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APPLICATION NUMBER:

125288Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

BLA: STN 125288	Submission Dates: 24 September 2010; 08 December 2010; 13 December 2010
Brand Name (proposed)	Nulojix™
Generic Name	Belatacept
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OCP Division	Division of Clinical Pharmacology IV
Clinical Division	Division of Special Pathogen and Transplant Products
Sponsor	Bristol-Myer Squibb
Relevant IND(s)	BB-IND 009,418
Submission Type; Code	Sponsor's Response to FDA Complete Response Action
Formulation; Strength(s)	Lyophilized Powder for IV infusion (250 mg single use vial) for reconstitution to 25 mg/mL
Proposed Indication	Prophylaxis of organ transplant rejection and preservation of functioning allograft in adult renal transplant recipients
PDUFA Date	16 June 2011

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1. Executive Summary

On 01 May 2010, the FDA issued a Complete Response (CR) Action to the Nulojix® (belatacept) Biologics License Application, citing Clinical, Product Quality, Product Quality Microbiology, and Facility Inspection deficiencies as the reasons for the CR action. To address these deficiencies, the sponsor provided responses that included the 36-month study reports from the Phase 3 trials, the revised Risk Evaluation and Mitigation Strategy (REMS) which includes a Medication Guide for patients and a Communication Plan for health care professionals, and the revised protocols of the three proposed postmarketing (observational/registry) studies.

Although both the More-Intensive (MI) and the Less-Intensive (LI) regimens of belatacept were evaluated in the two Phase 3 trials, the sponsor is seeking approval of the LI regimen because of its more favorable efficacy and safety profile. To mitigate the risk of Post-transplant lymphoproliferative disease (PTLD) development, it is proposed that the use of the belatacept LI regimen be contraindicated in kidney transplant recipients with EBV-negative or unknown serostatus.

1.1 Recommendations

Overall, the Clinical Pharmacology information presented in this submission is acceptable to support the approval of Nulojix® (belatacept) LI for the proposed indication of prophylaxis of organ rejection and preservation of functioning allograft in adult patients receiving kidney transplants, provided that satisfactory agreement is reached between the sponsor and the FDA regarding language in the package insert.

1.2 Post-Marketing Commitments

None.

1.3 Comments for Sponsor Regarding Ongoing and Future Clinical Trials

1.3.1. Collection of IgG concentration data

IgG concentration is a potential pharmacodynamic biomarker of the level of total or aggregate immunosuppression in belatacept treated patients. Based on the findings of the Clinical Pharmacology reviewer's exploratory analyses, IgG concentrations less than the lower limit of the normal range (<694 mg/dL) may have contributed to the incidence of adverse events in belatacept treated patients in the Phase 3 trials, particularly PTLD/CNS PTLD and PML. The sponsor should collect additional information in ongoing/future clinical trials to better understand the impact of low IgG concentrations on the risk of PTLD/CNS-PTLD, PML, and other serious adverse events in belatacept treated patients.

1.3.2. Collection of data on usage of concomitant non-study medications

Regarding the sponsor's proposed Post-Marketing Study IM103075ST, we note that the type and

the duration of antibody induction medications and other concomitant anti-rejection and maintenance immunosuppressive medications will be recorded. We recommend recording also the type and the duration of antiviral/antimicrobial agents used for prophylaxis or treatment of infections in this study. Additionally we recommend that you include, as a secondary study objective, the assessment of the concomitant therapies, including lymphocyte depleting therapy, as independent risk factors of PTLD/CNS-PTLD development in belatacept treated patients.

1.4 Summary of Additional Clinical Pharmacology Findings

In the Phase 3 trials, the IgG, IgA, and IgM concentrations were measured, per protocol, at baseline (immediately prior to transplant), and at Months 6 and 12 post-transplant. The sponsor reported that at Month 12, the mean reductions from baseline IgG, IgA, and IgM concentrations in belatacept-treated patients were greater than in cyclosporine-treated patients. However, low Ig levels at Month 12 were not associated with the frequency of serious infections and malignancies.

The Clinical Pharmacology reviewer's exploratory analyses indicate that belatacept-treated patients with IgG concentrations below the lower limit of normal (IgG<694 mg/dl) at Month 6 post-transplant had higher rates of adverse events (CNS-associated PTLD and infections, serious infections, malignancies, lower mean measured and calculated GFR, and death) at 36 months or at database lock, as compared to patients with normal IgG at Month 6. The following lines of evidence suggest that IgG is a potential pharmacodynamic biomarker of the level of total or aggregate immunosuppression in belatacept-treated patients: (1) The mean reduction from baseline IgG concentrations at Month 6, and the percentage of patients with IgG<LLN at Month 6 were greater with belatacept MI (the non-recommended regimen) than belatacept LI (the recommended regimen). (2) The IgG concentration-time profile reflects the time course of belatacept dosing, i.e., IgG concentrations were highest at Month 0, and lowest at Month 1 to 3 post-transplant. (3) There was a trend of decreasing IgG concentrations at Month 6 with increasing belatacept trough concentrations at Month 6. (4) The IgG concentrations at Month 6 were lower in belatacept-treated patients who also received -- for the treatment of acute rejection episodes -- supplementary immunosuppressive therapy (pulse steroids and/or thymoglobulin) during the 1st 6 months post-transplant.

The 36-month PK data in the Phase 3 trials indicate that the post-Month 12 mean belatacept trough concentrations did not significantly change as compared to Month 12 trough concentrations. This finding is expected given that the belatacept LI and MI patients (who participated in the long-term extension starting after Month 12 of the Phase 3 trials) received maintenance belatacept therapy equivalent to 5 mg/kg every 4 weeks.

Based on the sponsor's assessment of the 36-month data in the two Phase 3 trials, there was no significant change from 12-month efficacy and safety profiles of belatacept LI (the recommended belatacept regimen) compared to cyclosporine (CsA), with the exception of a higher rate of late-onset tuberculosis (that was attributed to patients originating from endemic areas) in belatacept LI versus CsA. At the 36-month follow-up, belatacept LI still demonstrated a comparable patient

and graft survival, and a higher renal function (cGFR) than cyclosporine. However, compared to CsA, belatacept LI showed a higher incidence of acute rejection and higher-grade acute rejection that mostly occurred during the first 6 months post-transplant; patients with acute rejection had a higher incidence of patient and graft loss, and lower cGFR. Additionally, the higher rate of PTLD in belatacept LI than CsA remains an important safety finding. Based on the sponsor's post-hoc analysis, the results in the overall study population were comparable to that in the EBV-seropositive subpopulation for which belatacept LI therapy will be indicated. Because there was no significant change in the efficacy and safety profile of belatacept at the Month 36 assessment, the Clinical Pharmacology reviewer did not perform additional exploratory PK-efficacy and PK-safety analyses beyond that done with the original BLA submission data.

