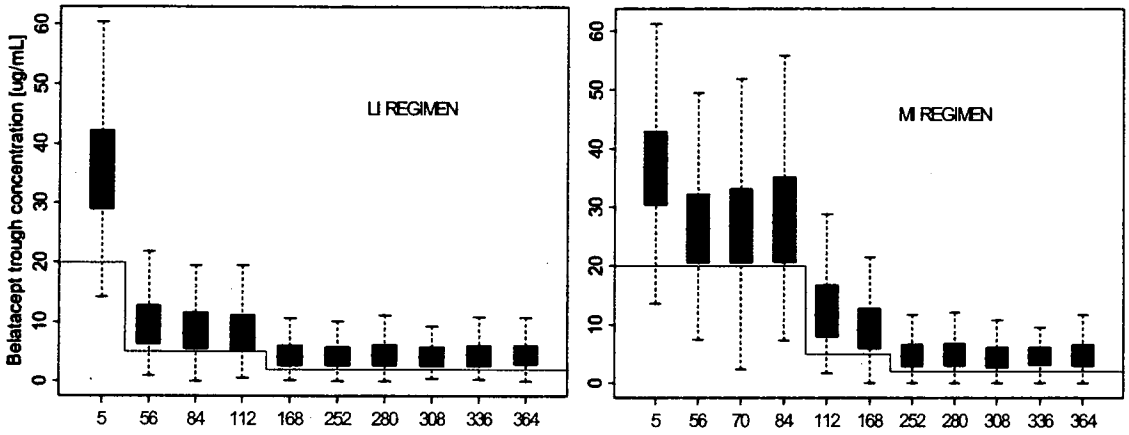
Source: Table 38, Statistical Review, BLA 125,288

Age/Gender/Race
Efficacy results were also examined according to subgroups of patients divided according to gender, race, and age. The detailed results are available in the Statistical Efficacy Review (see Table 30 through Table 32). Although the endpoint of BPAR (with death, graft loss, and missing data imputed as treatment failures) represented the basis for demonstrating the efficacy of belatacept in the overall population, the examination of efficacy results by subgroups considered not only that efficacy endpoint but also patient and graft survival and mean GFR. When examining the efficacy results by subgroups, comparisons across treatment groups within subgroups are more relevant than comparisons across subgroups within treatment groups. For instance, not surprisingly, the results suggest that patient and graft survival are worse for patients 65 years of age or older compared to patients younger than 65 years old. However, no reproducible observations across the Phase 3 trials suggested convincingly that belatacept lacked efficacy in any particular subgroup.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Belatacept
As described in Section 4.4.2, some conflicting evidence regarding belatacept dose response relationships emerged from analyses of the clinical trial data. As detailed in the Clinical Pharmacology Review, a pattern of increased efficacy with greater belatacept exposure (based on both AR and GFR endpoints) was detected within the belatacept MI and LI groups of the Phase 3 trials. However, outcomes based on those same endpoints were similar across the belatacept MI and LI in both of those trials despite a greater average belatacept exposure among the belatacept MI group than the belatacept LI group (see Figure 8).

Figure 8: Belatacept C_{trough} in *de novo* kidney transplant patients receiving the LI regimen (left panel) and the MI regimen (right panel). Data from Phase 3 trials IM103008 and 103027 were combined. The bottom and top of each box represent the inter quartile range (i.e., 25th and 75th percentiles, respectively). The bar inside each box represents the median C_{trough}. The whiskers represent 5th and 95th percentiles, respectively. The horizontal reference lines represent the targeted C_{trough} for each regimen.



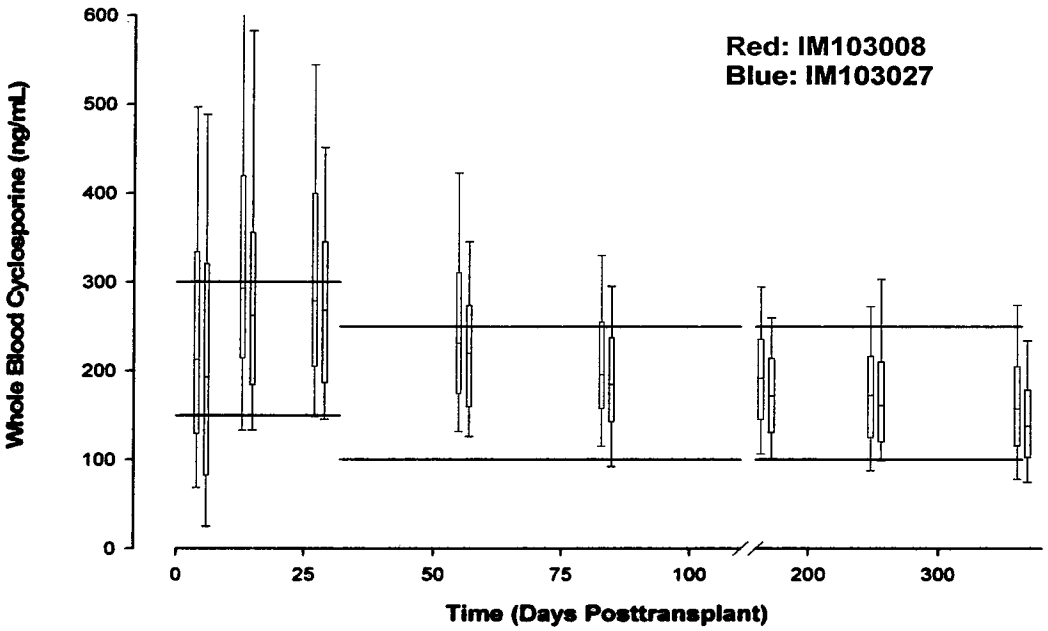
Source: Figure 1, Clinical Pharmacology Review, BLA 125,288

Cyclosporine (CsA)

While some aspects of dose-exposure relationships with belatacept require further elucidation, the experience with CsA over the past several decades has resulted in the opinion that the efficacy and toxicity of CsA both are both dose-dependent (leading to some current trends towards reductions in dosages of CsA).[25] The use of CsA in the Phase 3 belatacept trials was largely consistent with the specifications of the trial protocols, the labeling of CsA, and the use of CsA in other kidney transplant trials recently reviewed at FDA but tended towards the higher limits of each of these (see Figure 9).

25 Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. NEJM 2007; 357: 2562-75.

Figure 9: Whole Blood Trough Concentrations of CsA in Patients Randomized to CsA in the Phase 3 Studies IM103008 (red, left-side bars at each day) and IM103027 (blue, right-side bars at each day)



Source: Figure 3, Clinical Pharmacology Review, BLA 125,288

Reviewer comment: The relatively generous exposures to CsA observed among the control group may have contributed to the finding that belatacept, while effective, may have less efficacy than CsA. While it is possible that differences in rates of AR may have been less pronounced in the context of a different approach to CsA dosing, the toxicities observed among the CsA patients may have also been less severe. Overall, the use of CsA in the trials appears sufficiently consistent with current practices to validate the efficacy conclusions. It may be reasonable, however, to consider the pattern of CsA exposures while weighing the relative efficacy and safety of belatacept.

Mycophenolate Mofetil
In Phase 3 studies IM103008 and IM103027, the initial MMF dose was 2 g/day. However, the MMF dose was allowed to be adjusted at the physician's discretion based on clinical signs of adverse events or efficacy failure. There was no substantial difference in percent of patients who received MMF 2 g/day among the treatment groups in Studies IM103008 and IM103027. Approximately 60-75% of patients received 2 g/day of MMF across all treatment groups. The remainder of patients received less than 2 g/day of MMF.

Unlike belatacept, cyclosporine (CsA) inhibits enterohepatic recirculation of mycophenolic acid (MPA), the active form of MMF, and, consequently, lowers MPA

exposure. Thus, systemic exposure to MPA is expected to be higher in the belatacept arms and exposure to the main metabolite, MPA glucuronide (MPAG), would be lower, as compared to the CsA arm. In a subset of 21 kidney transplant patients enrolled in the two Phase 3 trials, the mean dose-normalized MPA C_{max} and AUC_{0-12} were higher by 20% and 40%, respectively, when MMF 2 g/day was co-administered with belatacept than when co-administered with CsA. The mean dose-normalized MPAG Cmax and AUC_{0-12} were lower by 25% and 30%, respectively, in those patients receiving belatacept and MMF as compared to those receiving CsA and MMF.

Reviewer comment: Despite the cyclosporine-associated decreased exposure to MPA, there was not a greater frequency of MMF-related toxicities, such as gastrointestinal adverse events (AEs) or leukopenia, among belatacept- versus CsA-treated subjects (see Section 7.4.1).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

As previously discussed, incidence of AR represented the most useful measure of efficacy of in the belatacept trials. While the rates of AR were numerically higher among belatacept patients than CsA patients, the difference between the groups was sufficiently small to demonstrate the efficacy of belatacept. Moreover, the vast majority of AR events which occurred among patients maintained on a belatacept regimen occurred early: in the Phase 3 trials, one third of all the AR events experienced by belatacept patients during the first year presented within the first month after transplantation and 97% (147/152) presented within the first six months.

Reviewer Comment: The Phase 3 trials suggested that belatacept may have less efficacy than CsA for the prophylaxis of AR, As discussed in Section 1.2, a risk-benefit analysis may potentially favor a less efficacious drug if it is also less toxic. In that context, the finding that most efficacy failures related to belatacept occurred early may favor belatacept, as one might expect that the disadvantages of decreased efficacy should have already manifested while the benefits of avoiding toxicities associated with CsA will continue to accrue among those patients managed on a belatacept regimen.

6.1.10 Additional Efficacy Issues/Analyses

During the era when the Phase 3 belatacept kidney transplant trials were designed and conducted, insufficient data supporting the safe and effective use of tacrolimus in conjunction with MMF had been submitted to the FDA to recommend the use of such a comparator in clinical trials. As described in Section 2.3 and 2.4, however, the majority of US kidney transplant patients are currently managed on regimens using combinations of these two drugs. Changes made to the Prograf labeling in May 2009 reflect the review of data supporting the use of tacrolimus in conjunction with MMF submitted to the FDA subsequent to the start of the Phase 3 belatacept trials. While the control regimen used in the Phase 3 belatacept trials still represents an acceptable standard-of-care, some physicians within the transplant community may express a

desire for trial data comparing the safety and efficacy of the proposed belatacept regimen with a tacrolimus-based immunosuppressive regimen.

7 Review of Safety

Safety Summary

The two Phase 3 kidney transplant trials, IM103008 and IM103027, were the key trials for demonstrating the relative safety of belatacept. In both trials, the control groups used a CsA-based immunosuppressive regimen. A related Phase 2 kidney transplant trial, IM103100, did not study a regimen identical to that proposed by the applicant for approval. In addition, the Phase 2 trial was designed as a one year study; while a long term extension (LTE) of the trial was implemented, only a third of the 73 patients in the CsA control group part participated. In effect, then, IM103100 lacked a control group after the first year of follow-up. For both of those reasons, the safety review focused on the Phase 3 trials, particularly for endpoints such as death, graft loss, and mean GFR where absence of a meaningful control group in the Phase 2 trial beyond two years complicated use of the Phase 2 data. Observations based on the data from IM103100, however, were consistent with the conclusions based on the data from the Phase 3 trials.

Size of the safety database is always a limitation in the review of trials of newer therapeutic agents for indications in kidney transplantation: due to the limited number of kidney transplants performed worldwide and due to the extensive monitoring required of each patients, individual trials are rarely larger than several hundred patients. The safety population of IM103008 included 666 patients (226 randomized to the belatacept LI regimen, 219 randomized to the belatacept MI regimen, and 221 randomized to the CsA regimen). The safety population of IM103027 included 543 patients (175 randomized to the belatacept LI regimen, 184 randomized to the belatacept MI regimen, and 184 randomized to the CsA regimen). Data for outcomes including death, graft loss, GFR, and PTLD were available for all Phase 3 patients at 2 years of follow-up. Given safety signals seen both in the context of the belatacept and with previous biologic agents, consideration was also given to the Phase 2 kidney transplant trial data -- and even to other trials in the belatacept developmental program -- for certain rare outcomes (e.g., PTLD, PML, CNS infections, graft thrombosis) despite concerns regarding differences in the belatacept regimens studied.

The most significant safety concerns associated with belatacept elucidated during the review of the BLA include PTLD (particularly PTLD involving the CNS), PML (and other CNS infections), and higher rates and grades of AR. The safety review, however, favored belatacept over the CsA control with regards to other important safety issues including mean GFR, blood pressure, new onset diabetes after transplantation, and dyslipidemia.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary clinical trials used to evaluate safety were the Phase 3 trials, IM103008 and IM103027. The review focused on those trials as they were the only ones to use the proposed belatacept LI regimen in a kidney transplant population. The Phase 2 trial, IM103100, used a similar regimen but omitted a 10 mg/kg dose on Day 5 and randomized half of the recipients to 5 mg/kg infusions every 8 weeks (instead of every 4 weeks) after Month 6. In addition, only 26 of the 73 patients in the CsA control group continued in the long-term extension study beyond Month 12 – in effect, making IM103100 an uncontrolled trial after the first year. While the Phase 3 trials represented the core of the data used in the review – specifically for endpoints such as patient and graft loss, ARs, GFR, and cardiovascular risk factors -- additional data were considered in some safety endpoints. In particular, for some of the more rare events (such as PTLD and PML), the Phase 2 kidney trial was included in order to capture as much safety information as possible. With regards to PTLD and PML, other trials conducted by the applicant which used belatacept for other indications were also given consideration: the safety evaluation also included a review of incidents in a Phase 2 study in *de novo* liver transplant patients where two events of PTLD and a single event of PML were observed. In order to obtain a more accurate point estimate of the expected rate of PTLD, by EBV status, among *de novo* kidney transplant recipients, additional clinical trial data was reviewed from previously submitted New Drug Applications (NDAs) as well as kidney transplant registry data from UNOS obtained through the United States Renal Data System (USRDS).

7.1.2 Categorization of Adverse Events

Most common and severe adverse events were categorized using the MedDRA dictionary of preferred terms. However, the safety events of particular interest, (including death, graft loss, AR episodes, PTLD, cardiovascular data (e.g., NODAT), and GFR) identified prospectively and were specifically measured and recorded into databases designed to allow analyses of these outcomes. Additional information was available in the patient narratives. Data captured in the clinical trials databases and/or narratives which specifically measured these outcomes were used preferentially to related data incidentally captured in the Adverse Events database to evaluate relevant safety outcomes.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data were pooled across the Phase 2 and Phase 3 kidney trials to evaluate the incidence of PTLD. As stated above, the data were pooled for this purpose due to the rarity of the event. Pooled analyses using data from all three trials were also conducted for serious adverse events, adverse events leading to treatment discontinuation, and infections reported as adverse events, including CNS infections. While the usual concerns regarding pooling applied to these analyses, it was deemed important to determine whether any patterns would emerge if the analyses of these events were given greater power. Most safety issues, however, were examined within the context of individual trials, with the focus on the Phase 3 trials.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Safety analyses were performed using the ITT populations for Studies IM103008 and IM103027, and as-treated population in IM103100, as shown in Table 23: Safety Population from Pooled Studiesbelow, and included 477 patients randomized to the belatacept MI regimen, 472 patients randomized to the belatacept LI regimen, and 476 patients randomized to the CsA containing regimen.

Table 23: Safety Population from Pooled Studies

Study Number	Belatacept MI	Belatacept LI	CsA
008	219	226	221
027	184	175	184
100	74	71	71
TOTAL	**477**	**472**	**476**

Source: Created by the Reviewer from the Clinical Safety Summary, BLA 125,288

One subject in the belatacept MI group (IM103027), 1 subject in the belatacept LI group (IM103027) and 13 subjects in the CsA group (6 in IM103008, 5 in IM103027 and 2 in IM103100) were included in the safety population, but did not receive study medication.

The number of subjects with at least 12 months of exposure to study medication was as follows: 365/476 (77%) in the belatacept MI group, 369/471 (78%) in the belatacept LI group, and 350/465 (75%) in the CsA group.

In the following discussion of safety, adverse events (AEs) are reported by Preferred Terms (PT) and by System Organ Class (SOC) using the Medical Dictionary for

Regulatory Activities (MedDRA). AEs are reported for the first 12 months of the Phase 2 (IM103100) and Phase 3 studies (IM103008, IM103027), with the exception of deaths and PTLD. Deaths are reported out to 24 months and also through the date of the Safety Update Report (SUR) (covering events occurring between the March 2009 BLA database lock and June/July 2009). In addition to reporting PTLD cases through database lock, the applicant has also forwarded all new cases as they occur.

7.2.2 Explorations for Dose Response

The Phase 2 and Phase 3 kidney transplant trials each examined belatacept MI and LI dosing regimens. The belatacept MI and LI regimens were similar, though not identical, across the two phases. Patients who remained on the treatment received belatacept dosing according to the protocol – dose titrations were not allowed nor observed.

For the most part, adverse events were similar between the MI and LI-treated patients, with the exception of CNS infections (Section 7.3.4).

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical testing was performed in various rodent and non-human primate models. Details may be found in the Pharmacology/Toxicology review. Belatacept is a second-generation biologic derived from the first-generation CTLA4-IgG fusion protein, abatacept. While belatacept is more potent than abatacept in humans and non-human primates, abatacept is more potent than belatacept in rodents. As described in the Pharmacology/Toxicology review, nonclinical studies were performed with both abatacept and belatacept and the nonclinical results in rodents for abatacept were felt to be more relevant than those obtained with belatacept.