Based on the recommendation of the OCP Genomics Review Team, the protocol of Postmarketing Study IM103075ST was amended to include, as a secondary objective, the assessment of recipient and donor CMV serostatus at the time of kidney transplant as an independent risk factor of PTLD development in EBV-seropositive transplant patients receiving belatacept therapy.

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2. Question Based Review

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Two Phase 3 clinical trials, IM103008 and IM103027 evaluated the efficacy and safety of the more intensive (MI) and less intensive (LI) dosing regimens of belatacept in *de novo* renal transplant patients, in comparison to cyclosporine. Both Phase 3 trials are multicenter, randomized, and were blinded with respect to belatacept regimen. The patients in IM103008 received kidneys from standard-criteria donors (SCD), whereas those in IM103027 received kidneys from extended-criteria donors (ECD). The adjunctive immunosuppressive therapy used in the belatacept treatment and cyclosporine control arms consisted of basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids.

Although the following two belatacept regimens were evaluated in Phase 3 trials, the less-intensive (LI) regimen is being proposed for approval.

- The MI regimen of 10 mg/kg of belatacept given IV on Day 1 (the day of transplantation, prior to implantation), Day 5, 14, 28, 42, and 56, and then every 4 weeks through 6 months after transplantation. Starting at Month 7 after transplantation, belatacept was administered at 5 mg/kg IV monthly.
- The LI regimen of 10 mg/kg of belatacept given IV on Day 1 (the day of transplantation, prior to implantation), Days 5, 14, 28, Month 2 and Month 3, and then at 5 mg/kg IV monthly starting at Month 4 after transplantation.

2.2.2. What is the basis of the dosage regimen selection?

The overall efficacy of belatacept was similar between the less intensive (LI) and more intensive (MI) dosing regimens, with some suggestion of a more favorable safety profile with the LI dosing regimen. Therefore, the LI dosing regimen is the recommended dosing regimen for belatacept.

2.2.3. What are the clinical endpoints used to assess efficacy in the pivotal clinical efficacy study? What is the clinical outcome in terms of safety and efficacy?

As per the sponsor's assessment, there were no remarkable changes in the efficacy and safety profile of belatacept at the 36-month follow-up, except with respect to the higher incidence of late-onset tuberculosis (TB) attributed to cases from areas of high TB endemicity. Following is a summary of the sponsor's 36-month assessment of belatacept efficacy and safety in Study IM103008 (Tables 1 and 2); the findings in this study reflected the findings in IM103027.

Efficacy:

Table 1. Efficacy Outcomes in Study IM103008 up to Month 36 post-transplant

Key Efficacy Outcomes			
	Belatacept MI N = 219	Belatacept LI N = 226	CsA N = 221
Subject and Graft Survival (n, %)			
Month 12^a	209 (95.4)	218 (96.5)	206 (93.2)
Difference from CsA (97.3% CI)	2.2 (-2.9, 7.5)	3.2 (-1.5, 8.4)	---
Graft Loss (n, %)	4 (1.8)	5 (2.2)	8 (3.6)
Death (n, %)	6 (2.7)	4 (1.8)	7 (3.2)
Imputed as Graft Loss or Death	0	0	1 (0.5)
Month 24^a	206 (94.1)	214 (94.7)	200 (90.5)
Difference from CsA (97.3% CI)	3.6 (-2.2, 9.6)	4.2 (-1.3, 10.1)	---
Graft Loss (n, %)	7 (3.2)	5 (2.2)	8 (3.6)
Death (n, %)	7 (3.2)	8 (3.5)	13 (5.9)
Imputed as Graft Loss or Death	0	0	1 (0.5)
Month 36 (from current CSR)	202 (92.2)	208 (92.0)	196 (88.7)
Difference from CsA (97.3% CI)	3.5 (-2.8, 10.0)	3.3 (-2.9, 9.8)	---
Key Efficacy Outcomes			
	Belatacept MI N = 219	Belatacept LI N = 226	CsA N = 221
Graft Loss (n, %)	10 (4.6)	9 (4.0)	10 (4.5)
Death (n, %)	9 (4.1)	10 (4.4)	15 (6.8)
Imputed as Graft Loss or Death	0 (0.0)	0 (0.0)	1 (0.5)
Mean (SD) measured GFR with Imputation^b (mL/min/1.73 m²)			
Month 12^a	65.0 (30.0)	63.4 (27.7)	50.4 (18.7)
Estimated diff. from CsA (97.3% CI)	14.6 (8.9, 20.4)	13.0 (7.3, 18.7)	---
P-Value	< 0.0001	< 0.0001	---
Month 24^a	65.0 (27.2)	67.9 (29.9)	50.5 (20.5)
Estimated diff. from CsA (97.3% CI)	14.5 (8.5, 20.5)	17.4 (11.5, 23.4)	---
P-Value	< 0.0001	< 0.0001	---
Month 36 (not performed per protocol)	---	---	---
Mean (SD) cGFR with Imputation^c (mL/min/1.73 m²)			
Month 12^a	65.2 (23.5)	65.4 (22.9)	50.1 (21.0)
Difference from CsA (97.3% CI)	15.1 (10.1, 20.1)	15.3 (10.3, 20.3)	---
Month 24^a	65.5 (24.8)	65.4 (25.2)	47.9 (23.0)
Difference from CsA (97.3% CI)	17.6 (12.0, 23.3)	17.5 (12.0, 23.1)	---
Month 36	65.2 (26.31)	65.8 (27.00)	44.4 (23.58)
Difference from CsA (97.3% CI)	20.8 (14.8, 26.9)	21.4 (15.4, 27.4)	---
Acute Rejection (n, %)^d			
Month 12^a	49 (22.4)	39 (17.3)	16 (7.2)
Difference from CsA (97.3% CI)	15.1 (7.9, 22.7) ^e	10.0 (3.3, 17.1)	---
Month 24^a	53 (24.2)	39 (17.3)	20 (9.0)
Difference from CsA (97.3% CI)	15.2 (7.5, 23.0)	8.2 (1.2, 15.4)	---
Month 36 (from current CSR)	53 (24.2)	39 (17.3)	21 (9.5)
Difference from CsA (97.3% CI)	14.7 (7.0, 22.6)	7.8 (0.6, 15.0)	---

^a Month 24 CSR.

^b Imputation Method: No imputation for subjects with graft loss or death, however, if a value was available, it was used in the analysis. For other missing data, measured GFR at other time-points or cGFR at the same time point was used to impute the missing values at Month 12 or 24.

^c For missing data due to graft loss or death, cGFR after graft loss or death was imputed as 0 (primary analysis) by Month 36.

^d Acute Rejection is defined as central biopsy proven rejection that was either (1) clinically suspected by protocol defined reasons or (2) clinically suspected by other reasons and treated.

^e The 20% non-inferiority margin was not met in the belatacept MI group.

EFFICACY RESULTS: All endpoints described below were evaluated in the ITT population. The general efficacy profile at Month 36 remained consistent with that observed at Month 24.

Death and Graft Loss:

- Comparable rates of death (4%, 4%, and 7%, respectively) and graft loss (5%, 4%, and 5%, respectively) from transplantation up to Month 36 were observed across the belatacept MI, LI, and CsA treatment groups, respectively.
- Subjects receiving belatacept experienced a delay in the time to progression to advanced renal dysfunction (CKD Stage 4 or 5), graft loss, or death as compared with subjects treated with CsA. By 3 years after transplantation, approximately 25% CsA subjects and 10% of belatacept subjects had reached this endpoint.

Acute rejection (AR):

- Up to Month 36, AR occurred in 24% (MI), 17% (LI), and 10% (CsA). Most cases of AR occurred by Month 6. More cases of AR were classified as Banff grade IIb and III in the MI (11%) or LI (5%) than in the CsA group (1%). After Month 24 no new cases occurred in MI or LI; 1 new case occurred in the CsA group.
- Through Month 36, there were comparable rates of the composite endpoint of biopsy-proven acute rejection (BPARG), death, graft loss, and loss to follow-up between treatment groups.

Renal Function:

- The difference in renal function, as assessed by cGFR, between belatacept and CsA seen at Months 12 and 24 was maintained; at Month 36 differences between both belatacept groups and CsA were ~ 21 mL/min/1.73 m². Measured GFR was not obtained at Month 36 according to the protocol.
- The annual rate of change in cGFR from Month 3 to Month 36 was 1.0, 1.2, and -2.0 mL/min/1.73 m²/year for the belatacept MI, LI, and CsA groups, respectively.
- Chronic kidney disease stage based on cGFR at Month 36 showed greater proportions of subjects with Stage 1 and 2 and fewer subjects with Stage 4 and 5 in the belatacept groups compared with CsA.

Impact of AR by Month 24 on outcomes up to Month 36:

- The overall rate of death by Month 36 in subjects with AR was 9% (5 subjects) in belatacept MI, 13% (5 subjects) in belatacept LI, and 0% in CsA; in subjects without AR the rate was 2% (4 subjects) in belatacept MI, 3% (5 subjects) in belatacept LI, and 8% (15 subjects) in CsA.
- The overall rate of graft loss by Month 36 in subjects with AR was 9% (5 subjects) in belatacept MI, 13% (5 subjects) in belatacept LI, and 5% (1 subject) in CsA; in subjects without AR the rate was 3% (5 subjects) in belatacept MI, 2% (4 subjects) belatacept LI, and 5% (9 subjects) in CsA.
- Renal function (cGFR as observed or with imputation) at Month 36 was lower in subjects with AR than without AR in all treatment groups.

Metabolic effects:

- Comparisons between the belatacept groups and the CsA group were statistically significant favoring belatacept for Total-C, non HDL-C, triglycerides and LDL-C.
- There was significantly less antihypertensive medication usage in the belatacept groups compared with the CsA group. At Month 36 SBP was lower in the belatacept MI and LI groups versus CsA by 8 and 6 mmHg, respectively. Diastolic BP was lower in the belatacept MI and LI versus CsA by 3 and 4 mmHg, respectively.
- No statistically significant differences between the belatacept groups and CsA in NODM were observed at Month 12, Month 24 or Month 36.

Safety:

Table 2. Safety Outcomes in Study IM103008 up to Month 36 post-transplant

Key Safety Results: -Randomization up to Month 36			
	MI	LI	CsA
	N = 219	N = 226	N = 221
Overall Summary- n (%):			
Deaths	9 (4.1)	10 (4.4)	15 (6.8)
SAEs	133 (60.7)	131 (58.0)	150 (67.9)
Related SAEs	62 (28.3)	50 (22.1)	68 (30.8)
Discontinued Due to SAEs	13 (5.9)	14 (6.2)	18 (8.1)
AEs	218 (99.5)	225 (99.6)	219 (99.1)
Related AEs	141 (64.4)	150 (66.4)	180 (81.4)
Discontinued Due to AEs	16 (7.3)	16 (7.1)	31 (14.0)
Events of Clinical Interest -n (%):			
Malignancies	18 (8.2)	10 (4.4)	12 (5.4)
PTLD (up to DBL)	3 (1.4)	2 (0.88)	1 (0.5)
Tuberculosis	4 (1.8)	2 (0.9)	1 (0.5)
Fungal Infections	50 (22.8)	46 (20.4)	45 (20.4)
Viral infections	84 (38.4)	86 (38.1)	81 (36.7)
CMV infections	22 (10.0)	26 (11.5)	25 (11.3)
Polyoma virus infections	18 (8.2)	10 (4.4)	18 (8.1)
Herpes Infections	29 (13.2)	26 (11.5)	21 (9.5)
Key Safety Results: -Randomization up to Month 36			
	MI	LI	CsA
	N = 219	N = 226	N = 221
Auto-immune Events	1 (0.5)	3 (1.3)	6 (2.7)
Pulmonary edema or CHF	11 (5.0)	9 (4.0)	11 (5.0)
Thrombotic and embolic events	18 (8.2)	14 (6.2)	13 (5.9)

Population: All Randomized and Transplanted Subjects.

SAFETY RESULTS: The following summarizes the safety findings for this addendum:

- The general safety at Month 36 profile remains consistent with that observed at Month 24.
- The rates of death, SAEs and AEs leading to discontinuations were lower in both belatacept groups relative to the CsA group.
- The incidence rates of all malignancies, all malignancies excluding non-melanoma skin cancers, and non-melanoma skin cancers remained relatively stable through database lock. Incidence rates of malignancies up to database lock were lower in the LI group than either the MI or CsA groups, driven primarily by a lower incidence of non-melanoma skin cancer.
 - By Month 36, 3, 2, and 1 subjects in the belatacept MI, belatacept LI, and CsA groups had PTLD; this includes 2 PTLD events that occurred after Month 12. There were no PTLD events reported after Month 18 in this study.
- The overall proportion of subjects with infections was comparable. The annual incidence rates of viral and fungal infections decreased over time in all 3 treatment groups. Imbalances are described below:
 - The incidence rate of BK polyoma viral infections up to database lock was lower in the belatacept LI group compared with the other groups.
 - The incidence rate of herpes infections up to database lock was higher in the belatacept groups compared with the CsA group.
 - The incidence rate of fungal infections up to database lock remained higher in the belatacept MI group compared with both the belatacept LI and CSA groups.
- A total of 7 subjects developed TB by Month 36: 4 (MI), 2 (LI), and 1 (CsA). One (MI) and 2 (LI) subjects developed TB after Month 24; 1 of the belatacept LI cases had been previously reported in the Month 24 CSR.