7.2.4 Routine Clinical Testing

Chemistry and hematology panels were sent to a central lab at baseline and again at Day 5, Month 1, Month 2, Month 3, Month 6, Month 9, and Month 12. Measured GFR samples were collected at Month 3, Month 12, and Month 24. Fasting glucose and lipids were collected at baseline, Month 1, Month 3, Month 6, and Month 12. Hemoglobin A1c was measured at Month 3, Month 6, and Month 12. Urinalysis samples were collected at baseline, Day 5, Month 1, Month 6, and Month 12. A kidney biopsy was collected at baseline and Month 12. Serum immunglobulins were collected at baseline, Month 6, and Month 12. CsA troughs were collected for patients randomized to the control groups at Day 5, Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, and Month 12.

7.2.5 Metabolic, Clearance, and Interaction Workup

Since belatacept is a protein molecule, traditional *in vitro* and *in vivo* drug interaction studies were not required or conducted. See Clinical Pharmacology review for a

request for a Post-Marketing Requirement (PMR) to study potential drug-drug interactions.

Reviewer comment: The Clinical Pharmacology Review raises the issue that therapeutic agents, such as belatacept, which affect cytokines may indirectly affect CYP450 pathways. That review suggests that this could potentially impact the metabolism of other medications metabolized by CYP450 enzymes which are co-administered with belatacept. The Clinical Pharmacology further suggests that further investigation of this potential interaction metabolized may be warranted. Examples of such co-administered drugs are HMG-CoA reductase inhibitors (statins), anti-hypertensive drugs (beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB)), oral hypoglycemic drugs, triazole antifungal and antiviral drugs metabolized through CYP450.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Abatacept is a related product. The primary warnings in the abatacept labeling relate to infection, (b) (4). The labeling also notes a higher rate of malignancies, including lymphomas, were observed in the abatacept clinical trials. Concerns related to autoimmunity have also been raised with abatacept. Each of these adverse events were considered by the applicant in its application and the FDA in its safety review. These issues are addressed individually throughout Section 7.

Given the concern with potential autoimmunity with belatacept (as discussed in Section 7.3.5), a consult was requested on February 2, 2010 from the Division of Pharmacovigilance II (DPV II) in the Office of Surveillance and Epidemiology to search the Adverse Event Reporting System (AERS) database for post-marketing reports of abatacept in association with selected autoimmune events (autoimmune thyroid disease, Hashimoto's thyroiditis, Graves' disease, Hemolytic anemia, Idiopathic Thrombocytopenic Purpura (ITP), lupus (SLE), and insulin-dependent diabetes (type 1).

The completed consult was dated February 18, 2010. DPV II did not identify any safety signal with abatacept and autoimmune events based upon 19 AERS reports of limited clinical information and confounding factors and low data mining scores.

See complete consult by Peter Diak, Pharm.D., M.P.H.

7.3 Major Safety Results

7.3.1 Deaths (and Graft Loss)

Due to the differences in the LI regimen between the Phase 2 and Phase 3 trials and poor enrollment in the control LTE of the Phase 2 trial, the discussion in this section will focus on the deaths reported in the Phase 3 trials. It may be worth noting, however, in the Phase 2 trial (IM1030100) that there were no deaths in either belatacept regimen reported at 12 months compared to two deaths in the CsA control group. In the LTE portion of the trial, there were three deaths reported among the 102 belatacept patients (MI and LI combined) who continued treatment compared to two deaths among the 26 CsA patients who continued treatment.

The observed rates of death in both Phase 3 trials were similar across treatment groups. While numerically fewer belatacept patients had died at 24 months in IM103008 and in the belatacept LI group of IM103027, one must consider that several belatacept patients in both trials alive at 24 months had already developed or would later develop PTLD. Given the significant mortality associated with PTLD – and particularly with CNS PTLD seen in the majority of the belatacept-associated cases – care should be taken when considering the numeric advantage observed in the belatacept groups in terms of overall death at 24 months. Despite such caveats, however, the data from the Phase 3 trials support that kidney transplant patients maintained on either belatacept regimen had similar mortality outcomes at 24 months to the CsA control regimen, even among a patient population which included EBV- recipients and despite the impact of the imbalance in PTLD presentations across treatment groups (see Table 24).

Table 24: Deaths Occurring in the Phase 3 Trials

	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						
Up to Month 12	6 (2.7)	4 (1.8)	7 (3.2)	8 (4.3)	5 (2.9)	8 (4.3)
Up to Month 24	7* (3.2)	8† (3.5)	13§ (5.9)	13 (7.1)	11‡ (6.3)	12 (6.5)
Through Safety Update Report	7* (3.2)	9† (4.0)	14 (6.3)	19 (10.3)	13‡ (7.4)	16 (8.7)

PTLD patient = patient diagnosed with PTLD at any time during trial
* = 3 PTLD patients alive at 24 months and at SUR
† = 2 PTLD patients alive at 24 months and at SUR
§ = 1 PTLD patient alive at 24 months (but not at SUR)
‡ = 3 PTLD patients alive at 24 months and at SUR; Note: All three patients in the belatacept LI treatment group of Study IM103027 with PTLD diagnoses who were alive at 24 months of follow up and at SUR have since died (PID 27-10-10029 and PID 27-138-10593, both in (b) (6)), and PID 27-91-10044, in (b) (6) All other patients in the Phase 3 studies who were alive at 24 months of follow up with PTLD diagnoses are still alive.
Source: Created by the Clinical Reviewer using the applicant's datasets and narratives, BLA 125,288

Death Narratives

Patient narratives summarizing the circumstances of death were reviewed. As expected among kidney transplant recipients, most deaths appeared attributable to cardiovascular causes or infection. Several occurred in the immediate post-operative setting. The most notable difference between patient groups is the three deaths due to CNS lymphoma that occurred by the 24 month time point among belatacept-treated patients. Of these three deaths, two occurred in EBV+ patients and one occurred in an EBV- patient. Table 25, Table 26, Table 27, Table 28, Table 29, and Table 30 below reflect the cause of death as inferred from the submitted death narratives by the Clinical Reviewer.

IM103008

Table 25: Narratives of Deaths among CsA Patients in IM103008 at 24 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
22-20679	1	38	M	Patient had "seizure" while driving, then died of MI in hospital
76-20171	1	55	M	Hemorrhagic shock immediately post-op, never received CsA
84-20700	1	48	F	Sepsis
89-20350	1	50	M	Cardiac arrest immediately post-operatively
98-20439	1	45	M	Suicide
118-20353	1	20	M	Pneumonia
123-20740	1	54	F	Sepsis, wound infection
10-20254	2	66	M	Cardiac arrest in setting of massive bleed on anticoagulation
41-20088	2	61	M	Cardiac arrest in setting of fever
48-20042	2	64	M	Pneumonia
84-20405	2	53	M	Pulmonary adenocarcinoma
91-20103	2	55	F	Hypoxia due to pulmonary edema
116-20453	2	37	F	Interstitial lung disease

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

Table 26: Narratives of Deaths among Belatacept LI Patients in IM103008 at 24 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
10-20037	1	55	M	Patient died on Day 358; distant history of wound infection, no other information available
46-20592	1	61	F	Sepsis immediately post-operatively
123-20230	1	19	F	Generalized bleeding (not witnessed)
124-20297	1	55	M	Myocardial infarction
9-20120	2	47	M	Metastatic sarcoma
25-20375	2	71	F	Non small cell lung cancer
57-20645	2	37	M	Bowel ischemia due to severe mesenteric artery occlusion
154-20618	2	26	M	No information available regarding circumstances of death

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

Table 27: Narratives of Deaths among Belatacept MI Patients in IM103008 at 24 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
46-20330	1	77	M	Hemorrhage from vascular anastamosis on Day 12
46-20650	1	74	M	Urosepsis
84-20669	1	41	F	Sudden cardiac death
85-20526	1	71	F	CMV colitis, sepsis
124-20561	1	72	M	Lung adenocarcinoma
159-20686	1	53	M	Bronchopulmonary aspergillosis
41-20344	2	46	M	Complications of West Nile Virus

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

IM103027

Table 28: Narratives of Deaths among CsA Patients in IM103027 at 24 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
2-10002	1	56	M	"Veered off road and collapsed"
32-10077	1	63	M	Rupture of mycotic aneurysm
57-10086	1	64	M	Pulmonary embolus
60-10260	1	73	M	Significant intragraft bleed immediately post-op, MI; never received CsA
85-10110	1	65	F	Sepsis
85-10531	1	72	M	Obstructive uropathy, sepsis
85-10572	1	70	F	Intestinal ischemia
105-10400	1	58	F	Renal vein thrombosis, GI hemorrhage, sepsis
10-10275	2	62	M	Sepsis (MRSA); also infected with pseudomonas and aspergillosis
17-10061	2	68	F	Fungal pneumonia, disseminated CMV disease
54-10502	2	79	M	Kaposi's Sarcoma
105-10573	2	68	F	Sepsis

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

Table 29: Narratives of Deaths among Belatacept LI Patients in IM103027 at 24 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
64-10372	1	65	M	Withdrew consent on Day 42; reported to have died on Day 353
66-10516	1	68	M	Sigmoid colon perforation; sepsis
85-10569	1	66	F	Necrotizing fascitis and sepsis on Day 3
91-10089	1	42	M	Disseminated tuberculosis, invasive CMV disease, sepsis
97-10452	1	75	M	Endocarditis, sepsis
26-10440	2	55	M	Complications related to transitional cell carcinoma
29-10427	2	68	M	Myocardial infarction
93-10037	2	49	M	Strongyloidiasis, CMV disease, pneumonia
101-10093	2	75	M	**CNS lymphoma (PTLD); Pt was EBV+ at baseline**
124-10466	2	55	M	Cryptococcosis, "cerebellar syndrome", seizures, coma; post-mortem cerebral cultures and biopsy were negative
124-10527	2	44	M	Patient found dead in house on Day 426; cause unknown

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

Table 30: Narratives of Deaths among Belatacept MI Patients in IM103027 at 24 Months

Patient	Year Died	Age	Sex	Cause of Death Inferred from Death Narrative
22-10496	1	70	F	Cardiac arrest on Day 3
53-10399	1	63	F	Surgical wound infection
58-10390	1	68	F	Ischemic heart disease
70-10447	1	65	M	**CNS lymphoma (PTLD); Pt was EBV- at baseline**
85-10249	1	50	M	Myocardial infarction
89-10114	1	79	M	Severe post-operative MI and sepsis; Pt ultimately died on Day 96 of multi-organ failure and sepsis
93-10027	1	65	M	Myocardial infarction
102-10494	1	58	M	Post-operative renal hemorrhage; ischemic bowel
30-10184	2	72	M	Severe aortic valve disease
35-10185	2	71	M	**CNS lymphoma (PTLD); Pt was EBV+ at baseline**
97-10453	2	73	M	Withdrew consent Day 13; Pt reported to have died on Day 669
102-10164	2	61	M	Pneumonia
125-10433	2	62	M	Osteomyelitis, staph sepsis

Source: Created by the Clinical Reviewer from death narratives provided by the applicant, BLA 125,288

Death, graft loss, and the combined endpoint of death and graft loss were evaluated in the Phase 3 trials IM103008 and IM103027 at 12 months and 24 months. Randomized clinical trials in transplantation lack the statistical power to rigorously evaluate the combined endpoint of patient death and graft loss. Numerically, however, more belatacept patients across the Phase 3 trials were alive with a functioning graft at both Month 12 and Month 24 (see Table 31 and Table 32). The numeric difference observed was driven by IM103008. Given the lack of statistical power, one cannot determine whether the numeric difference represents chance or true benefit with regard to GFR,

blood pressure, and diabetes on belatacept regimens. While one cannot conclude that belatacept patients had a more favorable outcome with respect to combined death and graft loss compared to CsA patients in the Phase 3 trial, it is somewhat reassuring that the numeric advantage persists despite the greater number of PTLD events among belatacept patients (even if all belatacept patients with PTLD reported as alive and with a functioning graft at 24 months were to be imputed as failures for the endpoint).

Table 31: Patient and Graft Status in the Phase 3 Trials

	IM103008			IM103027		
	Belatacept MI (n=219)	**Belatacept LI (n=226)**	**CsA (n=221)**	**Belatacept MI (n=184)**	**Belatacept LI (n=175)**	**CsA (n=184)**
At Month 12						
Alive and no GL	208	218	206	158	155	156
Graft Loss	4	5 (1 died)	8 (1 died)	17 (2 died)	16 (1 died)	20 (3 died)
Death w/ fxning graft	6	3	6	6	4	5
Unknown	1		1	3		3
At Month 24						
Alive and no GL	204	212	198	151	146	148
Graft Loss	7 (1 died)	5 (1 died)	8 (1 died)	18 (2 died)	20 (3 died)	22 (4 died)
Death w/ fxning graft	6	7	12	11	8	8
Unknown	2	2	3	4	1	6
Through Safety Update						
Alive and no GL	204	208	195	147	143	144
Graft Loss	7 (1 died)	8 (1 died)	10 (1 died)	18 (4 died)	21 (3 died)	22 (4 died)
Death w/ fxning graft	6	8	13	15	10	12
Unknown	2	2	3	4	1	6

Source: Created by Statistical Reviewer from applicant's datasets, BLA 125,288

Table 32: Death and/or Graft Loss at 12 and 24 Months and Safety Update

	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/Graft Loss						
Up to Month 12	10	8	14	23	20	25
Up to Month 24	13*	12†	20§	29	28‡	30
Through Safety Update	13*	16†	24	33	31‡	34
Death/Graft Loss/Unknown						
Up to Month 12	11	8	15	26	20	28
Up to Month 24	15*	14†	23§	33	29‡	36
Through Safety Update	15*	18†	26	37	32‡	40

PTLD patient = patient diagnosed with PTLD at any time during trial
* = 2 PTLD patients alive with functioning graft at 24 months and at SUR
† = 2 PTLD patients alive with functioning graft at 24 months and at SUR
§ = 1 PTLD patient alive with functioning graft at 24 months (but not at SUR)
‡ = 2 PTLD patients alive with functioning graft at 24 months and at SUR; Note: Both patients with PTLD alive with a functioning graft in the belatacept LI arm of Study IM103027 died after the Safety Update Report (PID 27-138-100592 died on (b) (6) and PID 27-91-10044 died in (b) (6))
Source: Created by the Clinical Reviewer using the applicant's datasets and narratives, BLA 125,288

7.3.2 Serious Adverse Events

PTLD

The applicant is seeking approval for the belatacept LI regimen studied in the Phase 3 trials. That regimen included an extra 10 mg/kg infusion of belatacept on Day 5 compared to the belatacept LI regimen studied in the Phase 2 trial. As will be discussed, six cases of PTLD (including 3 cases of CNS PTLD) developed among recipients of the Phase 3 belatacept LI regimen (6/401 patients) and no cases of PTLD developed among recipients of the Phase 2 belatacept LI regimen (0/71 patients). PTLD represents the major safety signal detected in the belatacept trials and it appears biologically plausible that the extra exposure to belatacept in the early post-transplant period may explain the development of PTLD among Phase 3 recipients of the LI regimen.

The numbers of patients across the Phase 2 and Phase 3 trials, who developed PTLD, while clinically significant, were too few to perform a meaningful exposure-response analysis. For that reason, many of the analyses of PTLD observed among belatacept-treated patients in comparison to CsA-treated patients pool patients across belatacept treatment groups and across the Phase 2 and Phase 3 trials. While the pooling represents a limitation of the analyses, the alternative of performing separate analyses

for each belatacept regimen was judged to have greater limitations. Nonetheless, one should keep this limitation in mind when considering the number needed to harm (NNTH) calculations presented.

The safety signal of PTLD appeared consistently across all three trials in both belatacept treatment groups and within various patient subgroups. To date, there have been eight (1.7%), six (1.3%) and two (0.4%) reported cases of PTLD in the belatacept MI, LI, and CsA groups respectively (see Table 33 and Table 34). Please note that many of the analyses of PTLD which follow reference the incidence of PTLD at 2 years of follow-up. The 2 year time point was selected as complete PTLD data were available for all patients for 2 years of follow-up; the use of the 2 year time point has the effect of censoring a case of CNS PTLD that developed in a patient (PID 103027-91-1044) in the belatacept LI regimen in IM103027 after 24 months in those analyses.