- The proportions of subjects in all 3 treatment groups with thrombotic/embolic events, pulmonary edema, heart failure, and proteinuria by Month 36 were comparable; few events occurred post-Month 12.
- By Month 36, few subjects in all 3 treatment groups reported autoimmune events: 3%, 3%, and 2% in the belatacept MI, LI, and CsA groups, respectively.
- The proportions of subjects with peri-infusional events by Month 36 were comparable in the 2 belatacept groups; most of these events were non-serious, unrelated to belatacept treatment (investigator assessment), and did not lead to discontinuation.

2.2.4. Belatacept Trough Concentrations (C_{trough}) Observed in Phase 3 Trials

Consistent with the use of 5 mg/kg every 4 weeks maintenance dosing starting at Month 4 of Belatacept LI and starting at Month 7 of Belatacept MI therapy, the mean belatacept trough concentrations were not observed to change significantly in LI after Day 112 and in MI after Day 168. Tables 3 and 4 show the summary statistics for belatacept C_{trough} IM103008 and IM103027, respectively.

Table 3. Mean and %CV of Belatacept Trough Concentrations ($\mu\text{g/mL}$) in Study IM103008

		LI and MI Regimens by Study Day														
Study Day	Day 5	Day 56	Day 70	Day 84	Day 112	Day 168	Day 252	Day 280	Day 308	Day 336	Day 364	Day 532	Day 728	Day 896	Day 1092	
LI	Geo Mean	34.8	8.4	NR	7.0	6.8	3.5	3.5	3.3	3.5	3.7	3.4	3.6	4.1	5.0	4.7
	CV%	59	49	NR	54	53	59	81	68	62	63	63	55	55	54	62
	N	208	197	NR	183	176	177	179	131	172	167	173	176	166	164	102
MI	Geo Mean	35.4	23.7	23.9	26.2	10.7	7.8	3.8	3.8	3.6	3.9	3.8	3.7	4.5	5.3	5.7
	CV%	32	59	42	38	79	66	60	81	56	49	51	78	58	65	57
	n	202	194	176	190	174	171	171	129	164	164	162	159	152	150	97

Table 4. Mean and %CV of Belatacept Trough Concentrations ($\mu\text{g/mL}$) in Study IM103027

		LI and MI Regimens by Study Day														
Study Day	Day 5	Day 56	Day 70	Day 84	Day 112	Day 168	Day 252	Day 280	Day 308	Day 336	Day 364	Day 532	Day 728	Day 896	Day 1092	
LI	Geo Mean	35.7	9.6	NR	8.5	8.0	4.3	3.9	4.1	4.4	4.2	4.3	4.4	4.1	5.6	5.3
	CV%	31	60	NR	83	57	57	52	78	61	55	57	55	71	66	60
	N	150	146	NR	139	130	131	126	119	120	119	114	110	107	104	95
MI	Geo Mean	38.3	26.4	27.2	27.7	12.9	9.3	4.2	4.2	4.4	4.4	4.1	4.3	4.8	5.6	6.0
	CV%	54	40	34	64	46	46	61	55	55	52	54	58	102	63	86
	n	155	151	136	141	128	136	130	119	121	124	119	109	112	101	89

Source: Table S.8.2.1

CV = co-efficient of variation; LI = less intensive; MI = more intensive; NR = not reported.

Belatacept was not dosed on Day 70 for subjects randomized into the LI group.

2.2.5. Are there any pharmacodynamic parameters that could potentially impact the clinical efficacy and safety?

In Phase 3 trials, the study protocol specified measurement of the concentrations of IgG, IgA, and IgM at Month 0 (baseline, prior to transplant), and at Months 6 and 12 post-transplant; a smaller subset of the patient population had immunoglobulin measurements at other times during the 36-month study period. Based on the sponsor's analysis of immunoglobulin (Ig) concentrations at Month 12, there were greater reductions from baseline in mean IgG, IgM, and IgA concentrations in belatacept-treated patients than cyclosporine-treated patients. However, the sponsor also stated there were no associations found between these low Ig concentrations and the frequency of serious infections and malignancies.

In the Clinical Pharmacology reviewer's analysis, there was a statistically significant association between the IgG concentrations at Month 6 and the incidence of CNS-PTLD and PML up to database lock in belatacept (LI + MI) treated patients (Figure 1); the probability of these CNS events increased with decreasing IgG concentrations, particularly at IgG concentrations below the lower limit of normal (<LLN; <694 mg/dL). Furthermore, the incidence of CNS-PTLD and PML in both belatacept LI and belatacept MI treatment arms was higher in the patients with hypogammaglobulinemia (HGG; IgG<694 mg/dL) at Month 6 than in the patients with normal IgG concentrations (NGG; Table 5).

(See the **Executive Summary**, 1.3.1. Comment for the Sponsor. See also **4. Individual Submission Review A** for the detailed findings of the analyses that explored the association between hypogammaglobulinemia and belatacept PK, and CNS PTLT and CNS infections, in addition to other clinical endpoints.

Figure 1. Plot of CNS PTLD and PML as a function of log-transformed IgG concentrations at Month 6 in belatacept patients in the Phase 3 trials

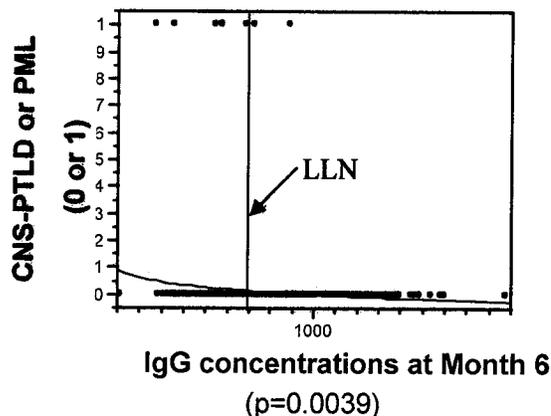


Table 5. Proportion of Patients with CNS PTLD and PML up to database lock – n/N (%)

TREATMENT	Hypogammaglobulinemia (HGG; IgG < 694 mg/dL)	Normogammaglobulinemia (NGG; IgG = 694-1618 mg/dL)	HGG/NGG ratio
Belatacept LI	1.1 (1/95)	0.5 (1/204)	2.2
Belatacept MI	3.4 (4/118)	0.6 (1/174)	5.9
Cyclosporine	0 (0/86)	0 (0/198)	-

EXTRINSIC FACTORS

2.4.3 Drug-Drug interactions

2.4.3.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interaction?