Table 33: All PTLD Cases for Belatacept Trials 008, 027 and 100

	Bela MI N = 477	Bela LI N = 472	CsA N = 478	Diff (pooled LI/MI–CsA)	Diff (M1–CsA)	Diff (LI–CsA)
PTLD in all patients	8 (1.7) (0.7, 3.3)	6 (1.3) (0.5, 2.7)	2 (0.4) (0.1, 1.5)	(-0.1, 2.1)	(-0.1, 2.9)	(-0.4, 2.4)
EBV+ PTLD in EBV+	N = 404 2 (0.5) (0.1, 1.8)	N = 401 4 (1.0) (0.3, 2.5)	N = 399 0 (0) (0, 0.9)	(-0.2, 1.6)	(-0.5, 1.8)	(0, 2.5)*
EBV- PTLD in EBV-	N = 45 5 (11.1) (3.7, 24.1)	N = 51 2 (3.9) (0.5, 13.5)	N = 57 1 (1.8) (0, 9.4)	(-2.5, 13.1)	(-0.3, 22.3)	(-5.9, 11.9)
EBV unknown PTLD in EBV unknown	N = 28 1 (3.6)	N = 20 0 (0)	N = 22 1 (4.5)	(-20.3, 8.2)	(-19.4, 14.7)	(-23.0, 13.2)

* exact p-value < 0.05
All confidence intervals reported are exact confidence intervals due to the small number of events.
Note: Table based on the pooled ITT population and not the safety population. Therefore, the denominator for the CsA group is 478 instead of 476. These two additional patients, who did not receive any study medication, had an unknown EBV serostatus.
Source: Created by the Statistical Reviewer using the applicant's datasets, BLA 125,288

At 24 months of follow-up, three belatacept MI patients from the Phase 3 trials had already died from complications related to PTLD (and are therefore reflected in the total deaths presented in the 24 month efficacy and safety data). To date, three belatacept LI patients and one CsA patient from the Phase 3 trials have died from complications related to PTLD beyond the 24 month follow up period (and are therefore not reflected in the total deaths presented in the 24 month efficacy and safety data). Three additional belatacept MI patients and three additional belatacept LI patients from the Phase 3 trials who developed PTLD remain alive and at significant risk of death and other complications. A post hoc central pathology review of the PTLD cases suggests the

possibility that two of the three belatacept LI patients who remain at risk may have been misdiagnosed with PTLD. One (PID 103008-113-20060) of those two patients, however, underwent six courses of rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP) based on the local pathology read; the other (PID 103008-122-20256) had PCR evidence of a clonal population with specific rearrangement of the heavy chain, consistent with a diagnosis of PTLD. No additional CsA patients from the Phase 3 trials, other than the single patient who has already died, have developed PTLD to date.

Table 34: Summary of PTLD Cases Observed in Belatacept Trials 008, 027 and 100

	Belatacept MI (N=477)			**Belatacept LI*** (N=472)			**CsA** (N=478)		
Trial	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		$2^{\Omega,\dagger}$							
Non-CNS PTLD			$1^{\ddagger}$						$1^{\ddagger}$
IM103008									
CNS PTLD	1^{Ω}	1^{Ω}							
Non-CNS PTLD		1^{Ω}		$2^{\Omega,\Omega}$				$1^{\ddagger}$	
IM103027									
CNS PTLD	$1^{\dagger}$	$1^{\dagger}$		$2^{\dagger,\ddagger}$	$1^{\ddagger}$				
Non-CNS PTLD					$1^{\ddagger}$				
Total	***2 (0.5)***	***5 (11.1)***	***1 (3.6)***	***4 (1.0)***	***2 (3.9)***	***0***	***0***	***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 24 months; ‡ = Patient died after first 24 months
Source: Created by the Clinical Reviewer using PTLD narratives, BLA 125,288

Narratives of PTLD Cases Observed in the Pivotal Kidney Transplant Trials by Treatment Group

CsA:

IM103008-101-20019: 35 year old EBV-, CMV+ male who received an EBV+, CMV+ kidney. Patient experienced immediate Grade 1A AR requiring pulse steroids and increased CsA dosing. At Day 82, another for-cause biopsy showed borderline rejection requiring additional pulse steroids. On Day 163, the patient underwent re-implantation of his ureter due to stricture. On Day 168, a liver ultrasound obtained in the setting of elevated LFTs identified four liver nodules. Subsequent work up confirmed a diagnosis of PTLD (large B cell lymphoma) involving liver, lung, and allograft kidney. The patient underwent 6 courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and appeared to have a good response: PET scan on Day 344 showed no residual evidence of PTLD lesions. The patient began sirolimus on Day

337. The patient appeared for a clinic visit on Day 803 where he appeared well. At home, however, he developed vomiting and rigors and died on Day 804. Cause of death was reported as lobar pneumonia.

IM103100-3-25: 53 year old male with unknown EBV status who received a kidney from a donor with unknown EBV and CMV serologies. On Day 1417, the patient presented with fever, chills, and nausea. Serum LDH was elevated and a CT scan of the abdomen revealed soft tissue masses involving the liver and allograft kidney. Liver biopsy confirmed a diagnosis of large B-cell PTLD. The patient was treated with rituximab from Days 1422-1437. The patient developed a mucormycosis infection (sinus) on Day 1440 and died on Day 1473.

Belatacept MI:

IM103008-142-30548: 25 year old EBV-, CMV- male who received a kidney from an EBV-, CMV- donor. The subject received thymoglobulin on Days 4-8 in the setting of graft dysfunction. Renal doppler and angiography studies on Day 9 were consistent with renal vein thrombosis; the RVT resolved with enoxaparin. On Day 498, the patient presented with convulsions and tongue-biting. Head CT showed a lesion in the left frontal lobe. On Day 506, a craniotomy and partial excision of tumor was performed – the tumor was consistent with PTLD but stained negative for EBV. On Day 516, the patient began 4 courses of methotrexate, leucovorin, and procarbazine. MRI prior to the fourth cycle showed a new nodule in the right occipital lobe and evidence of residual tumor. On Day 581, PET scan showed evidence of disease in the frontal lobe, L2 vertebra, and axillary and pelvic nodes. The patient received additional treatment with rituximab and temozolomide. As of March 2009, the patient was still alive and with a functioning allograft.

IM103008-27-20039: 22 year old EBV-, CMV- male who received a kidney from an EBV+, CMV- donor. A for-cause biopsy on Day 76 showed Grade IIA AR. The patient received 10 doses of thymoglobulin, stress dose steroids; belatacept was stopped and tacrolimus was started. A follow-up biopsy on Day 90 showed PTLD (diffuse large B cell lymphoma) and BK nephropathy. Repeat biopsy on Day 95 showed Grade III AR and confirmed the PTLD diagnosis. Rituximab was started on Day 97; IVIg was also given for rejection. PET scan on Day 125 (b) (6) was compatible with PTLD involving the neck, right axilla, and left inguinal region. As of June 2009, the patient was alive but had returned to dialysis.

IM103008-76-20734:38 year old EBV+, CMV- male who received a kidney from an EBV+, CMV+ donor. A for-cause biopsy on Day 43 was consistent with Grade IA AR; the patient received 15 days of pulse steroids, followed by 5 days of thymoglobulin and additional steroids. On Day 154, the patient was hospitalized with CMV colitis. On Day 281, another for-cause biopsy was consistent with BK viral associated nephropathy. On Day 427, the patient developed aphasia, vomiting, and disorientation. An MRI showed 2 cerebral lesions; brain biopsy revealed PTLD (large B cell lymphoma). The patient was

treated with methotrexate, rituximab, and cytarabine. On Day 499 (b) (6)) follow up CT showed some improvement of the cerebral lesions. Additional severe adverse events that have been subsequently reported include renal impairment on Day 525, pulmonary embolism on Day 586, neutropenia on Day 712, and lung disorder on Day 712. As of June 2009, the patient was reported as alive with a functioning graft.

IM103027-35-10185: 71 year old EBV+, CMV+ male who received a kidney from an EBV+, CMV+ donor. On Day 305, the patient developed CMV infection treated with valgancyclovir. The patient was also treated with heparin for phlebitis. In the setting of anticoagulation, the patient experienced a brain hemorrhage; cerebral MRI on Day 325 showed a bifrontal lesion. Brain biopsy on Day 367 confirmed PTLD (large B cell lymphoma). The patient was treated with radiotherapy and rituximab. On Day 402, the patient became comatose and developed a bronchial superinfection. The patient died on Day 415.

IM103027-70-10447: 65 year old EBV-, CMV+ male who received a kidney from an EBV+, CMV+ donor. On Day 256, the patient presented with left hemiparesis. Head CT demonstrated a right frontal lesion. Patient underwent surgical excision on Day 272; pathology was consistent with PTLD (large B cell lymphoma). Patient developed convulsions of Day 296; methotrexate, vincristine, procarbazine, and dexamethasone were initiated on Day 301. On Day 322, the patient developed *E. coli* sepsis and died on Day 322.

IM103100-1-6: 36 year old EBV-, CMV- male who received a kidney from a donor with unknown serologies. A for-cause biopsy on Day 27 was consistent with Grade III AR. The patient was treated with OKT3 for 10 days. Belatacept was discontinued immediately; tacrolimus was started on Day 39. On Day 337, the patient developed left-sided headaches in the setting of a pneumonia. MRI showed a lesion at the base of the skull. PET scan was consistent with activity at the neck, esophagastric junction, and at L2-L3 and L3-L4. Cervical node biopsy demonstrated PTLD (large B-cell lymphoma). The patient received treatment with cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone (CHOP) and rituximab. On Day 477, whole body CT scans were unremarkable. Clinically, the patient has been in remission since 2004; the patient was reported alive with a functioning graft in March 2009.

IM103100-9-4: 23 year old EBV-, CMV+ male who received a kidney from an EBV+, CMV+ male. On Day 109, the patient was hospitalized with a CMV infection (fever, neutropenia). On Day 262, the patient developed headache, nausea, vomiting, and behavioral changes. MRI showed a lesion near the basal ganglia; stereotactic needle biopsy confirmed PTLD (large B cell lymphoma). The patient was treated with high-dose steroids and radiation, On Day 424, the patient was hospitalized with PCP pneumonia and evidence of CMV disease. The subject died on Day 440 (autopsy indicated that patient was in full remission with regards to lymphoma).

IM103100-3-31: 42 year old CMV+ female (EBV serostatus unknown) who received a kidney from CMV+ donor (EBV serostatus unknown). A for-cause biopsy on Day 60 was consistent with Grade IA rejection; the patient was treated with pulse steroids. On Day 93, the patient developed urethral obstruction requiring nephrostomy and ureteral stent insertion. The patient required another for-cause renal biopsy on Day 111 which demonstrated PTLD (large B cell lymphoma). The patient received treatment with R-CHOP. On Day 122, the patient experienced graft loss. On Day 210, the lymphoma was considered resolved. The patient died from septicemia in 2006 while awaiting re-transplant.

Belatacept LI:

IM103008-113-20060: 30 year old EBV+, CMV- male who received a kidney from an EBV+, CMV- donor. A for-cause renal biopsy on Day 73 showed a differentiated monomorphic T cell infiltrate. Pt was asymptomatic; serum LDH was normal. Serum creatinine was 1.5 mg/dL. On Day 78, head CT was unrevealing; chest and abdominal CT showed two small lesions in the liver, but no lymphadenopathy. On Day 86, PET scan showed no findings supportive of PTLD. On Day 93, follow-up renal biopsy showed no evidence of AR or PTLD. Based on the prior biopsy, however, the patient received six cycles of rituximab, vincristine, and cyclophosphamide. Of note, a post hoc central pathology reading disputed the diagnosis of PTLD on the original biopsy. As of March 2009, the patient was reported alive with a functioning graft.

IM103008-122-20256: 44 year old EBV+, CMV- male who received a kidney from an EBV+, CMV- donor. A for-cause renal biopsy on Day 93 showed a B cell infiltrate suggestive of PTLD. PCR provided evidence of a clonal population with specific rearrangement of the heavy chain, consistent with a diagnosis of PTLD. Chest and abdomen CT scans were unremarkable; serum LDH was normal. Patient was treated with bolus prednisolone (20 mg/day for two weeks, then increased to 30 mg/day); belatacept and MMF were stopped. No other treatment was provided. Serum creatinine of Day 135 was 0.95 mg/dL. Follow-up renal biopsy on Day 161 showed no evidence of lymphoma. Patient converted treatment with tacrolimus and MMF on Day 220 (b) (6) . Of note, the post hoc central pathology reading also disputed this diagnosis of PTLD. As of March 2009, the patient was alive with a functioning graft.

IM103027-101-10093: 75 year old EBV+, CMV- male who received a kidney from a donor with unknown serologies. On Day 81, the patient developed fever and cough. He began treatment for CMV disease with IV gancyclovir on Day 97; the CMV infection did not resolve until Day 185 (despite discontinuing belatacept). The patient began treatment with everolimus on Day 245. Due to failure to thrive, patient was hospitalized on Day 504. Bone marrow biopsy on Day 508 showed megaloblastic changes. Head CT on Day 509 suggested lymphoma. MRI on Day 511 showed two nodular lesions. Stereotactic biopsy on Day 523 was consistent with PTLD (diffuse large B-cell lymphoma). On Day 594, the patient died.

IM103027-10-10029: 78 year old EBV-, CMV+ female who received a kidney from a donor with unknown serologies. On Day 82, the patient underwent a for-cause biopsy which was consistent with PTLD (large B-cell lymphoma). MRI of abdomen showed multiple nodules in the renal allograft and enlarged retroperitoneal and pelvic lymph nodes. Head CT did not show any intracranial disease. The patient received 3 doses of rituximab. Belatacept and MMF were stopped; sirolimus was started. On Day 109, serum creatinine increased to 5.3 mg/dL and hemodialysis was initiated. A transplant nephrectomy was performed. Tissue obtained from the nephrectomy confirmed the diagnosis of PTLD. The patient died in June 2009 secondary to a "lung problem" per family report. No other information regarding circumstances of death is available.

IM103027-138-10593: 38 year old EBV-, CMV- male who received a kidney from an EBV+, CMV- donor. On Day 221, the patient was hospitalized with fever, nausea, vomiting, and hypoglycemia. On Day 231 (b) (6), head CT showed multiple enhancing lesions. Brain biopsy on Day 242 showed PTLD (large B-cell lymphoma with T-cell reactive component). The patient was treated with dexamethasone, methotrexate, prednisone, and radiotherapy. Follow up MRI on Day 324 showed some improvement, but patient died on (b) (6) secondary to "deterioration of cognitive ability."

IM103027-91-10044: 66 year old EBV+, CMV+ male who received a kidney from a donor with unknown serologies. The patient initially enjoyed an unremarkable post-transplant course. On Day 1233, however, he began to lose weight. On Day 1405, he began to complain of malaise and anorexia. On Day 1461, he developed confusion and was hospitalized with a serum sodium of 116 mEq/L. Head CT revealed a mass in the left anterior cerebral region. Cerebral stereotactic biopsy confirmed a diagnosis of PTLD (diffuse large B cell lymphoma). The patient died on Day 1542.

Preponderance of CNS PTLD among Belatacept Treated Patients

Other than perhaps the overall incidence, the preponderance of CNS involvement among the kidney transplant recipients who received belatacept constitutes the most striking aspect of the PTLD presentations. PTLD involving the CNS typically is a rare event among kidney transplant patients. For example, a retrospective analysis of 1,094 post- transplant lymphomas reported to the Collaborative Transplant Study registry, for instance, reported involvement of the CNS in only 11.7% of cases.26 In contrast, nine out of fourteen (or 64.3%) of the PTLD cases observed in belatacept groups from the three kidney trials involved the CNS. A post hoc central evaluation of the biopsy material casts doubt on the accuracy of two of the diagnoses of PTLD, both of which represented non-CNS cases (PID 103008-113-20060 and 103008-122-20256). If one accepted this unplanned second opinion, the rate of CNS PTLD among all PTLD cases

[26] Opelz G. Döhler, B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Amer J of Transplantation 2003; 4: 222-30.

would become nine out of twelve (or 75%) of the PTLD cases observed in the context of kidney transplant patients exposed to belatacept presented in the CNS.

Inspection of the PTLD patient narratives underlines that the morbidity and mortality associated with CNS presentations of PTLD differ from non-CNS presentation. Adverse events associated with CNS presentation included seizures, hemiparesis, aphasia, cognitive dysfunction, and behavioral changes. In a non-belatacept context, the literature reports a significantly higher mortality rate among kidney transplant patients who develop CNS PTLD compared to those who develop non-CNS PTLD.[27]

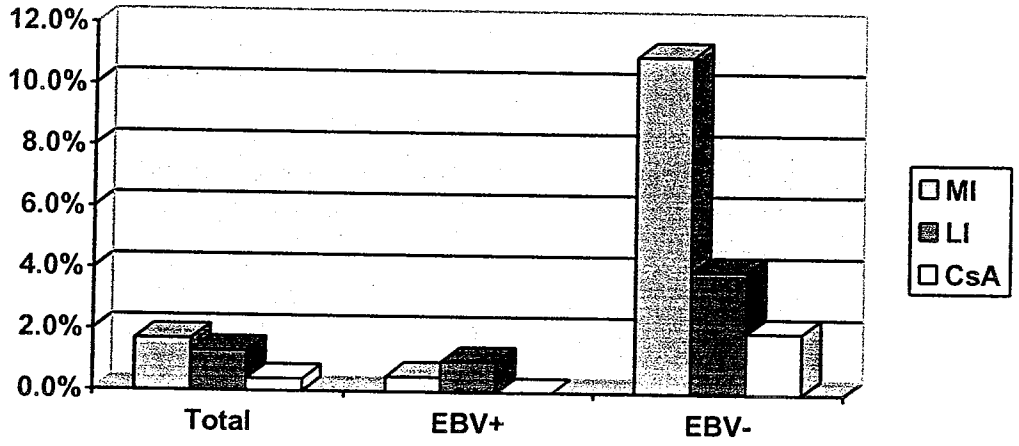
The significance of the CNS involvement goes beyond any immediate implications with respect to mortality and morbidity. The unusual pattern of PTLD presentations provides additional context to other CNS-related signals detected in the belatacept clinical development program, such as the two isolated cases of PML and the seven CNS infections distributed across the belatacept MI groups in IM103100, IM103008, and IM103027 (including three cases of cryptococcal meningitis, one case of West Nile Virus, one case of cerebral aspergillosis, one case of neurological herpes zoster, and one of the PML cases) compared to only one event among the belatacept LI groups (cryptococcal meningitis) and one event among the CsA groups (also cryptococcal meningitis), see Table 48. Even more importantly, however, the pattern of presentations implies that – unless kidney transplant patients maintained on belatacept compensate by developing fewer cases of non-CNS PTLD than those maintained on CsA – overall incidence of PTLD is increased among patients with exposure to belatacept.