Belatacept inhibits the production of cytokines *in vitro* (see **Section 12.1** of the Nulojix USPI). Cytokines may affect the mRNA expression of CYP450 metabolizing enzymes, which in turn may result in alterations of the systemic concentrations of the co-administered drug that is a CYP450 substrate (See the reviewer's recommended language in **Section 7.1** of the Nulojix USPI).

2.4.3.2 What other co-medications are likely to be administered to the target patient population?

In the clinical trials, the belatacept-based regimens also consisted of mycophenolate mofetil and corticosteroids. In these clinical trials, additional medications were typically used by belatacept treated patients to prevent viral infections (e.g., ganciclovir), and to treat acute rejections (e.g., lymphocyte-depleting agents).

The use of lymphocyte-depleting therapy is a known risk factor of PTLD. In response to an information request made by the Clinical Pharmacology reviewers, the sponsor reported that the use of lymphocyte-depleting therapy (e.g., thymoglobulin) for the treatment of acute rejection was associated with a higher incidence of CNS events (Belatacept MI), malignancies (Belatacept LI), death or graft loss (Bela LI, MI, and cyclosporine), and lower calculated GFR (Bela LI, MI, and cyclosporine). However, the sponsor considers the interpretation of the impact of concomitant antibody product therapy on therapeutic outcomes of belatacept treated patients to be challenging given the numerous confounding variables including co-morbidities and other concomitant therapies.

3. PROPOSED LABELING

(b) (4)

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

4. Individual Submission Reviews

A. Clinical Pharmacology Review of Sponsor's Response to 10/1/2010 Information Request Regarding IgG (SN-062, submitted on 08 December 2010)

I. BACKGROUND:

Belatacept is a fusion protein that is partially derived from the Fc portion of the modified human IgG₁.

On 01 October 2010, the Clinical Pharmacology reviewer shared with the sponsor the findings of an exploratory analysis that evaluated the impact of hypogammaglobulinemia (HGG; IgG < 694 mg/dL) at Month 6 on the therapeutic outcomes in the belatacept Phase 3 trials (Reviewer's Tables 1 to 3). *Based on the results, the belatacept LI and MI-treated patients with HGG at Month 6 versus those with normal IgG concentrations (NGG; IgG ≥ 694 mg/dL) had a higher incidence of CNS-PTLD [2.1% (4/193) versus 0.3% (1/294)], PML [0.5% (1/193) versus 0% (0/294)], serious infections [43.5% (84/193) versus 32.3% (95/294)] and malignancies [9.8% (19/193) versus 2.7% (8/294)], acute rejections including high-grade acute rejections [20.7% (40/193) versus 10.2% (30/294)], lower mean measured or calculated GFR, and death [6.2% (12/193) versus 1.7% (5/294)].*

The communication stated: *The clinical implications of these findings with respect to use of belatacept, or use of other immunosuppressant drugs in general, are not known. However, these findings suggest that IgG titers (concentrations) may serve as a potentially useful biomarker of undesirable outcomes of the immunosuppressant drug regimen, including belatacept, in kidney transplant patients.*

Additionally, the Clinical Pharmacology reviewer recommended that the sponsor perform further exploratory analyses to investigate the potential influence of concomitant treatment with immune globulin containing preparations (e.g., IVIG, thymoglobulin, cytogam) on the safety and efficacy of belatacept and cyclosporine, as well as on belatacept trough concentrations in the Phase 3 trials.

Table 1: Effect of Reductions in IgG Titers at Month 6 on the Incidence of Serious Infections, CNS Events, and Malignancies Observed in Phase 3 Trials (%n/N)

Treatment Group	IgG Level at Month 6	Serious Infections	CNS Events^a	Malignancies
Belatacept Less-Intensive (LI)	Normal Range (694-1618 mg/dL)	30.49 (50/164)	0.61 (1/164)	1.83 (3/164)
	Below LLN (<694 mg/dL)	39.08 (34/87)	2.30 (2/87)	5.75 (5/87)
	Above ULN (>1618mg/dL)			
Belatacept More-Intensive (MI)	Normal Range (694-1618 mg/dL)	34.62 (45/130)	2.31 (3/130)	3.85 (5/130)
	Below LLN (<694 mg/dL)	47.17 (50/106)	4.72 (5/106)	13.21 (14/106)
	Above ULN (>1618mg/dL)			
Belatacept Less-Intensive (LI) and More-Intensive (MI)	Normal Range (694-1618 mg/dL)	32.31 (95/294)	1.36 (4/294)	2.72 (8/294)
	Below LLN (<694 mg/dL)	43.52 (84/193)	3.63 (7/193)	9.84 (19/193)
	Above ULN (>1618mg/dL)			
Cyclosporine	Normal Range (694-1618 mg/dL)	36 (54/150)	0 (0/150)	6.67 (10/150)
	Below LLN (<694 mg/dL)	45.83 (33/72)	0 (0/72)	11.11 (8/72)
	Above ULN (>1618mg/dL)	50 (1/2)	0 (0/2)	

^a total of CNS infections, CNS-PTLD, PML, and other CNS infections

Table 2: Effect of Reductions in IgG Titers at Month 6 on the Incidence of Acute Rejections, Death, and Graft Loss Observed in Phase 3 Trials (%n/N)

Treatment Group	IgG Level at Month 6	Acute Rejections (AR)		Death	Graft Loss
		Total AR	High-grade AR ^a		
Belatacept Less-Intensive (LI)	Normal Range (694-1618 mg/dL)	9.15 (15/164)	2.44 (4/164)	0.61 (1/164)	3.05 (5/164)
	Below LLN (<694 mg/dL)	18.39 (16/87)	3.45 (3/87)	8.05 (7/87)	1.15 (1/87)
	Above ULN (>1618mg/dL)				
Belatacept More-Intensive (MI)	Normal Range (694-1618 mg/dL)	11.54 (15/130)	6.92 (9/130)	3.08 (4/130)	0.77 (1/130)
	Below LLN (<694 mg/dL)	22.64 (24/106)	9.43 (10/106)	4.72 (5/106)	3.77 (4/106)
	Above ULN (>1618mg/dL)				
Belatacept Less-Intensive (LI) and More-Intensive (MI)	Normal Range (694-1618 mg/dL)	10.20 (30/294)	4.42 (13/294)	1.70 (5/294)	2.04 (6/294)
	Below LLN (<694 mg/dL)	20.73 (40/193)	6.74 (13/193)	6.22 (12/193)	2.59 (5/193)
	Above ULN (>1618mg/dL)				
Cyclosporine	Normal Range (694-1618 mg/dL)	8.00 (12/150)	0.67 (1/150)	3.33 (5/150)	0.67 (1/150)
	Below LLN (<694 mg/dL)	15.28 (11/72)	0 (0/72)	4.17 (3/72)	0 (0/72)
	Above ULN (>1618mg/dL)	0 (0/2)	0 (0/2)	0 (0/2)	50 (1/2)