Incidence of PTLD in Relation to EBV Serostatus

Known risk factors for the development of PTLD among recipients of kidney transplants include EBV seronegativity, the development of CMV disease post-transplant, and exposure to lymphocyte depleting agents.[28,29,30] Not surprisingly, then, the increased risk of PTLD was most evident among the EBV- patients in the belatacept trials (see Figure 9). While the PTLD signal among EBV+ patients was smaller across all treatment groups, however, the rates were still appreciably higher among patients in the belatacept treatment groups than among patients in the CsA treatment groups: two events out of 404 EBV+ patients in the belatacept MI groups and four events out of 401 EBV+ patients in the belatacept LI groups, compared to zero events out of 399 EBV+ patients in the CsA groups.

[27] Opelz G. Döhler, B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Amer J of Transplantation 2003; 4: 222-30.
[28] Opelz G. Döhler, B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Amer J of Transplantation 2003; 4: 222-30.
[29] Caillard S, Dharnidharka V, Agodoa L, et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 2005; 80: 1233-43.
[30] Shahinian V, Miurhead N, Jevnikar AM, et al. Epstein-Barr virus seronegativity is a risk factor for late onset posttransplant lymphoproliferative disorder in adult renal allograft recipients. Transplantation. 2002; 75: 851-6.

Figure 10: Overall Incidence of PTLD by EBV Serostatus and Treatment Groups in the Belatacept Kidney Trials



Source data: PTLD Narratives provided by the applicant, BLA 125,288

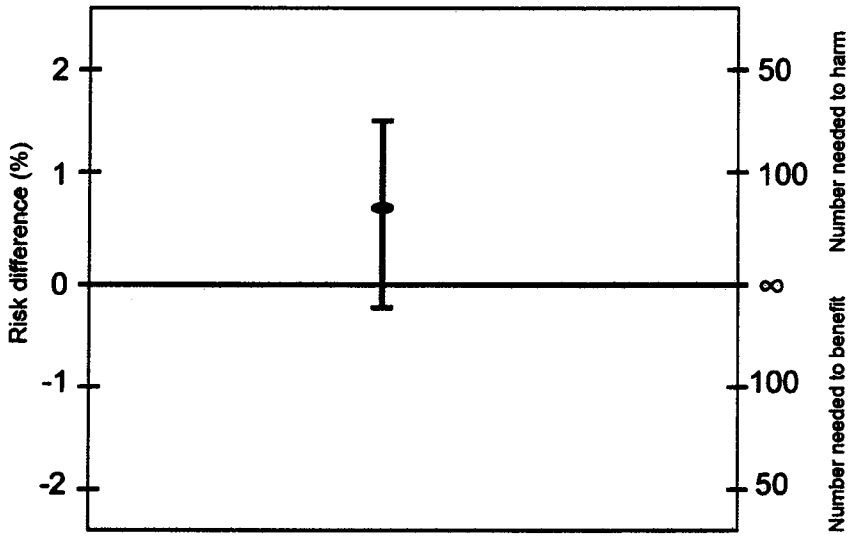
The applicant suggests that the rate of PTLD in EBV+ patients observed in the CsA control group across the trials was unexpectedly low and that rates observed in the belatacept groups among EBV+ patients is consistent with estimates using registry data. Findings from an FDA review of multiple clinical trials obtained from other NDAs for other immunosuppressants that included similar control groups and analyses of registry databases refute the applicant's suggestion (see below and Statistical Safety Review for further details).

Calculation of Number of Patients Needed to Harm (NNTH) Using Data from the Belatacept Trials

A simple point estimate of the number of EBV+ kidney transplant recipients needed to treat with a belatacept-based regimen rather than a CsA-based regimen in order to observe one additional case of PLTD can be derived by taking the inverse of the difference in incidence of PTLD among the belatacept treated patients and the incidence of PTLD among the CsA treated patients in the clinical trials. This number will be referred to as the number need to harm (NNTH). At 24-months post-transplant, there were 5/805 and 0/399 PTLD cases in the pooled belatacept (MI and LI) and CsA control respectively resulting in an estimated NNTH of 161 (i.e. [1/(5/805-0/399)]) EBV+ kidney transplant recipients with exact 95% confidence interval of (-341, 68). This is interpreted as ranging from as few as 68 belatacept subjects need to be treated for one case of PTLD to as many as 341 CsA subjects for one case of PTLD at two years of follow up (see Figure 11). As previously noted, the selection of the 2 year time point has the effect of censoring a known case of CNS PTLD which occurred in an EBV+

belatacept LI patient. The two year time point, however, reflects the latest time point at which complete PTLD data exist for all patients.

Figure 11: NNTH Estimate from Belatacept Trials



Graph adapted from method used in Altman, D "Confidence intervals for the number needed to treat." *BMJ* 1998;317:1309-1312 (7 November). Graphing method used to help interpret confidence intervals for number needed to harm/benefit when CI contains infinity.
Source: Figure 2, Statistical Safety Review, BLA 125,288

Incidence rate per person-years (PYs) was calculated to allow for comparison to registry data. Additionally, given that not all patients in the safety population in the clinical trials had a full two years of follow-up due to early discontinuation, it is useful to consider incidence per person-years. The point estimate of the number needed to harm calculated based on the difference between incidences per person-years is slightly higher. Please see the Statistical Safety Review for the derivation of the incidence of PTLD in person-years observed among EBV+ patients receiving belatacept in the clinical trials (the result is 0.35 per 100 patient years). Given an incidence/PY of 0.0035 of the pooled data from the belatacept MI and LI regimens and of 0.0 in the CsA regimen from studies 008, 027 and 100, we estimate a number needed to harm (NNTH) of 145 (95% CI: -532, 64) patients (see Table 35). This suggests that for every 145 EBV+ patients treated with a belatacept-based regimen instead of a CsA-based regimen for two years, one would expect at least one additional case of PTLD. The range for this NNTH suggests that as few as 63 belatacept patients to as many as 532 CsA patients need to be treated for two years to expect at least one case of PTLD. Similar results are shown when comparing belatacept LI alone vs. CsA and MI alone vs. CsA.

Table 35: Estimated Number Needed to Harm in EBV+ Patients based on Incidence of PTLD: Belatacept Trials 008, 027 and 100

EBV+	Belatacept LI and MI	Belatacept LI	Belatacept MI	CsA
Incidence/PY	0.0035	0.0041	0.0028	0.0000
ARRI (vs CsA)	0.0069	0.0082	0.0056	NA
2-YR NNTH	144.7	122.0	178.8	NA
95% CI NNTH	-531.6, 63.7	-726.0, 56.3	-431.7, 74.1	NA

PY=person-year
AARI: annualized absolute risk increase (events $_{belatacept}$/(person-yrs $_{belatacept}$/2)-events $_{CsA}$ /(person-yrs $_{CsA}$ /2) (assumes constant risk)
NNTH: 1/AARI
Source: Table 10, Statistical Safety Review, BLA 125,288

PTLD rates among EBV+ Kidney Transplant Recipients Observed in the CsA Control Groups from Randomized Controlled Trials Previously Submitted to FDA

The applicant has implied that the incidence of PTLD observed among EBV+ kidney transplant recipients in the CsA treated groups of the belatacept clinical trials underestimates the true rate of PTLD in this population, as the rate is known to be non-zero. A review of previous randomized clinical trials of *de novo* kidney transplantation submitted to the FDA, however, confirms that the rate may be close to zero. We identified three randomized trials that collected information on patients for at least 12-months post-transplant (including baseline EBV status) and that included a control group treated with CsA, MMF, corticosteroids, and IL-2 antagonist induction treatment group. Among 534 EBV+ kidney transplant recipients who received a CsA-based regimen, zero cases of PTLD were reported. Therefore, the estimated overall incidence of PTLD among EBV+ patients from these three trials previously submitted to FDA by other applicants was: 0% (0/534), 95% exact CI (0, 0.0069). Refer to Statistical Safety Review for additional analyses including estimates of NNTH using these data.

PLTD rates among EBV+ Kidney Transplant Recipients According to Registry and Claims Data

The applicant has previously suggested that analyses of registry data and Centers for Medicare and Medicaid Services (CMS) claims data estimate incidences of PTLD in the general kidney transplant EBV+ population that are similar to that seen in the EBV+ patients maintained on belatacept in the clinical trials. The applicant has made this argument based on the UNOS/OPTN registry data and the Collaborative Transplant Study (CTS) registry data as well as the CMS claims data. The FDA performed separate and independent analyses of the UNOS registry data to estimate PTLD incidence by EBV serostatus. Results (described below) from these analyses also support the findings from the randomized controlled trials. Specifically, these analyses

found that the incidence of PTLD among EBV+ patients on a comparable CNI based regimen was indeed lower than the incidence of PTLD among EBV+ patients maintained on a belatacept regimen.

The Scientific Registry of Transplant Recipients (SRTR) is a non-profit private group which holds the OPTN contract awarded by the Health Resources and Services Administration (HRSA) for the statistical analyses of UNOS/OPTN data. The FDA and SRTR independently performed analyses of the UNOS/OPTN registry data and produced remarkably consistent results: both groups concluded that, at 2 years of follow-up, the rate of PTLD observed among belatacept treated EBV+ patients in the clinical trials was seven times higher than that observed in CNI treated EBV+ patients in the UNOS registry given similar induction therapy. The applicant performed its own analysis on the registry data and found a slightly higher incidence than FDA and SRTR. However, even the results produced by the applicant yield a rate more than 3-fold lower that that observed among belatacept treated EBV+ patients in the clinical trials (see Table 36).

The Collaborative Transplant Study is a registry database based out of the University of Heidelberg in Germany. The CTS is maintained by Dr. Gerhard Opelz. While the primary datasets of the CTS were not available for analysis by the FDA, Dr. Opelz published data in 2009 which suggests that the incidence of non-Hodgkin's lymphoma among EBV+ kidney transplant recipients at 2 years of follow-up is approximately one-third of that observed among the belatacept-treated EBV+ patients in the clinical trials.[14] In a personal communication to the FDA, Dr. Opelz confirmed that his data supported a much lower incidence of PTLD among EBV+ kidney transplant recipients than was observed among the belatacept patients (see Table 36).

Table 36: 2-year PTLD incidence rates/100 Person-Years among EBV+ Belatacept Patients in IM103100, IM103008, and IM103027 compared to EBV+ Patients Maintained on CNI-based Regimens Followed in the UNOS and CTS Registries

	Belatacept (pooled MI and LI) N = 805	**BMS UNOS* N = not specified**	**FDA UNOS* N = 77,203**	**SRTR UNOS* N = 83,929**	**Opelz (CTS Analysis)**
	2-year Rate (95% Exact CI)	**2-year Rate (95% CI)**	**2-year Rate (95% Exact CI)**	**2-year Rate**	**2-year Rate**
EBV Positive	0.346 (0.112, 0.807)	0.09 (0.06, 0.12)	0.051 (0.026, 0.089)	0.050	0.12

* UNOS analyses consider all recipients with CsA or tacrolimus maintenance regimens
Source: Table 9, Statistical Safety Review, BLA 125,288

Calculation of Number of Patients Needed to Harm using Registry Data

The estimated numbers needed to harm based on the comparisons between the incidence/person-years of 0.0035 of the pooled belatacept (LI and MI) to the estimated incidences among *de novo* kidney transplant recipients on a CsA or tacrolimus regimen from the three analyses of the UNOS/OPTN data (BMS, FDA and SRTR) and to the estimated incidence from the analyses of the CTS data by Dr. Opelz are shown below in Table 37.

Table 37: Estimated Number Needed to Harm (NNTH) based on registry data

EBV+ Kidney Transplant Recipients	FDA UNOS	BMS UNOS	SRTR UNOS	Opelz (CTS Analysis)
2-Year Incidence/PY	0.00051	0.0009	0.00050	0.0012
2-YR NNTH *	169.6	192.3	168.9	217.4
95% CI NNTH	(115.5, 319.2)	**	(110.9, 354.3)	**

*NNTH (number need to harm) is based on the difference in the 2-yr incidence per person-years between the pooled belatacept (MI and LI) incidence of 0.0035 and the respective registry incidence
**Unable to estimate confidence intervals given level of information provided
PY=person-year
NNTH: 1/AARI where AARI=annualized absolute risk increase=events $_{belatacept}$/(person-yrs $_{belatacept}$/2)-events $_{CsA}$ /(person-yrs $_{CsA}$ /2) (assumes constant risk)
Source: Created by Statistical Safety Reviewer, BLA 125,288

Limitations of Registry and Claims Data

UNOS/OPTN

The UNOS/OPTN registry is composed of data generated by every kidney transplant program located in the United States; reporting to UNOS is mandatory and monitored. The registry includes data regarding every organ donation and transplant event in the U.S. since October 1, 1987. A required transplant recipient follow-up form 6-month post transplant is generated six months post-transplant and on the treatment anniversary for every living organ recipient. Included on this form is a section for post transplant malignancy with a specific query regarding "De Novo Lymphoproliferative disease and Lymphoma." While UNOS/OPTN data are regarded as the 'gold-standard' source of information for U.S. transplant patients, the data from any registry may under-estimate the true rates of reported events. Additionally, while reporting to UNOS/OPTN is a requirement for participating transplant programs, the quality of reporting can vary. One must also recognize that the patient population followed by UNOS/OPTN is not identical to that studied in the belatacept kidney trials; comparisons across these populations, then, must be interpreted with caution.

CTS

The Collaborative Transplant Study (CTS) is a registry based out of the University of Heidelberg in Germany; its member centers are predominantly located in Europe. Unlike UNOS/OPTN, reporting to CTS is voluntary. The CTS recently published an article regarding the epidemiology of non-Hodgkin's lymphoma in its registry population.31 While neither the applicant nor FDA obtained primary data from CTS to perform independent analyses, Dr. Gerhard Opelz – the director of CTS and the primary author of the publication – provided his result for incidence at PTLD among EBV+ kidney recipients at 2 years follow-up. While the peer-reviewed publication did not provide that specific numeric result, it did contain a figure which is consistent with that personal communication (see Figure 11 below and Statistical Safety Review for further details). The CTS analysis included only those patients whose transplant centers confirmed that complete malignancy information had been reported. Therefore, the CTS registry analysis has potential for over-reporting as well as under-reporting. One must also recognize that the patient population followed by CTS is not identical to that studied in the belatacept kidney trials; comparisons across these populations, then, must be interpreted with caution.

CMS Claims Data

The sponsor provided estimates of PTLD incidence based on an analysis of CMS inpatient and outpatient claims data where cases were identified via specific ICD-9 codes (i.e. 200.x, 202.x and 204.x) which have not been validated to correspond to PTLD. This analysis was limited to only kidney transplant recipients who had Medicare as primary payer at the time of transplantation and therefore represents only a subset of the overall kidney transplant population. Additionally, this analysis identified cases of PTLD only using ICD-9 codes without supporting clinical information to confirm the presence or absence of PTLD. A recent SRTR analysis of CMS data using the same ICD-9 codes, found that the most commonly reported ICD-9 code (among the searched list) was 202.80 and that the number of events reported using this code from 2001 to 2008 increased in an unusual fashion: the events reported in 2001-2008 were 67, 130, 145, 184, 241, 295, 289 and 322 respectively (each of these numbers represents events reported that calendar year, not cumulatively to that point). The reason for the geometric progression of events reported using this code is unclear but is not thought to correlate with a true increase in the incidence of PTLD during the study time. The most likely explanation would appear to relate to coding errors and differences in reporting practices across medical centers. While FDA obtained the CMS datasets through USRDS to evaluate the applicant's claim, the FDA ultimately determined that the approach did not add value to its understanding of PTLD in EBV+ patients and therefore has elected not to present any estimation of NNTH based on the CMS data.

[31] Opelz G, Daniel V, Naujokat C, et al. Epidemiology of Pretransplant EBV and CMV Serostatus in Relation to Posttransplant Non-Hodgkin Lymphoma. Transplantation 2009; 88: 962-7.

Given these limitations outlined above, it is inappropriate to rely on results from any one analyses or comparison of registry data. Instead, results across all sources of data should be considered in order from least potentially biased (i.e. comparing rates of PTLD between treatment groups within the randomized clinical trials) to the more potentially biased (i.e. comparing incidence from belatacept to outside sources such as other randomized trials and registries).