^a Acute Rejection Grade IIB and higher

Table 3: Effect of Reductions in IgG Titers at Month 6 on the Incidence of Renal Function Observed in Phase 3 Trials [Mean \pm SD (n) or % (n/N)]

Treatment Group	IgG Level at Month 6	Measured GFR (mGFR; mL/min/1.73m ²) (Mean \pm SD)	Calculated GFR (mGFR-MDRD; mL/min/1.73m ²) (Mean \pm SD)	Decrease in mGFR \geq 10 mL/min from Month 3 to Month 12 (mGFR10; n%)	Change in cGFR from Month 0 to Month 12 ^a (mL/min/1.73m ²) (Mean \pm SD)
Belatacept Less-Intensive (LI)	Normal Range (694-1618 mg/dL)	61.3 \pm 26.1 (n = 163)	64.2 \pm 20.1 (n = 156)	26.99 (44/163)	55.4 \pm 20.7 (n = 146)
	Below LLN (<694 mg/dL)	55.1 \pm 27.8 (n = 85)	60.3 \pm 16.7 (n = 78)	34.12 (29/85)	50.8 \pm 16.5 (n = 69)
	Above ULN (>1618mg/dL)				
Belatacept More-Intensive (MI)	Normal Range (694-1618 mg/dL)	62.4 \pm 28.6 (n = 129)	65.8 \pm 21.3 (n = 120)	22.66 (29/128)	56.6 \pm 22.8 (n = 109)
	Below LLN (<694 mg/dL)	55.0 \pm 25.1 (n = 103)	56.5 \pm 19.8 (n = 156)	27.18 (28/103)	46.0 \pm 20.6 (n = 97)
	Above ULN (>1618mg/dL)				
Belatacept Less-Intensive (LI) and More-Intensive (MI)	Normal Range (694-1618 mg/dL)	61.8 \pm 27.2 (n = 292)	64.9 \pm 20.6 (n = 276)	25.09 (73/291)	55.9 \pm 21.6 (n = 255)
	Below LLN (<694 mg/dL)	55.1 \pm 26.3 (n = 188)	58.1 \pm 18.6 (n = 180)	30.32 (57/188)	48.0 \pm 19.1 (= 166)
	Above ULN (>1618mg/dL)				

II. SPONSOR'S RESPONSE:

A. Regarding IgG Concentrations and/or Low IgG Levels as Biomarker:

The sponsor acknowledged that it is plausible to consider IgG levels as a surrogate marker for overall level of immunosuppression. However, the sponsor does not consider low IgG level as a suitable surrogate biomarker for future adverse events because of its low positive predictive value (PPV), i.e., < 38% for serious infections, and <12% for CNS events, malignancies, death and graft loss (see data in Table 4, as provided by the sponsor). Based on Table 4, there was a greater frequency of serious infections, malignancies, and death in both belatacept LI and belatacept MI-treated patients with IgG below LLN versus patients with IgG within the normal range; the rate of CNS events up to Month 36 was only higher for belatacept MI (not LI and CsA).

The sponsor did not include acute rejections in their analyses because most episodes occurred before the Month 6 timepoint for IgG measurement. Likewise, renal function was not included in the sponsor's analyses because GFR is a continuous (rather than a binary outcome) variable.

B. Regarding the Impact of Concomitant Immunoglobulin Use on Belatacept PK, Efficacy and Safety in the Phase 3 Trials:

Figures 2A and 2B show the observed belatacept trough concentrations in subjects in the Phase 3 studies who were treated with belatacept LI and belatacept MI, respectively. The circles represent the belatacept trough concentrations subsequent to treatment with Ig-containing preparations whereas the boxplots represent the belatacept trough concentrations in subjects who had not received such treatment, or were observed prior to receiving such treatment. Co-treatment with Ig-containing preparations did not appear to have an effect on belatacept trough concentrations, as indicated by the largely superimposed distributions of the circles with the boxplots.

To explore the effect of Ig-containing preparations on the efficacy and safety of belatacept, the sponsor compared the results of clinical endpoints, stratified by use of at least 1 dose of antibody product (Table 5). The use of antibody product was comparable for the belatacept MI and CsA treatment groups and lower for the LI group (17.9%, 18.5% and 14.7%, respectively). The majority of antibody product use was Thymoglobulin for treatment of AR. The results of the analysis showed that the frequency of serious infection by Month 36 did not appear to be impacted by use of antibody product in any treatment group. Additionally, for those who received antibody product, an increased frequency of CNS events was observed in the MI group and an increased frequency of malignancy in the LI group. These findings are consistent with the known safety profile of Thymoglobulin, the most commonly used antibody product in the phase 3 clinical trials. Furthermore, the decreased mean GFR and increased frequency of death and graft loss observed with the use of antibody product across all three treatment groups is consistent with the observed impact of AR on renal function and graft survival. However, direct causality of antibody products cannot be firmly established due to the potential role of other confounding

factors such as diabetes, HTN and infections on these efficacy outcomes. Small numbers of events and numerous confounding variables preclude definitive interpretation.