PTLD in the Belatacept Liver Transplant Program

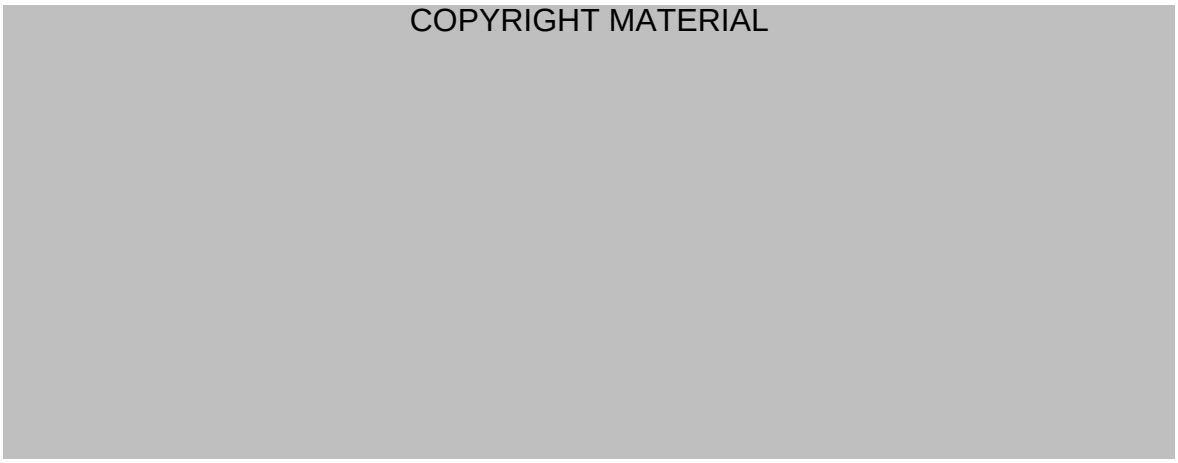
Study IM103045 is a Phase 2 *de novo* liver transplant study of about 250 EBV+ patients; 146 patients have been enrolled into one of three belatacept treatment groups, while around 100 patients have been enrolled into one of two control groups. To date, two patients from the belatacept groups have developed PTLD within the allograft compared to zero patients in the control groups. One of the patients who developed PTLD has died; at autopsy, that patient was noted to have CNS involvement.

The epidemiology of PTLD among liver transplant patients differs from kidney transplant patients. PTLD is a more common event in liver transplantation. One explanation for this may be that EBV+ serostatus does not appear to confer the protection against PTLD in the liver transplant context that it affords in the kidney transplant context: while incidence of PTLD in EBV- liver transplant recipients approximates that of EBV- kidney transplant recipients, the incidence of PTLD in EBV+ liver transplant recipients is much higher than that of EBV- kidney transplant recipients and is, in fact, similar to that of EBV- liver and kidney recipients (see Figure 12).[32]

The observations in IM103045 and the known epidemiology of PTLD in liver transplant patients may indicate a need for caution in the liver transplant program and measures to mitigate the possibility of the off-label use of belatacept among liver transplant patients.

[32] Opelz G, Daniel V, Naujokat C, et al. Epidemiology of Pretransplant EBV and CMV Serostatus in Relation to Posttransplant Non-Hodgkin Lymphoma. Transplantation 2009; 88: 962-7.

Figure 12: Cumulative incidence of non-Hodgkin's Lymphoma according to EBV status in kidney, heart, and liver transplant recipients in the Collaborative Transplant Study registry data



Source: Opelz, G et al. Transplantation 2009; 88: 962-7

Progressive Multifocal Leukoencephalopathy (PML)

A patient from the belatacept MI group in IM103027 was diagnosed with PML in Month 23; that patient died shortly after Month 24 (see summary of death narrative below). The incidence of PML in the general kidney transplant population has been estimated at 14 cases per 100,000 patient-years.33 While the observation of even that single case of PML in IM103027, then, is remarkable, it is difficult to extrapolate too much from a single event. In addition, however, a second case of PML was diagnosed in the belatacept liver transplant program (in Study IM103045) in October of 2009. At the time of diagnosis, the patient was confused, had memory recall problems, had significant motor impairments and gait abnormalities. The patient subsequently died of complications related to PML. Two occurrences of PML in the context of a drug development program constitute a safety signal. While the impact of an increased risk of PML on the overall risk-benefit profile of belatacept is potentially small, given that the outcome remains rare, the signal is important because it supports other data suggesting that belatacept may have specific effects on CNS immunity (e.g., the increased incidence of CNS PTLD, the increased rates of CNS infections seen in the belatacept MI treatment group).

> *Death Narrative for IM103027-15-10045*: 63 year old white female treated with belatacept MI regimen presented on Day 711 with homonymous hemianopia and recent history of falls. On Day 725, patient developed worsened vision and short-term memory loss. On that same day, MRI revealed a lesion in the right occipital

33 Neff RT, Hurst FP, Falta EM, et al. Progressive Multifocal Leukoencephalopathy and Use of Mycophenolate Mofetil after Kidney Transplantation. Transplantation 2008; 86(10): 1476-8.

lobe extending into the posterior right temporal lobe consistent with PML. She was hospitalized on Day 730 for progressive neurological deterioration. Lumbar puncture and PCR confirmed the presence of JC virus. CMV viremia was also detected. On Day 742, patient was discharged to home hospice care with PML with symptoms of cortical blindness, memory disturbance, gait abnormalities, and headaches. The patient died on Day 754.

Other Serious Adverse Events

An analysis of serious adverse events (SAEs), defined as events that were either life-threatening, required hospitalization, or prolonged hospitalization, reported in Studies 008, 027, and 100 by Month 12 was performed. The analysis, shown in Table 38, suggested that SAEs were distributed evenly across treatment groups, though it did provide some additional support that serious AR episodes were more common among patients maintained on belatacept (please see Section 6.5 for a discussion of safety issues associated with the higher rate and grades of AR observed among belatacept patients). The major adverse events associated with MPA exposure include leucopenia and diarrhea. Despite the 25% to 40% higher MPA exposure among the belatacept treated patients (see Clinical Pharmacology Review); the analysis did not detect any difference in serious adverse events due to leucopenia.

Table 38: Serious Adverse Events in at least 2% of Patients at Month 12

System Organ Class Preferred Term	Pooled Trials (008, 027, and 100) Belatacept MI N=477	Belatacept LI N=472	CsA N=476
Total Patients with SAE	289 (60.6)	263 (55.7)	298 (62.6)
Infections and Infestations	128 (26.8)	108 (22.9)	129 (27.1)
Cytomegalovirus Infection	26 (6.5)	28 (5.9)	25 (5.5)
Urinary Tract Infection	25 (5.2)	24 (5.1)	30 (6.3)
Pneumonia	9 (1.9)	6 (1.3)	6 (1.3)
Pyelonephritis	10 (2.1)	6 (1.3)	6 (1.3)
Renal and Urinary Disorders	68 (14.3)	64 (13.6)	83 (17.4)
Renal Failure Acute	6 (1.3)	7 (1.5)	13 (2.7)
Ureteric Stenosis	5 (1.0)	7 (1.5)	10 (2.1)
Injury, Poisoning, and Procedural Complications	59 (12.4)	59 (12.5)	80 (16.8)
Graft Dysfunction	15 (3.1)	13 (2.6)	21 (4.4)
Therapeutic Agent Toxicity	0	0	10 (2.1)
Vascular Disorders	24 (5.0)	35 (7.4)	47 (9.9)
Lymphocele	5 (1.0)	9 (1.9)	17 (3.6)
General Disorders and Administration Site Conditions	35 (7.3)	27 (5.7)	34 (7.1)
Pyrexia	24 (5.0)	22 (4.7)	22 (4.6)
Investigations	28 (5.9)	24 (5.1)	36 (7.8)
Blood Creatinine Increased	19 (4.0)	19 (4.0)	28 (5.9)
Blood and Lymphatic System Disorders	28 (5.9)	18 (3.8)	24 (5.0)
Leucopenia	12 (2.5)	3 (0.6)	10 (2.1)
Immune System Disorders	19 (4.0)	21 (4.4)	10 (2.1)
Transplant Rejection	16 (3.4)	18 (3.8)	8 (1.7)

Source: Adapted from Applicant's Summary of Clinical Safety, BLA 125,288

7.3.3 Dropouts and/or Discontinuations

The proportion of subjects with AEs leading to study drug discontinuation up to Month 12 in Studies 008, 027, and 100 was highest in the CsA group (14%) and comparable in the belatacept LI (11%) and MI groups (10%), as shown in Table 39.

As previously discussed, numerically more patients receiving belatacept than CsA discontinued treatment in the Phase 3 trials due to efficacy failure (primarily AR). Given that efficacy failures received separate consideration already, such events were not

included in the analysis of adverse events leading to treatment discontinuation. In contrast, numerically more patients receiving CsA than belatacept discontinued treatment in those trials due to adverse events. An inspection of the reported SOC and PTs associated with the responsible adverse events suggested that most classes of events were distributed proportionately among treatment groups. In each study, however, four CsA patients discontinued due to hirsutism (compared to zero belatacept patients). In IM103027 only, more belatacept patients discontinued due to renal vein thrombosis and graft thrombosis.

Table 39: Adverse Events Leading to Treatment Discontinuation in ≥1% of Patients Up to Month 12 (Pooled Trials 008, 027, and 100)

System Organ Class **Preferred Term**	**Belatacept MI** **N=477** **n (%)**	**Belatacept LI** **N=472** **n (%)**	**Cyclosporine** **N=476** **n (%)**
Total Number of Patients with AE Leading to Treatment Discontinuation	**47 (9.9)**	**54 (11.4)**	**66 (13.9)**
Injury, Poisoning and Procedural Complications	8 (1.7)	14 (3.0)	22 (4.6)
Graft Loss	3 (0.6)	2 (0.4)	4 (0.8)
Chronic Allograft Nephropathy	0	2 (0.4)	5 (1.1)
Complications of Transplanted Kidney	0	6 (1.3)	1 (0.2)
Renal and Urinary Disorders	8 (1.7)	9 (1.9)	11 (2.3)
Renal Vein Thrombosis	5 (1.0)	2 (0.4)	0
Immune System Disorders	10 (2.1)	11 (2.3)	5 (1.1)
Transplant Rejection	9 (1.9)	9 (1.9)	3 (0.6)
Infections and Infestations	8 (1.7)	12 (2.5)	6 (1.3)
Cytomegalovirus Infection	2 (0.4)	5 (1.1)	0
Skin and Subcutaneous Tissue Disorders	0	0	10 (2.1)
Hirsutism	0	0	8 (1.7)

Source: Table 2.1.4 in the Summary of Clinical Safety, BLA submission

7.3.4 Significant Adverse Events

Acute Rejection
As discussed previously, AR at Month 12 in the Phase 3 trials occurred more frequently among recipients of belatacept than recipients of CsA in IM103008: while the belatacept LI regimen met a 20% NI margin for the endpoint of AR (implying that belatacept has some efficacy for the indication of prophylaxis of AR), it appeared inferior to the CsA regimen in that trial for the endpoint of AR. In addition, the numbers of Banff grade II and III rejections were numerically greater among recipients of belatacept than among recipients of CsA, especially in IM103008 (see Table 40).

Table 40: Acute Rejection (as Defined by the Applicant) at 12 Months

Study		Belatacept MI	Belatacept LI	CsA
008	Acute Rejection	49/219 (22.4)	39/226 (17.3)	16/221 (7.2)
	Mild IA	7	4	3
	Mild IB	3	8	5
	Moderate IIA	16	16	6
	Moderate IIB	20	10	2
	Severe III	2	1	0
	Difference from CsA (97.3% CI)	15.2 (7.4, **23.0**)	10.1 (2.9, **17.3**)	
027	Acute Rejection	33/184 (17.9)	31/175 (17.7)	26/184 (14.1)
	Mild IA	0	4	2
	Mild IB	7	2	2
	Moderate IIA	11	17	17
	Moderate IIB	15	8	5
	Severe III	0	0	0
	Difference from CsA (97.3% CI)	3.8 (-5.2, **12.8**)	3.6 (-5.5, **12.7**)	

Source: Adapted from Tables 5 and 15, Statistical Review, BLA 125,288

Prevention of AR episodes has represented a basis for drug approval in transplantation over the past three decades. Acute rejection has been viewed as an important clinical event largely because data suggesting that it is associated with decreased graft life.[34,35] Some epidemiologic data suggest, however, that decreases in early AR rates have not been associated with improved long-term outcomes.[36,37] That literature may reflect,

[34] Matas AJ, Humar A, Payne WD et al. Decreased acute rejection in kidney transplant recipients is associated with decreased chronic rejection. Ann Surg 1999; 230: 493-8.
[35] Hariharan S, Johnson CP, Bresnahan BA, et al. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med 2000; 342: 605-12.
[36] Meier-Kriesche H-U, Schold JD, Kaplan B. Long-term renal allograft survival: Have we made significant progress or is it time to rethink our analytic and therapeutic strategies? Am J Transplant 2004; 4: 1289-95.
[37] Meier-Kriesche H-U, Schold JD, Srinivas TR, et al. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant 2004; 378-83.

however, decreases in low grade rejections (which are typically the drivers of overall rejection rates).

The trend towards higher grades of rejection among belatacept patients, then, is particularly concerning. The literature dissecting the clinical significance of higher grade rejections suggests that high grade Banff lesions are associated with worse outcomes, including lower GFR and graft loss.[38,39]

A full recovery of GFR after an episode of AR correlates with better long term graft outcomes while a poor recovery of GFR after an episode of AR correlates with worse long term graft outcomes. However, an analysis based on recovery of GFR after a rejection episode to baseline GFR could not be performed as many of the rejection episodes occurred in the first month after transplantation before a baseline GFR had been established. For that reason, mean GFRs at 12 months were compared within treatment groups between those patients who experienced AR and those patients who did not. In IM103008, the difference in mean GFR between patients without AR and patients with AR was 8 mL/min in the belatacept MI arm, 19.7 mL/min in the belatacept LI arm, 5.8 mL/min in the CsA arm. In IM103027, the number of ARs and histopathologic grades of AR were more similar across all treatment groups. In that trial, the difference in mean GFRs at 12 months between patients who developed ARs and those who did not were 8.2 mL/min in the belatacept MI arm, 6.1 mL/min in the belatacept LI arm, 12.4 mL/min in the CsA arm (see Table 41 below). These differences are consistent with the conclusion that some of these rejections were clinically significant.

[38] Mengel M, Sis B, Halloran PF. SWOT analysis of Banff: strengths, weaknesses, opportunities, and threats of the international Banff consensus process and classification system for renal allograft pathology. Am J Transplant 2007; 7: 2221-6.
[39] Mueller A, Schneulle P, Waldherr R, et al. Impact of the Banff '97 classification for histological diagnosis of rejection on clinical outcome and renal function parameters after kidney transplantation. Transplantation 2000; 69:1123-27.

Table 41: Calculated GFR at 12 months by Rejection Status at 12 months

Trial	Acute Rejection Status by Month 12		Belatacept MI	Belatacept LI	CsA
103008	AR	Mean (sd) at Month 12 95% CI # in analysis	58.2 (23.3) (51.5, 64.9) 49	48.0 (21.6) (41.0, 55.0) 39	44.3 (17.8) (34.8, 53.8) 16
	No AR	Mean (sd) at Month 12 95% CI # in analysis	66.2 (23.0) (62.7, 69.7) 170	67.7 (21.7) (64.5, 70.9) 184	49.8 (21.5) (46.8, 52.7) 203
103027	AR	Mean (sd) at Month 12 95% CI # in analysis	36.1 (17.0) (30.0, 42.1) 33	38.9 (20.5) (31.4, 46.5) 31	25.2 (18.8) (17.6, 32.8) 26
	No AR	Mean (sd) at Month 12 95% CI # in analysis	44.3 (22.7) (40.7, 48.0) 150	45.0 (21.5) (41.4, 48.5) 144	37.6 (20.3) (34.4, 40.7) 158

Missing cGFR at 12 month imputed as 0 if graft loss or death within first 12 months and last observation carried forward (locf) otherwise.
Source: Table 10, Statistical Review, BLA 125,288

The results of the analyses presented in the above table should be interpreted with caution because of limitations in the data due to the following reasons:

- Missing GFR at 12 months in some patients;
- Not all patients remained on study therapy for the entire 12 months but may have switched to a regimen containing a CNI;
- These subsets of patients are based on an outcome variable that is affected by treatment.

The data and the analyses are consistent with the literature which suggests that AR events negatively impact the GFR of kidney transplant patients. In Study IM103008, where AR episodes were both more frequent and also of higher histopathologic grades among patient receiving belatacept maintenance rather than CsA maintenance, the impact of AR on mean GFR appeared greater among belatacept LI patients than among CsA patients.

Reviewer comment: The analysis of the impact of AR of GFR above relied on calculated GFRs at Month 12; in cases of missing data at Month 12, the analyses relied on an imputed GFR based on the last observed calculated GFR prior to Month 12 (last observation carried forward) unless the patient had a graft loss or died before Month 12 and then a value of 0 was imputed. Data from these same trials presented at the American Transplant Congress (ATC) in 2009 and published in the American Journal of Transplantation (AJT) suggested that differences in mean GFR between patients who experienced did and did not experience AR were minimal across all treatment

groups.[40,41] Those analyses, however, relied on measured GFR observed at Month 12 and censored those patients with missing data at that time point. For example, data were only captured for 25 of the 39 patients with AR in the belatacept LI group in IM103008; as a result, those other analyses presented a mean measured GFR of belatacept MI patients who experienced AR of 61 mL/min compared with the mean calculated GFR of 48 mL/min determined in the analysis above. The conclusion presented at ATC and published in the AJT – that the rejection episodes observed in the belatacept trials did not have a clinically significant impact on GFR – were potentially misleading.

Beyond the implications to graft life, AR episodes have clinical significance due to the morbidity associated with their reversal. High grade rejection episodes, in particular, may be associated with significant morbidity as they often require treatment with lymphocyte depleting therapies (e.g., thymoglobulin, rituximab). Such agents have been associated with higher rates of several serious adverse events in transplant patients including PTLD, CMV disease, and BK virus associated nephropathy. In keeping with the higher rates of BPAR and higher grades of rejection observed among the belatacept patients, lymphocyte depleting therapy (LDT) was used more often in the belatacept groups than the CsA groups for treatment of AR in the Phase 3 trials (see Table 42). More patients in the CsA groups received exposure to lymphocyte depleting agents in the context of anticipated delayed graft function (DGF).