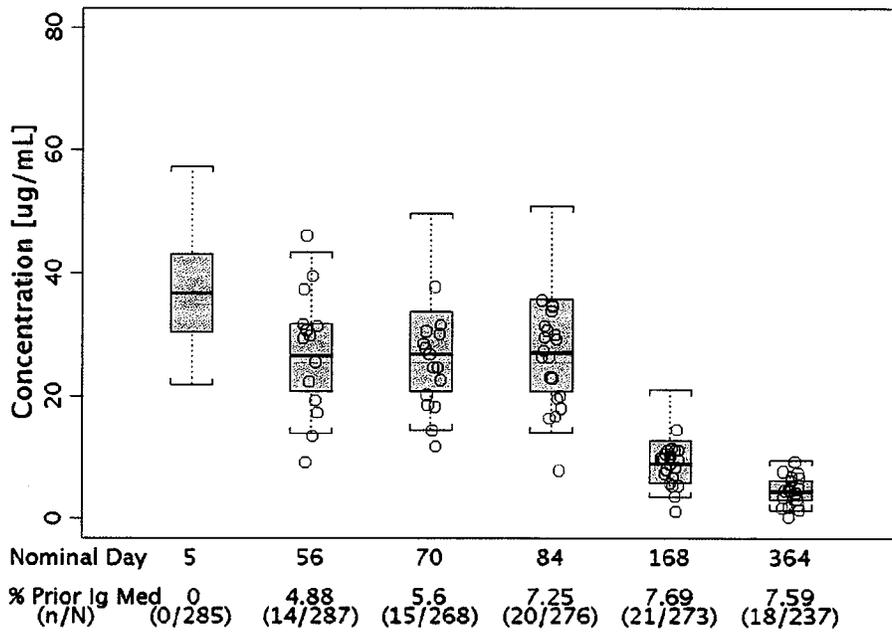
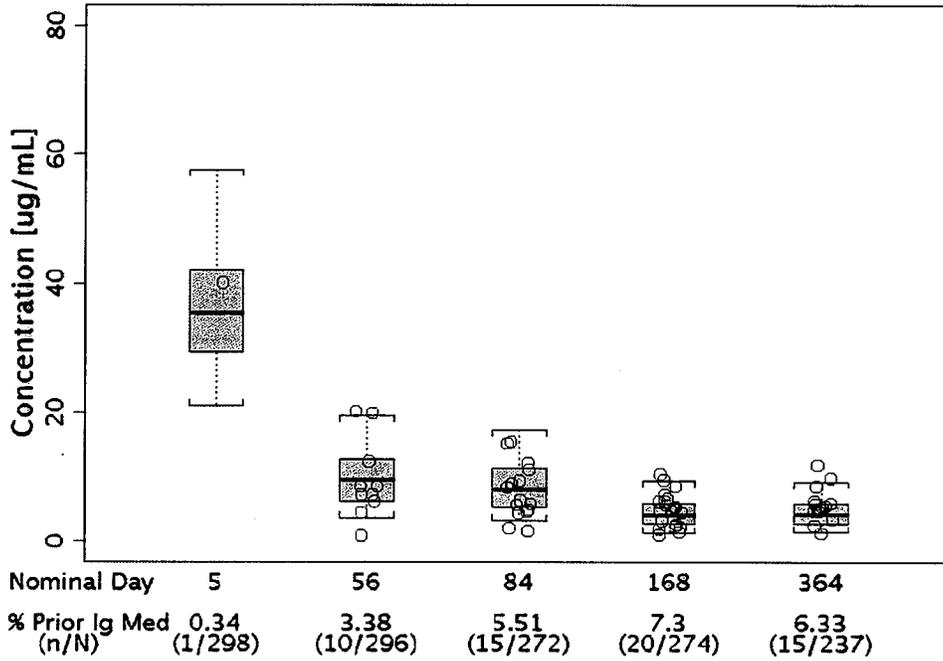
Regarding the role of concomitant immune globulin treatment on the resolution of acute rejection or of an adverse event (e.g., serious infection), the sponsor stated: "Use of immune globulin (antibody) products in the treatment of AR and DGF are standard practice in the care of renal transplant recipients. ...the Phase 3 protocols recommended the use of such products in the setting of Banff Grade IIb or higher AR, or anticipated DGF (CsA subjects only). The impact of antibody products on the time to resolution of AR is unclear based upon a review of the literature. Further, the increased immunosuppressive burden that results from their administration could theoretically delay the time to resolution of events such as serious infections." The sponsor indicated that the mean/median duration (6 to 7 days) of antibody product use for each acute rejection episode (regardless of biopsy grade) was comparable among the three treatments, and that the longer median duration of AR in subjects who received LDT (MI: 22.5; LI 14.5; and CsA 25.0 days) versus those who did not receive LDT (MI: 13; LI: 12.0; and CsA: 14.5 days) is consistent with clinical expectations.

Table 4. Summary of Efficacy/Safety Endpoints Post Month 6 and up to Month 36 Stratified by IgG Levels at Month 6 in Subjects with IgG Values within Normal Range at Baseline (All Randomized and Transplanted Subjects from Studies -008 and -027)

	Belatacept - MI (N=403)			Belatacept - LI (N=401)			Cyclosporine (N=405)		
	IgG at Month 6			IgG at Month 6			IgG at Month 6		
	Below ULN N = 102	Normal Range N = 134	Above ULN N = 0	Below ULN N = 91	Normal Range N = 171	Above ULN N = 0	Below ULN N = 79	Normal Range N = 153	Above ULN N = 2
Serious Infection									
Yes	41 (37.6)	33 (24.6)	0	30 (33.0)	40 (23.4)	0	26 (32.9)	42 (27.5)	0
No	68 (62.4)	101 (75.4)	0	61 (67.0)	131 (76.6)	0	53 (67.1)	111 (72.5)	2 (100)
Positive PV/Negative PV(%)	37.6/75.4			33.0/76.6			32.9/72.9		
CNS Events									
Yes	5 (4.6)	2 (1.5)	0	1 (1.1)	2 (1.2)	0	0	0	0
No	104 (95.4)	132 (98.5)	0	90 (98.9)	169 (98.8)	0	79 (100)	153 (100)	2 (100)
Positive PV/Negative PV(%)	4.6/98.5			1.1/98.8			0.0/100.0		
Malignancies									
Yes	13 (11.9)	7 (5.2)	0	8 (8.8)	4 (2.3)	0	8 (10.1)	12 (7.8)	0
No	96 (88.1)	127 (94.8)	0	83 (91.2)	167 (97.7)	0	71 (89.9)	141 (92.2)	2 (100)
Positive PV/Negative PV(%)	11.9/94.8			8.8/97.7			10.1/92.3		
Death or Graft Loss									
Yes	12 (11.0)	5 (3.7)	0	10 (11.0)	7 (4.1)	0	5 (6.3)	7 (4.6)	0
No	97 (89.0)	129 (96.3)	0	81 (89.0)	164 (95.9)	0	74 (93.7)	146 (95.4)	2 (100)
Positive PV/Negative PV(%)	11.0/96.3			11.0/95.9			6.3/95.5		
Death									
Yes	8 (7.3)	5 (3.7)	0	9 (9.9)	3 (1.8)	0	5 (6.3)	6 (3.9)	0
No	101 (92.7)	129 (96.3)	0	82 (90.1)	168 (98.2)	0	74 (93.7)	147 (96.1)	2 (100)
Positive PV/Negative PV(%)	7.3/96.3			9.9/98.2			6.3/96.1		

Only Subjects with Normal Baseline IgG Values were included in the analysis.
 Below ULN: < 694 mg/dl, Normal Range: 694-1618 mg/dl, Above ULN: > 1618 mg/dl.
 Positive Predictive Value= # of subjects with events in IgG below ULN group / total number of subjects in IgG below ULN group.
 Negative Predictive Value= # of subjects without events in IgG >= ULN group / total number of subjects in IgG >= ULN group.
 MedDRA Version: 13.0
 Program Source: /gbs/prod/clin/programs/im/103/bia-renal/sur2010/scs/fda_request/rt-adiagg1-endpts-postm6-pv-v01.sas 03DEC2010:11:18

Figure 2A and 2B. Observed Belatacept Trough Concentrations in Phase 3 Trials (+/- Ig Medication), by Nominal Study Day (Top panel: LI Regimen; Bottom panel: MI Regimen)



Source: /global/pkms/data/TM/103/C02/prd/fda.igg.response/sp/scripts/plot_cmin_ivig.ssc

Boxplots: Belatacept trough concentration distributions in subjects who had not received IG containing treatment by the corresponding day. The boxes represent the median and inter-quartile range, and the whiskers represent the 5th and 95th percentiles

Circles: Belatacept trough concentration values of subject who had received IG containing treatment prior to the corresponding day.