Table 42: Use of Lymphocyte Depleting Therapy Through Month 24

	IM103008			IM103027		
	Belatacept MI (n=219)	**Belatacept LI (n=226)**	**CsA (n=221)**	**Belatacept MI (n=184)**	**Belatacept LI (n=175)**	**CsA (n=184)**
For Treatment of AR	**27 (12.3)**	**22 (9.7)**	**4 (1.8)**	**16 (8.7)**	**8 (4.6)**	**6 (3.3)**
Initial Treatment of AR	13 (5.9)	10 (4.4)	3 (1.4)	14 (7.6)	7 (4.0)	4 (2.2)
Steroid Resistant AR	14 (6.4)	12 (5.3)	1 (0.5)	2 (1.1)	1 (0.6)	2 (1.1)
For Anticipated DGF	**1 (0.5)**	**1 (0.4)**	**8 (3.6)**	**0**	**0**	**27 (14.7)**

Source: Created by the Statistical Reviewer using the applicant's datasets, BLA 125,288

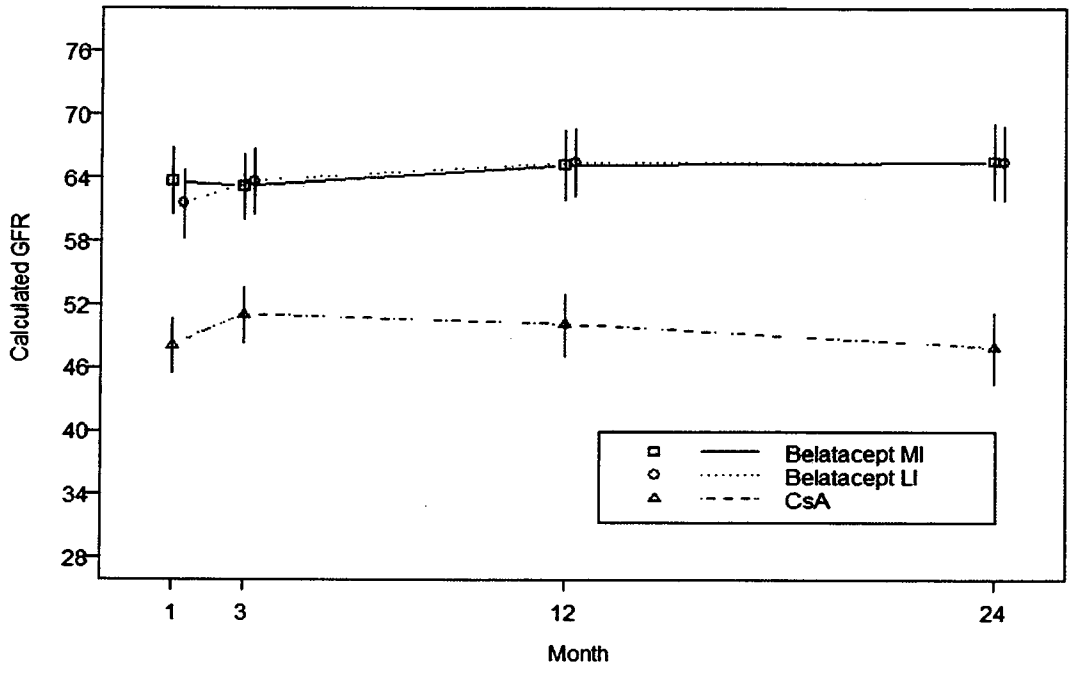
[40] Vincenti F, Grinyo JM, Charpentier B, et al. Primary Outcomes from a Randomized, Phase III Study of Belatacept vs Cyclosporine in Kidney Transplant Recipients (BENEFIT Study). American Transplant Congress, Boston, MA, Plenary Session I, May 31, 2009.
[41] Vincenti F, Charpentier B, Vanrenterghem L, et al. A Phase III Study of Belatacept-based Immunosuppression Regimens versus Cyclosporine in Renal Transplant Recipients (BENEFIT Study), American Journal of Transplantation 2010; 10(3): 535-46.

Differences in the rates of PTLD observed between the belatacept and CsA groups are discussed in Section 7.3; events of PTLD for all groups have been closely monitored and carefully documented with complete data for all patients at 24 months of follow-up and with partial data for many patients beyond 24 months. Despite the greater overall exposure of belatacept patients to LDT agents in IM103008, rates of CMV disease and BK virus associated nephropathy were similar across all treatment groups in this study (and also in IM103027 and IM103100).

Glomerular Filtration Rate

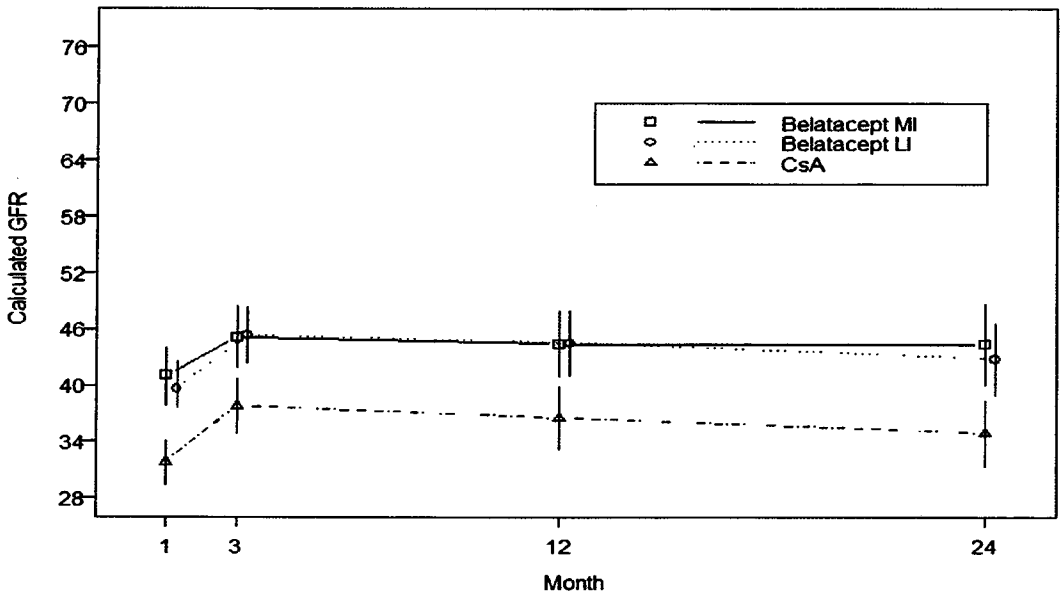
Mean calculated GFRs were substantially higher throughout the 24 months of the Phase 3 trials among the belatacept treatment groups compared to the CsA treatment groups (see Figure 13 and Figure 14). Due to the vasoconstrictive effects of CsA on the afferent renal artery, it remains unclear whether the superior GFRs observed in belatacept patients reflect a healthier transplant kidney, more favorable renal hemodynamics, or both.

Figure 13: Mean Calculated GFR (mL/min) in Trial IM103008



Error bars represent 95% confidence interval of the mean
Source: Figure 1, Statistical Safety Review, BLA 125,288

Figure 14: Mean Calculated GFR (mL/min) in Trial IM103027



Error bars represent 95% confidence interval of the mean
Source: Figure 2, Statistical Safety Review, BLA 125,288

While a difference in measured GFRs in favor of patients in both belatacept groups relative to the CsA control group is clearly evident in both Phase 3 trials, it is less obvious that any difference exists between the groups with respect to their change in GFR over time. A pre-specified calculation for slope of GFR based on a Month 3 starting time numerically favors the belatacept groups (see Table 43), but visual inspection of Figure 12 and Figure 13 confirms what the confidence intervals pertaining to that calculation suggest: the existence of a difference with regards to GFR progression over time between the belatacept and CsA groups is uncertain.

Table 43: Slope for Calculated GFR from Month 3 to 24

Study		**Belatacept MI**	**Belatacept LI**	**CsA**
008	Slope* (standard error) 95% Confidence Interval	0.96 (0.71) (-0.43, 2.36)	1.19 (0.70) (-0.18, 2.57)	-1.73 (0.79) (-3.16, -0.30)
027	Slope* (standard error) 95% Confidence Interval	-0.74 (0.78) (-2.28, 0.79)	-0.93 (0.77) (-2.44, 0.58)	-1.88 (0.78) (-3.40, -0.34)

*mL/min/1.73 m^2/year
Source: Table 19, Statistical Safety Review, BLA 125,288

Higher GFRs have been correlated with improved patient outcomes, both in the general chronic kidney disease population and also specifically in the renal transplant patient

population. A recent multivariate analysis of Australia and New Zealand Dialysis and Transplant (ANZDATA) registry data, for instance, showed that cardiovascular death rates were significantly lower among patients with a GFR greater than 48 mL/min at one month compared to those with GFR less than 38 mL/min at one month (risk ratio, 0.66; 95% confidence interval, 0.45-0.95).[42] A Cox regression analysis of OPTN registry data showed that cardiovascular death rates were significantly higher among renal transplant patients whose serum creatinine at 1 year was higher than 1.5 mg/dL compared to those whose serum creatinine at 1 year was less than1.5 mg/dL.[43] As cardiovascular deaths are the leading cause of deaths in the renal transplant population, reductions in cardiovascular deaths would impact significantly on overall death rates. Higher GFRs at one year have also been correlated with improved graft life: an analysis of OPTN registry data also showed that serum creatinine at 1 year predicted long-term graft survival.[44] Whether the higher GFRs observed among the belatacept patients in the Phase 3 trials reflected structural or hemodynamic differences, then, it may be reasonable to infer that the improved GFRs afforded a clinical benefit.

Cardiovascular Risk Factors

Cardiovascular disease is the leading cause of mortality among renal transplant patients.[45] Independent risk factors for cardiovascular death in the renal transplant patient population include diabetes, hypertension, and dyslipidemias.[46,47] Poor renal function represents another important cardiovascular risk factor.[48] Hypertension, dyslipidemias, and new onset diabetes after transplantation (NODAT) are all class effects of CNIs. The applicant has suggested that, as a biologic agent with a highly specific target, belatacept may be less likely to induce similar effects and prospectively studied endpoints related to hypertension, dyslipidemia, and diabetes. (b) (4) however, differences in hypertension, dyslipidemia, and diabetes across approaches to kidney transplantation constitute an

[42] Pilmore H, Dent H, Chang S. Reduction in Cardiovascular Death after Kidney Transplantation. Transplantation 2010; epublished ahead of print.
[43] Meier-Kriesche HU, Baliga, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. Transplantation 2003; 75: 1291.
[44] Hariharan S, McBride MA, Cherikh WS, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int 2002; 62: 311-8.
[45] Aakhus S, Dahl K, Wideroe TE. Cardiovascular morbidity and risk factors in renal transplant patients. Nephrol Dial Transplant 1999; 14: 648-54.
[46] Aakhus S, Dahl K, Wideroe TE. Cardiovascular morbidity and risk factors in renal transplant patients. Nephrol Dial Transplant 1999; 14: 648-54.
[47] Kasiske BL, Chakkera HA, Roel J. Explained and unexplained ischemic heart disease risk after renal transplantation. J Am Soc Nephrol 2000; 11: 1735-43.
[48] Pilmore H, Dent H, Chang S. Reduction in Cardiovascular Death after Kidney Transplantation. Transplantation 2010; epublished ahead of print.

important safety consideration. For that reason, the Division examined those prospectively measured endpoints from the point-of-view of clinical safety.

Hypertension

Mean systolic and diastolic blood pressures were significantly lower at Month 12 for patients in both belatacept groups relative to the CsA control group in both Phase 3 trials (see Table 44).

Table 44: Mean Blood Pressure at Month 12

Study		Mean (Standard Deviation) Number in Analysis		
		Belatacept MI	Belatacept LI	CsA
008	Systolic Blood Pressure	132.7 (16.2)* n=191	131.4 (16.5)* n=193	138.7 (20.0) n=187
	Diastolic Blood Pressure	79.3 (11.5)* n=191	78.7 (10.9)* n=193	81.9 (11.1) n=187
027	Systolic Blood Pressure	141.4 (21.3)* n=137	140.9 (21.1)* n=140	149.5 (19.8) n=124
	Diastolic Blood Pressure	77.8 (13.8)* n=137	78.3 (10.6)* n=140	81.8 (11.7) n=124

*comparison of mean value of belatacept regimen to CsA p-value<0.027
Source: Table 23, Statistical Review, BLA 125,288

The benefits of blood pressure control are well-established in the general population but have been shown to be particularly important in the renal transplant population. For instance, a retrospective analysis of the Collaborative Transplant Study registry data showed that renal transplant recipients with a systolic blood pressure at 1 year less than 140 mmHg had significantly reduced rates of graft loss and cardiovascular death compared with those with a systolic blood pressure at 1 year greater than 140 mmHg.[49] While it is difficult to quantify the clinical benefit in a renal transplant patient population of the differences in systolic and diastolic blood pressures observed, it is reasonable to infer that some benefit should accrue for differences of the magnitude measured in the trial.

New Onset Diabetes After Transplantation (NODAT)

The trials defined NODAT as the use of an antidiabetic agent for more than 30 days or at least two fasting plasma glucose values ≥ 126 mg/dL in a subject who was not diabetic at entry into the study. Across all treatment groups in the Phase 3 trials, relatively few patients developed NODAT by Month 12. A trend towards fewer cases of NODAT was apparent in both trials (see Table 45).

[49] Opelz G, Dohler B. Improved long-term outcomes after renal transplantation associated with blood pressure control. Am J Transplant 2005; 5: 2725-2731.

Table 45: Incidence of New Onset Diabetes After Transplantation at Month 12

Study	Belatacept MI	Belatacept LI	CsA
008	11/156 (7.1)	7/168 (4.2)	16/162 (9.9)
027	3/133 (2.3)	7/136 (5.1)	11/118 (9.3)
Pooled	14/289 (4.8)	14/304 (4.6)	27/280 (9.6)

Denominator is number of subjects with out diabetes at transplant
Source: Adapted from Table 7.6.1 in Clinical Study Reports for Studies IM103008 and IM103027, BLA 125,288

Although the incidence of NODAT in the patients in the belatacept groups was approximately 50% less than the incidence of NODAT in the patients in the CsA groups, the absolute reduction in the incidence was only about 5%. The impact of the measured 50% reduction of NODAT in the Phase 3 trials, then, may have been limited by the overall low incidence of NODAT in the trials. The prevalence of NODAT in the general US transplant population has been estimated at 15-20%, somewhat higher than observed in the context of the belatacept Phase 3 trials.[50,51,52] It is unclear whether the low incidence of NODAT across the treatment groups reflected the demographics of the patients studied or the use of a CsA, rather than tacrolimus, control arm. As the incidence of cardiovascular death has been estimated to be 3-fold higher among transplant patients with diabetes compared to transplant patients without diabetes,[53] the low rates of NODAT observed in the context of belatacept would be clinically significant if reproducible in the general US population

Dyslipidemia

Mean non-HDL cholesterol and mean triglyceride levels at Month 12 were significantly lower in patients in both belatacept groups relative to the CsA control group in both Phase 3 trials (see Table 46). The difference in non-HDL between the two groups appeared to be driven by the contribution of triglycerides, as LDL levels at Month 12 were more similar across groups

[50] Bodziak KA, Hricik DE. New-onset diabetes mellitus after solid organ transplantation. Transplant Int 2009; 22: 519-30.
[51] Woodward RS, Schnitzler MA, Baty J, et al. Incidence and cost of new onset diabetes mellitus among US wait-listed and transplanted renal allograft recipients. Am J Transplant 2003; 3: 590-8.
[52] Moore R, Ravindran V, Baboolal K. The burden of new-onset diabetes mellitus after transplantation. Clin Transplant 2006; 20: 755-61.
[53] Lindholm A, Albrechtsen D, Frodin L, et al. Ischemic heart disease – major cause of death and graft loss after renal transplantation in Scandinavia. Transplantation 1995; 60: 451.

Table 46: Serum Lipids at Month 12

Study		Belatacept MI	Belatacept LI	CsA
008	Non-HDL cholesterol	131.7 (36.8)* n=192	131.5 (38.2)* n=195	144.1 (47.3) n=189
	LDL cholesterol	100.8 (29.5) n=183	102.1 (33.4) n=186	107.3 (39.6) n=187
	Triglycerides	155.0 (85.1)* n=183	149.4 (87.3)* n=186	184.6 (106.4) n=187
027	Non-HDL cholesterol	135.9 (46.3)* n=144	134.4 (41.1)* n=142	153.0 (46.3) n=133
	LDL cholesterol	105.5 (38.8) n=133	102.5 (37.2) n=135	109.8 (40.9) n=124
	Triglycerides	169.6 (120.8)* n=134	152.9 (67.2)* n=135	211.3 (120.6) n=124

Mean (standard deviation)
Number in analysis
*comparison of mean value of belatacept regimen to CsA p-value<0.027
Source: Table 24, Statistical Review, BLA 125,288

Lipid panels in ESRD patients awaiting transplantation are poorly understood: while elevated LDL and total cholesterol levels are associated with cardiovascular disease in the general population, the relationship of LDL cholesterol and cardiovascular death is less clear in the dialysis population.[54,55] Low LDL levels in patients on dialysis are common, but the significance of such LDL levels in that population is not entirely clear: generalized inflammation and poor nutrition may drive down LDL levels. Serum LDL and triglycerides typically increase after transplantation, reflecting both physiologic changes after transplantation but also adverse effects of immunosuppressive drugs.[56] Treatment of dyslipidemias in the general CKD and ESRD population remain controversial. After renal transplantation, however, management of lipids appears to improve cardiovascular outcomes.[57,58] In the context of the controversies regarding interpretation

[54] Cheung AL. Is lipid control necessary in hemodialysis patients? Clin J Am Soc Nephrol 2009; S1: S95-101.
[55] Kanbay M, Turgut F, Covic A, et al. Statin treatment for dyslipidemia in chronic kidney disease and renal transplantation: a review of the evidence. J Nephrol 2009; 22(5): 598-609.
[56] Moore R, Hernandez D, Valantine H. Calcineurin inhibitors and post-transplant hyperlipidaemias. Drug Saf 2001; 24 (10): 755-66.
[57] Holdaas H, Fellström B, Jardine AG, et al. Assessment of Lescol in Renal Transplantation (ALERT) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomized, placebo-controlled trial. Lancet. 2003; 361: 2024-31
[58] Cosio FG, Pesavento TE, Kim S, et al. Patient survival after renal transplantation: Part IV: impact of post-transplant diabetes. Kidney Int 2002; 62: 1440-6.

of lipid panels in these populations, it is difficult to quantify a clinical benefit but the differences in effects on triglycerides appeared favorable to belatacept.

Infections

Overall rates of infections at 12 months appeared similar across treatment arms of the three clinical trials in an analysis of reported adverse events (see Table 47). An imbalance, however, existed with regards to herpes infections: belatacept patients had reported significantly more episodes of herpes infections at the time of the database lock.

Table 47: Infections Reported as Adverse Events up to 12 Months in Trials 008, 027, and 100

	Through Month 12: n, (%)			Through Database Lock: n, (%)		
	Bela MI (N=477)	**Bela LI (N=472)**	**CsA (N=476)**	**Bela MI (N=477)**	**Bela LI (N=472)**	**CsA (N=476)**
Infections reported as SAEs	128 (26.8)	109 (23.1)	130 (27.3)	169 (35.4)	142 (30.1)	166 (34.9)
AEs in SOC of Infections and Infestations	337 (70.7)	339 (71.8)	351 (73.7)	378 (79.2)	376 (79.7)	381 (80.0)
PTs Related to Viral Infections						
CMV	53 (11.1)	56 (11.9)	65 (13.7)	65 (13.6)	62 (13.1)	69 (14.5)
Polyoma Virus	23 (4.8)	11 (2.3)	23 (4.8)	30 (6.3)	16 (3.4)	26 (5.5)
Herpes	38 (8.0)	31 (6.6)	29 (6.1)	67 (14.0)	57 (12.1)	41 (8.6)
PTs Related to Fungal Infections	66 (13.8)	52 (11.0)	72 (15.1)	99 (20.8)	78 (16.5)	95 (20.0)

SOC = System Organ Class
PT = Preferred Term
Source: Adapted from Table 2.1.5.3.A in Summary of Clinical Safety BLA submission

CNS Infections

The high incidence of CNS PTLD and the single case of PML observed in the clinical trials prompted a review of all CNS infections observed in these trials in order to elucidate possible interactions between belatacept and CNS immunity. Similar rates of CNS infections were seen among the belatacept LI patients and the CsA patients (one each across the three trials through the time of database lock). Among the belatacept MI patients, however, seven CNS infections were observed across the three trials through the time of database lock (see Table 48).

Table 48: Cases of CNS Infections in Trials 008, 027, and 100 up to Database Lock

Study	Belatacept MI	Belatacept LI	CsA
100	Herpes Zoster Neurological	--	--
	Cryptococcal Meningitis		
008	Cryptococcal Meningitis	Cryptococcus Meningitis	Cryptococcal Meningitis
	Cryptococcal Meningitis/ Chagas Encephalitis		
	West Nile Virus		
027	Cerebral Aspergillosis	--	--
	PML		

Source: Adapted by Clinical Reviewer from Table 2.1.5.3Q in the Clinical Safety Summary, BLA 125,288

Tuberculosis

An imbalance in cases of tuberculosis was observed across treatment arms in the Phase 3 trials through the time of the database lock (see Table 49). Most of the cases of tuberculosis involved extra-pulmonary sites: among the belatacept patients, tuberculosis presented as disseminated disease twice, laryngeal tuberculosis once, tuberculosis synovitis once, in a cervical ganglion once, and as gastrointestinal tuberculosis once. The lone case of tuberculosis among the CsA patients presented within the intra-thoracic lymph nodes. The vast majority of the patients lived in locations where tuberculosis is endemic.

Table 49: Cases of Tuberculosis in the Phase 3 Trials at Database Lock

	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	3	0	1	2	3	0
Extra-pulmonary	2	0	1	1	3	0
Fatal	0	0	0	0	1	0

Source: Adapted by the Clinical Reviewer from Table 2.1.5.3N in the Summary of Clinical Safety, BLA 125,288

Thrombosis

An excess number of graft losses due to primary graft thrombosis was observed among patients receiving both the belatacept MI regimen (n=7) and the belatacept LI regimen (n=8), compared to patients receiving CsA (n=2), in IM103027, a study which exclusively enrolled recipients of ECD kidneys. As recipients of ECD kidneys are at higher risk of primary graft thrombosis, one might postulate either that IM103027 might represent the study most likely to capture a safety signal related to graft thrombosis or that the CsA group in IM103027 experienced surprisingly few events of primary graft thrombosis. Despite the imbalance in primary graft thrombosis, fewer belatacept patients (17 for belatacept MI, 16 for belatacept LI) in IM103027 experienced graft loss in the first 12 months than CsA patients (n=20). Graft loss due to thrombosis was equivalent across groups in IM103100 (one with belatacept MI, one with belatacept LI, and two with CsA) and IM103008 (one with belatacept MI, one with belatacept LI, and three with CsA). A post hoc analysis of other adverse events related to thrombosis (e.g., deep vein thrombosis) did not suggest a clear correlation between belatacept exposure and increased thromboses.

Infusion-Related

Adverse events that have been reported during or around the infusion of belatacept include headache, flushing, hypotension, and hypertension. Approximately 5% of patients receiving belatacept in the clinical trials reported an infusion related adverse event during the course of the study. Anaphylaxis and/or hypersensitivity have not been observed in the setting of a belatacept infusion.

7.3.5 Submission Specific Primary Safety Concerns

Proteinuria

Proteinuria was first identified in the Phase 2 study, IM103100, as an adverse event more frequently observed among patients receiving belatacept than CsA. The observation was confirmed in both Phase 3 trials. The development of proteinuria is an especially important clinical event in kidney transplant recipients where its presence correlates strongly with decreased graft life. Unfortunately, however, the Phase 2 and Phase 3 trials were poorly designed to capture data regarding proteinuria. Rather than measuring urine protein to creatinine (UP/C) ratios, proteinuria was assessed by urine dipstick assessments. According to the protocol, proteinuria was defined as 2+ on dipstick assessment on 2 consecutive visits. Using that criteria, belatacept patients exhibited proteinuria at 12 months more frequently than CsA patients. Reported rates in IM103008 were 6% for belatacept MI patients, 4% for belatacept LI patients, and 3.7% for CsA patients; reported rates in IM103027 were 10.9% for belatacept MI patients, 10.1% for belatacept LI patients, and 6.8% for CsA patients. It is difficult to assess the

clinical significance of this observation without more quantitative data (such as would be provided by UP/C measurements). Like GFR, proteinuria is affected by renal hemodynamics: in the presence of CsA, proteinuria should be reduced. Insufficient data exist to conclude whether the differences in proteinuria derive from that physiologic effect or from structural differences at the level of the glomerulus. While relatively few patients on either CsA or belatacept met the protocol definition of proteinuria, insufficient data exists to determine how many patients exhibited a clinically significant degree of proteinuria.

Immunogenicity

A minority of study patients developed antibodies against belatacept. During the Phase 3 trials, 25/796 patients (3.1%) developed anti-belatacept antibodies at some point during treatment. Following discontinuation of treatment (i.e. ≥ 56 days post last dose or discontinuation), 7 of the 88 patients evaluated who were previously seronegative became seropositive (8%). For the long term extension phase (LTE) of the phase 2 trial, in both the 4- and 8-week dosing regimens, 16/95 patients (16.8%) were seropositive at some point during observation. An approximately equal number of patients were defined as having transient positive anti-belatacept antibody titers as those defined as persistently positive. Interestingly, a high proportion of the antibodies were directed against the CTLA-4 domain of belatacept: fourteen of the twenty five patients (56%) in the phase 3 trials and 12 of the 16 patients (75%) in the phase 2 LTE who developed anti-belatacept antibodies had antibodies which were reactive with the CTLA-4 domain of belatacept. The sponsor has not examined whether such antibodies bind native CTLA4 on human T cells, but if so, they could conceivably induce autoimmunity similar to that experienced with the investigational anti-CTLA4 antagonist antibody ipilimumab. Conversely, such antibodies could act as agonists and potentially trigger signaling through CD28.

There appears to be a trend towards higher rates of graft loss, death, and AR in those patients who were seropositive or indeterminate than in those who were seronegative to anti-belatacept antibodies. However, the complexity and the small numbers of clinical cases, and the limited immunogenicity and belatacept concentration data taken around the time of the event of interest do not support a causal or temporal association between the development of anti-belatacept antibodies and any of these events.

In terms of mean and median belatacept clearance, there was no significant difference among seropositive, seronegative and indeterminate patients, as well as among neutralizing antibody (NAB)-positive and other patients.

Autoimmunity

Although there was no evidence of autoimmunity in toxicology studies with belatacept in monkeys, nonclinical studies of a related product, abatacept, showed evidence of inflammation and autoimmunity in rats, one of three animal species tested. Abatacept

differs from belatacept by two amino acid substitutions and, in rodents, has greater *in vitro* binding affinity and *in vivo* inhibition of a T-cell dependent antibody response than belatacept. Belatacept has greater binding affinity and inhibition of T-cell proliferation and activation than abatacept in human *in vitro* studies. Toxicology studies of abatacept in rodents are therefore considered to be relevant to the belatacept safety assessment.

In studies with abatacept at clinically relevant doses, inflammation and autoimmunity (insulitis and thyroiditis) were observed in juvenile and adult rats. The incidence and/or severity of the autoimmune findings in rats increased during 2-3 month treatment-free recovery periods. In a peri- post-natal study, thyroiditis was observed in one out of twenty rat off-spring exposed *in utero* and during lactation, at the highest of three doses (200 mg/kg, a maternal abatacept exposure ~11-times higher than the estimated belatacept clinical exposure). The thyroids were not examined in maternal animals. Autoimmunity was not observed in chronic toxicology studies with abatacept in mice and monkeys; therefore, the autoimmunity described in rats may represent a rat-specific effect of abatacept. While these findings may indicate a need for vigilance when abatacept is used in patients including pregnant women, the relevance of these findings to patients or pregnant women treated with belatacept remains unclear.

Adverse events related to autoimmune disease appeared evenly distributed across all treatment groups in the belatacept kidney trials: approximately 2% of patients in IM103100, IM103008, and IM103027 reported autoimmune events. Psoriasis was seen in three belatacept MI treated patients and three belatacept LI treated patients; hyperthyroidism was reported in three CsA treated patients and no belatacept treated patients. An episode of Guillain-Barré syndrome was reported in one patient in IM103027 in the belatacept MI group. Diabetes mellitus was reported in 5% of belatacept patients and 10% of CsA patients.

Patients who receive solid organ transplants generally require lifelong immunosuppression, and immunosuppression could mask the appearance of autoimmunity. In the Phase 3 trials of belatacept, 20% to 30 % of patients stopped belatacept and the majority were switched to another form of immunosuppression. Therefore, the lack of any significant autoimmune signal during the kidney transplant trials may mean that (a) a signal was not seen because belatacept does not increase the risk for autoimmunity in adult transplant patients, (b) systematic evaluation for the development of autoimmunity was not done, (c) patients were receiving other immunosuppressive products that masked/treated the autoimmune adverse reaction. It remains unclear, however, whether the use of belatacept could result in autoimmunity in cases where treatment with (exposure to) belatacept was stopped and no other immunosuppression was instituted. Discontinuation of immunosuppression in the setting of graft loss represents one scenario where a paucity of data on whether or not autoimmunity would be seen exists. *In utero* exposure to belatacept represents another important instance where belatacept exposure would be present during gestation but would stop upon birth of the infant. The concern regarding autoimmunity in the offspring of a woman receiving belatacept is supported by the finding of thyroiditis in one of

twenty rat off-spring after exposure to abatacept *in utero* and during lactation. Finally, the difference in maturation of the immune system between pediatric patients and adult patients may also have implication on the differential risk for immunity.

Abatacept is currently marketed as Orencia® for the treatment of adult rheumatoid arthritis and juvenile idiopathic arthritis (pediatric patients 6 years or older). In the currently approved Orencia® labeling,[59] the potential risk of autoimmunity is addressed in the Pregnancy Section 8.1, the Pediatric Use Section 8.4, and the Animal Toxicology and/or Pharmacology Section 13.2.

Given the concerns regarding a potential association between belatacept and autoimmunity, a consult was requested from the Division of Pharmacovigilance II (DPV II) to search the Adverse Events Reporting System (AERS) database for evidence of an association between abatacept and autoimmunity. DPV II did not identify any significant evidence of a safety signal with abatacept related to autoimmunity.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Other than the specific issues addressed above, the adverse event profile of the belatacept regimen and the CsA regimen were similar as observed by the AEs reported up to Month 12 in Studies 008, 027, and 100. That observation is perhaps somewhat surprising as one might have anticipated more of an imbalance reflecting known class effects of CsA and mycophenolic acid (MPA). Known adverse events associated with CsA include hyperkalemia, hypertension, dyslipidemias, hyperglycemia, and tremor. One would expect the control arm to have experienced more of those adverse events. Known adverse events associated with MPA include GI toxicities (diarrhea, nausea, abdominal pain, vomiting) and bone marrow suppression (anemia and leucopenia). While the observed dosages of MMF were similar across the belatacept groups and the CsA groups, a 25 to 40% greater MPA exposure was achieved among the belatacept groups (due to the impact of CsA on the enterohepatic recirculation of MPA; see Clinical Pharmacology Review) – suggesting that the belatacept arms might have been expected to have experienced more adverse events related to MPA. Therefore, in addition to carefully examining AEs associated with belatacept, particular attention was also therefore afforded to reporting of those AEs known to be associated with CsA and MPA. An analysis of these selected AEs, however, suggests that the true differences across groups were mild (see Table 50): CsA patients only appeared to experience dyslipidemia (but not hypercholesterolemia) and tremor more frequently.

[59] http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125118s0086lbl.pdf

Table 50: Selected Adverse Events Associated with Class Effects Up to Month 12

SOC/PT	IM103008			IM103027		
	MI N=219	LI N=226	CsA N=221	MI N=184	LI N=175	CsA N=184
Metabolism and Nutritional Disorders	155 (70.8)	159 (70.4)	161 (72.9)	129 (70.1)	127 (72.6)	135 (73.4)
Hypokalemia	39 (17.8)	37 (16.4)	17 (7.7)	31 (16.8)	31 (17.7)	32 (17.4)
Hyperkalemia	14 (6.4)	38 (16.8)	32 (14.5)	38 (20.7)	42 (24.0)	35 (19.0)
Dyslipidemia	38 (17.4)	39 (17.3)	55 (24.9)	19 (10.3)	17 (9.7)	30 (16.3)
Hypercholesterolemia	26 (11.9)	19 (8.4)	19 (8.6)	16 (8.7)	16 (9.1)	18 (9.8)
Hyperglycemia	30 (13.7)	32 (14.2)	30 (13.6)	32 (17.4)	25 (14.3)	28 (15.2)
Infections and Infestations	152 (69.4)	158 (69.9)	157 (71.0)	130 (70.7)	129 (73.7)	142 (77.2)
Urinary tract infections	54 (24.7)	63 (27.9)	50 (22.6)	55 (29.9)	57 (32.6)	62 (33.7)
Upper respiratory tract infection	24 (11.0)	22 (9.7)	26 (11.8)	11 (6.0)	11 (6.3)	14 (7.6)
Cytomegalovirus infection	13 (5.9)	17 (7.5)	19 (8.6)	21 (11.4)	24 (13.7)	24 (13.0)
Gastrointestinal System Disorders	139 (63.5)	157 (69.5)	154 (69.7)	122 (66.3)	130 (74.3)	136 (73.9)
Constipation	59 (26.9)	72 (31.9)	60 (27.1)	52 (28.3)	57 (32.6)	73 (39.7)
Diarrhea	58 (26.5)	56 (24.8)	56 (25.3)	54 (29.3)	58 (33.1)	47 (25.5)
Nausea	47 (21.5)	48 (21.2)	56 (25.3)	42 (22.8)	37 (21.1)	41 (22.3)
Vomiting	30 (13.7)	34 (15.0)	35 (15.8)	25 (13.6)	38 (21.7)	31 (16.8)
Abdominal Pain	24 (11.0)	27 (11.9)	25 (11.3)	19 (10.3)	28 (16.0)	25 (13.6)
Blood and Lymphatic Systems Disorders	103 (47.0)	124 (54.9)	101 (45.7)	114 (62.0)	103 (58.9)	122 (66.3)
Anemia	68 (31.1)	82 (36.3)	64 (29.0)	87 (47.3)	85 (48.6)	92 (50.0)
Leucopenia	34 (15.5)	36 (15.9)	34 (15.4)	44 (23.9)	30 (17.1)	49 (26.6)
Nervous System Disorders	66 (30.1)	75 (33.2)	75 (33.9)	53 (28.8)	55 (31.4)	66 (35.9)
Headache	39 (17.8)	37 (16.4)	21 (9.5)	21 (11.4)	22 (12.6)	21 (16.8)
Tremor	9 (4.1)	12 (5.3)	35 (15.8)	11 (6.0)	14 (8.0)	23 (12.5)

Source: Adapted by the Clinical Reviewer from Table 2.1.1B in the Summary of Clinical Safety, BLA 125,288

7.4.2 Laboratory Findings

Routine clinical testing was described above in Section 7.2.4. On the basis of fasting blood glucoses, small differences in the incidence of NODAT were observed between belatacept and CsA treatment groups in the clinical trials (see Section 7.3.4). On the basis of hemoglobin A1c, however, no differences were note across treatment groups. Larger decreases in serum immunoglobulin were noted among patients maintained on either belatacept regimen compared to the CsA regimen, though significant decreases were observed across all treatment groups. The clinical significance of these decreases is not clear.

Laboratory findings related to measured and calculated GFR, protocol graft biopsies, and serum lipids are discussed in pertinent sections of the review.

7.4.3 Vital Signs

Vital signs were collected at Day 5, Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, and Month 12. Differences in blood pressures observed across treatment groups are discussed in Section 7.3.4.

7.4.4 Electrocardiograms (ECGs)

A consult request was sent August 21, 2009 to the QT Interdisciplinary Review Team (QT-IRT). In their completed consult (dated November 23, 2009), the QT-IRT concluded: Based upon review of the ECG data and narratives for cardiac-related deaths in clinical trials IM103008 and IM103027, there does not appear to be any large effect of belatacept on the QT interval.

Belatacept is a large fusion protein with a molecular weight of approximately 91 kDa and with high specificity for its target; therefore a thorough clinical QT study was not conducted. Non-clinical evaluations have suggested no evidence of cardiovascular or hemodynamic abnormalities. In both Phase 3 studies, 12-lead ECGs were obtained at baseline prior to transplant, prior to administration of study drug at week 12 and at week 52. Assessments were based upon local, non-standardized evaluations. Patients were not excluded from the study based on any ECG criteria. Bazett's correction for QT interval was used.

Increases in the QTc interval > 60 msec compared with baseline were observed in ≤ 7% of patients in all treatment groups at Month 3 and Month 12. No clinically relevant effects on the PR or QRS intervals were apparent. A review of narratives relating events of cardiac arrest, cardiopulmonary events, or sudden death did not identify any reports of QT prolongation associated with those events. There were no reports of *Torsade de Pointes* or other significant ventricular arrhythmias with temporal association to belatacept administration.

7.4.5 Special Safety Studies/Clinical Trials

An epidemiological study (IM103028) based on CMS claims data was commissioned by the applicant to help evaluate the PTLD safety signal observed among EBV+ patients in the clinical trials. The study examined patterns of ICD-9 codes among kidney transplant patients in the CMS database. As described elsewhere in the review, the applicant could not provide the CMS database nor the computer programming used to generate the report in a timely fashion. The relevant databases were obtained directly from USRDS by the clinical and statistical review teams. However, inspection of the

databases led the reviewers to the conclusion that the approach did not add value to their understanding of PTLD among EBV+ patients.

7.4.6 Immunogenicity

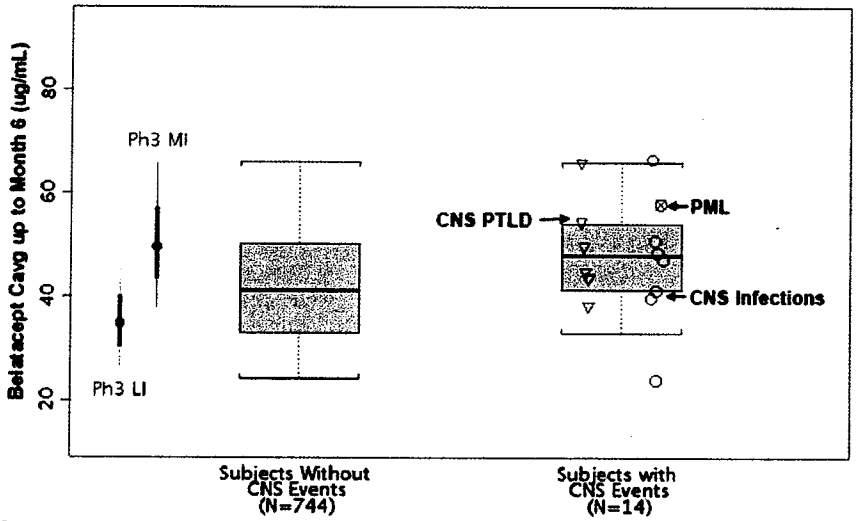
Immunogenicity issues related to belatacept are discussed in Section 7.3.5.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A post-hoc analysis by the applicant suggested that patients in the belatacept kidney transplant trials who developed CNS PTLD, PML, or other CNS infections tended to have greater exposure to belatacept in the first six months post-transplant than those patients who did not experience a CNS event (see Figure 15).

Figure 15: Distribution of belatacept average concentrations (C_{avg}) up to 6 months after transplantation (C_{avg} = cumulative AUC divided by time) in subjects treated with belatacept who did and did not develop CNS events in the belatacept kidney transplant trials.



Source: Figure 6 in the Clinical Pharmacology Review. Adapted from the applicant's Advisory Committee briefing book

Reviewer comment: The applicant proposed the belatacept LI regimen, but not the belatacept MI regimen, for approval based on the premise that the LI regimen appeared as efficacious as the MI regimen but that it was associated with fewer toxicities. Seven of the eight CNS infections, including the PML event, observed among kidney transplant patients maintained on belatacept occurred among recipients of the belatacept MI

regimen. In addition, six of the nine CNS PTLD events presented among belatacept MI patients.

7.5.2 Time Dependency for Adverse Events

The most significant adverse events associated with belatacept more than with CsA were AR, PTLD, and PML. Most of the AR events experienced by patients maintained on belatacept regimen occurred relatively early after transplantation: 147 of the 152 (or 97%) rejection episodes which presented in the first year occurred within 6 months of transplantation. Similarly, 13 of the 14 PTLD events experienced by patients maintained on belatacept occurred within the first 18 months of transplantation, suggesting that the incidence rate of PTLD decreases over time (an observation consistent with the epidemiology of PTLD in a non-belatacept context). The single event of PML in the kidney transplant trials presented, however, twenty-three months after transplantation.

Reviewer comment: The risks associated with belatacept appear to present (or fail to present) relatively early after transplantation, while the toxicities associated with CsA continue to have a cumulative effect over time. The long-term impact of the early AR events experienced by the belatacept patients, however, is not yet entirely clear. The three-year follow-up data from the Phase 3 trials should provide additional insight into the differences in outcomes between these groups over time.

7.5.3 Drug-Demographic Interactions

Age/Gender/Race
Outcomes of the Phase 3 trials were examined according to subgroups of patients divided according to gender, race, and age. As discussed in Section 6.1.7, outcomes related to patient and graft survival, AR, and mean GFR did not suggest that belatacept was particularly appropriate or inappropriate for any subgroups based on gender, race, or age. In addition, the incidence of serious adverse events and adverse events experienced within each treatment group was examined according to gender, race, and age. Inspection of the incidence of events, both at the level of System Organ Class and at the level of Preferred Term, did not reveal any subgroups based on gender, race, or age for which the relative safety profile of belatacept compared to CsA appeared to alter the risk-benefit relationship of those two drugs.

7.5.4 Drug-Disease Interactions

As discussed throughout the review, a significant drug-disease interaction exists between belatacept and EBV seronegative patients: EBV- patients maintained on belatacept had a disproportionately high incidence of PTLD in comparison to EBV+ patients maintained on belatacept. This observation is consistent with the epidemiology of PTLD in a non-belatacept context. Given the increased rate of PTLD associated with belatacept overall, however, the applicant has proposed contraindicating the use of belatacept among EBV- kidney transplant recipients.

The Clinical Pharmacology review team conducted an exploratory investigation to identify other risk factors predictive of PTLD in belatacept-treated patients. An ROC analysis of potential risk factors identified CMV serostatus as another possible predictive risk factor for PTLD among EBV+ patients. Specifically, among EBV positive patients, those patients with CMV negative serology were more likely to develop PTLD than those patients with CMV positive serology (1.91% vs. 0.34%), representing an approximately 6-fold higher risk (OR 5.76 [1.05, 31.7], see Table 51).

Table 51: PTLD events among EBV+ patients maintained on belatacept in Phase 2 and Phase 3 kidney transplant trials

		PTLD-No[a]	PTLD-Yes[a]	Total[a]	PTLD Rate
CMV	+	590	2	592	0.34%
	-	205	4	209	1.91%
Total		795	6	801	0.75%

[a]: Number of Patients
Source: Table 5, Clinical Pharmacology Review, BLA 125,288

Reviewer comment: Unlike EBV serostatus, CMV serostatus has not been clearly identified as a risk factor for the development of PTLD in a non-belatacept context. Such an association is biologically plausible; however, as CMV disease has been established as a risk factor for the development of PTLD. The Clinical Pharmacology team has suggested that the labeling reflect the above data and that the relationship between CMV serostatus and PTLD in the context of exposure to belatacept receive further study. Given that CMV serostatus is a routinely collected pre-transplant laboratory value, the conduct of such a study should be relatively straightforward (see also Reviewer Comment in Section 1.4).

7.5.5 Drug-Drug Interactions

Belatacept is a fusion protein which consists of the functional binding domain of modified CTLA-4 and the Fc domain of an IgG immunoglobulin, suggesting that direct drug-drug interactions are relatively unlikely. Given that belatacept inhibits the production of several cytokines, however, it may potentially affect the mRNA expression and functional activities of hepatic CYP450 metabolizing enzymes.

Reviewer comment: The Clinical Pharmacology review team introduced this potential source of drug-drug interactions in its review. The review suggests that the Clinical Pharmacology team may ultimately recommend additional investigations to evaluate the effect of belatacept on concomitant medications metabolized through CYP450 enzymes.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Other than the excess events of PTLD associated with belatacept, the incidence of malignancies appeared similar across treatment groups in IM103100, IM103008, and IM103027. Non-melanoma skin cancer was the most common malignancy detected in all groups (3.1% of belatacept MI patients, 1.3% of belatacept LI patients, and 2.3% of CsA patients at time of database lock in a pooled analysis of all three studies). Despite the excess of PTLD events among the belatacept group, the number of patients with malignant neoplasms excluding non-melanoma skin cancers remained similar across all patient groups (6.7% of belatacept MI patients, 4.9% of belatacept LI patients, and 4.8% of CsA patients at time of database lock in a pooled analysis of all three studies).

7.6.2 Human Reproduction and Pregnancy Data

No data related to drug exposure in pregnant or lactating women were included in the BLA submission.

7.6.3 Pediatrics and Assessment of Effects on Growth

Belatacept was granted Orphan Drug status. As such, the Pediatric Research Equity Act of 2003 (PREA) does not apply: the FDA has no authority to request pediatric data for such products. As the kidney transplantation trials excluded patients younger than 18 years of age, no relevant data exist.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The belatacept developmental program did not include any experience with overdoses of belatacept. Belatacept would not appear to have any abuse potential.

The development of anti-belatacept antibodies occurred more frequently in the setting of withdrawal of belatacept. Anti-belatacept antibodies may have the potential to decrease the efficacy of belatacept or to induce autoimmune disease.

As discussed elsewhere in the review, thyroiditis and insulitis were observed in rat studies of abatacept (an analog of belatacept more suited to studies in rodents). The incidence and severity of the autoimmune findings increased during treatment-free recovery periods. This observation suggests the possibility that any potential association between belatacept and autoimmunity could be increased after

discontinuation of belatacept (see Section 7.3.5 for full discussion regarding autoimmunity).

7.7 Additional Submissions / Safety Issues

All data relevant to the clinical review which has been submitted to the BLA at the time of this writing is reflected in the review. Additional data is expected after all patients in the Phase 3 kidney transplant trials complete 3 years of follow up.

8 Postmarket Experience

None

9 Appendices

9.1 Literature Review/References

References are incorporated in the body of the review as footnotes.

9.2 Labeling Recommendations

Final labeling revisions were not proposed during this review cycle due to a recommended Complete Response action.

9.3 Advisory Committee Meeting

The following is an internal report prepared by the Advisors and Consultants Staff of the Cardiovascular and Renal Drugs Advisory Committee meeting held on March 1, 2010.

A verbatim transcript will be available approximately four to six weeks following the date of the meeting at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm192863.htm

5 Pages have been removed. See entire transcript at www.fda.gov/AdvisoryCommittees

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: BL 1252888 **Applicant:** Bristol Myers Squibb **Stamp Date:** July 1, 2009

Drug Name: Belatacept **NDA/BLA Type:** BLA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	BLA application
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: IM103100 (Phase 2) Study Title: Open-Label, Randomized, Controlled, Multiple-Dose Study of Efficacy and Safety of BMS-224818 as Part of a Quadruple Drug Regimen in Renal Transplant Recipients Sample Size: 228 Arms: 3(5) Location in submission: Module 5.3.5.1				Arms of study included CSA active comparator, a "more intensive" belatacept arm, and a "less intensive" belatacept arm. At Day 85, the belatacept arms were reallocated to more or less frequent dosing schedules. The Phase 3 trials also tested "more intensive" and a "less intensive" arms

	Content Parameter	Yes	No	NA	Comment
					that were similar (but not identical) to those in the Phase 2 study. No reallocation occurred in the Phase 3 studies at Day 85.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 IM103008 – Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppresion Trial (BENEFIT) Indication: Prophylaxis of organ rejection and preservation of organ structure and function in renal transplant recipients Pivotal Study #2 IM103027 – Belatacept Evaluation of Nephroprotection and Efficacy as Firstl-line Immunosuppression Trial Extended Criteria Donors (BENEFIT-EXT) Indication: Prophylaxis of organ rejection and preservation of organ structure and function in renal transplant recipients	X			Note that the proposed indication includes "preservation of organ structure and function in renal transplant recipients" which would represent an indication never before granted by FDA.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			They conform to previous Agency agreements. The endpoint of GFR, however, may be difficult to interpret due to physiologic effects not accounted for at the time of those agreements.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		The applicant should submit such a rationale, as the US transplant population has outcomes distinct from the non-US transplant population (especially with regards to incidence of rejection episodes and PTLD)
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously requested by the Division?				
19.	Has the applicant submitted adequate information to assess the arhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			The product is a biologic and therefore not likely to have an arhythmogenic potential; a TQT study was deemed unnecessary; ECGs were obtained in Phase 3 trials
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			A total of 1436 subjects (just under the ICH recommend 1500) received belatacept across the 16 completed or ongoing BMS-sponsored studies; otherwise the guidelines have been met.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		unable to locate it in the eCTD
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Additional information regarding the evolution of the PTLD cases may be requested of the applicant during the course of the review
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*,			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	label comprehension, self selection and/or actual use)?				
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	The product received an orphan drug designation
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		The applicant should submit such a rationale, as the US transplant population has outcomes distinct from the non-US transplant population (especially with regards to incidence of rejection episodes and PTLD)
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			We have asked the applicant to also submit datasets with embedded formatting to facilitate the use of jREVIEW as a tool.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			To the extent determined during this 45 day cycle
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			We are now also requesting a 10% random sample of CRFs for verification purposes and may request additional CRFs during the review cycle.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			The submission, however, is missing information for several investigators; applicant claims due

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					diligence in obtaining the information
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1) A rationale for assuming the applicability of foreign data to U.S. population/practice of medicine as approximately 75% of the patients in the pivotal phase 3 trials were non-U.S. patients could not be located in the eCTD. If such a rationale was submitted, please direct us to its location. If such a rationale was not provided, please submit one.
2) A coding dictionary used for mapping investigator verbatim terms to preferred terms could not be located in the eCTD. If such a dictionary was submitted, please direct us to its location. If not, please submit one.
3) A random sample of 10% of the phase 3 pivotal trial population has been generated. Some of the CRFs in the random sample corresponded to CRFs already included in the submission (i.e., deaths, SAEs, discontinuations). Please provide the additional CRFs from this sample for validation purposes. see Appendix.

Reviewing Medical Officer — Date: 9/9/09

Clinical Team Leader — Date

Appendix

IM103027-105-10177
IM103027-110-10190
IM103027-2-10007
IM103027-2-10258
IM103027-20-10208
IM103027-24-10548
IM103027-28-10265
IM103027-31-10287
IM103027-32-10149
IM103027-34-10082
IM103027-35-10145
IM103027-35-10551
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IM103027-97-10357
IM103027-97-10455
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IM103008-10-20233
IM103008-10-20525
IM103008-100-20517
IM103008-108-20388
IM103008-108-20724
IM103008-109-20187
IM103008-116-20387
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IM103008-116-20450
IM103008-118-20487
IM103008-118-20714
IM103008-120-20420
IM103008-125-20320
IM103008-131-20671

IM103008-146-20490
IM103008-149-20530
IM103008-150-20482
IM103008-16-20080
IM103008-17-20395
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IM103008-36-20300
IM103008-37-20701
IM103008-42-20306
IM103008-45-20008
IM103008-51-20360
IM103008-58-20349
IM103008-62-20077
IM103008-64-20225
IM103008-64-20695
IM103008-66-20244
IM103008-76-20057
IM103008-85-20680
IM103008-91-20021
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