**Table 5. Summary of Month 36 Efficacy/Safety Endpoints Stratified by Thymoglobulin Usage Status
(All Randomized and Transplanted Subjects from Studies -008 and -027)**

	Belatacept - MI (N=403)		Belatacept - LI (N=401)		All Belatacept (N=804)		Cyclosporine (N=405)	
	Thymoglobulin Usage		Thymoglobulin Usage		Thymoglobulin Usage		Thymoglobulin Usage	
	Yes N = 59	No N = 344	Yes N = 37	No N = 364	Yes N = 96	No N = 708	Yes N = 58	No N = 347
Serious Infection	23 (39.0)	136 (39.5)	14 (37.8)	135 (37.1)	37 (38.5)	271 (38.3)	21 (36.2)	140 (40.3)
CNS Events	3 (5.1)	7 (2.0)	0	3 (0.8)	3 (3.1)	10 (1.4)	0	1 (0.3)
Malignancies	3 (5.1)	31 (9.0)	6 (16.2)	19 (5.2)	9 (9.4)	50 (7.1)	4 (6.9)	27 (7.8)
Acute Rejection								
MILD ACUTE (IA)	0	7 (2.0)	4 (10.8)	4 (1.1)	4 (4.2)	11 (1.6)	6 (10.3)	1 (0.3)
MILD ACUTE (IB)	6 (10.2)	3 (0.9)	4 (10.8)	6 (1.6)	10 (10.4)	9 (1.3)	1 (1.7)	10 (2.9)
MODERATE ACUTE (IIA)	15 (25.4)	13 (3.8)	9 (24.3)	25 (6.9)	24 (25.0)	38 (5.4)	4 (6.9)	20 (5.8)
MODERATE ACUTE (IIB)	23 (39.0)	15 (4.4)	15 (40.3)	10 (2.7)	32 (33.3)	25 (3.5)	5 (8.6)	3 (0.9)
SEVERE ACUTE (III)	1 (1.7)	3 (0.9)	1 (2.7)	0	2 (2.1)	3 (0.4)	0	0
Death or Graft Loss	11 (18.6)	42 (12.2)	11 (29.7)	38 (10.4)	22 (22.9)	80 (11.3)	13 (22.4)	47 (13.5)
Death	5 (8.5)	26 (7.6)	5 (13.5)	20 (5.5)	10 (10.4)	46 (6.5)	2 (3.4)	30 (8.6)
Graft Loss	8 (13.6)	20 (5.8)	7 (18.9)	23 (6.3)	15 (15.6)	43 (6.1)	12 (20.7)	21 (6.1)
Calculated GFR *								
N	34	304	26	318	60	622	40	274
MEAN (SD)	41.7 (31.29)	56.6 (28.52)	28.7 (29.26)	57.4 (27.58)	36.1 (30.85)	57.0 (28.02)	27.9 (23.31)	40.1 (23.50)
MEDIAN	47.0	61.6	31.7	61.2	41.1	61.4	30.5	42.2
RANGE	0.0 - 95.6	0.0 - 150.1	0.0 - 89.1	0.0 - 126.1	0.0 - 95.6	0.0 - 150.1	0.0 - 68.0	0.0 - 106.5
Q1-Q3	0.0 - 65.9	45.1 - 74.7	0.0 - 46.9	44.8 - 75.2	0.0 - 61.0	44.9 - 74.8	0.0 - 48.1	26.9 - 57.1

* Calculated GFR at Month 36 is based on imputed values

Program Source: /gbs/prod/clin/programs/im103/bia-renal/sur2010/scs/fda_request/rt-adiggl-thym-m36-v01.sas

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III. REVIEWER'S COMMENTS:

A. Regarding IgG Concentrations and/or Low IgG Levels as Biomarker:

1. In the Phase 3 trials, the protocol-specified timepoints for measurement of immunoglobulin (Ig) concentrations were Month 0 (baseline, prior to kidney transplant), and Months 6 and 12 post-transplant. Consistent with the sponsor's proposed labeling statement in Section 12.2 *Pharmacodynamics*, there were greater mean reductions from baseline in immunoglobulin (IgG, IgA, IgM) concentrations at Month 12 post-transplant in belatacept treated patients than in cyclosporine treated patients (Table 6); a similar conclusion can be reached for Month 6. At Month 6, there was higher proportion of belatacept MI patients than belatacept LI patients who were below the normal IgG concentration range (<694 mg/dL; Table 7). However, there were similar proportions of belatacept MI and belatacept LI patients who were below the normal range of IgM and IgA concentrations at Month 6.

Table 6 . Mean Change from Baseline Immunoglobulin Concentrations (mg/dL) at Month 6 and Month 12 post-transplant

TREATMENT	n	Month 6			n	Month 12		
		IgG	IgM	IgA		IgG	IgM	IgA
Cyclosporine								
Belatacept LI	328	-364	-32	-72	337	-350	-32	-80
Belatacept MI	323	-393	-30	-76	339	-344	-27	-77
Cyclosporine	318	-352	-2	-66	328	-291	+2	-58

Negative sign of the Ig concentration indicates decrease from baseline; plus sign indicates increase from baseline.

Table 7. Proportion (%) of Patients with Ig < LLN at Month 6

Treatment (RANDGRP)	↓ IgG	↓ IgM	↓ IgA	↓ IgG & IgM	↓ IgG, IgA, & IgM
Belatacept LI (n=328)	33	38	7.6	20	4.3
Belatacept MI (n=323)	43	38	6.2	22	4.0
Cyclosporine (n=318)	36	21	5.3	13	0.9

Ig < LLN: IgG < 694; IgM < 60; IgA < 68 mg/dL

2. Based on a scrutiny of the sponsor's analysis datasets, Ig concentrations were also measured at other times during the 36-month study period in small subsets of the patient population. Based on the similar numbers across treatment arms of patients included in each of these non-protocol specified timepoints, it is possible that patient selection for these unscheduled Ig concentration measurements was random rather than triggered by manifested adverse events. Overall, the mean/median IgG concentration-time profiles for the three treatments were consistent with the protocol-specified changes in the intensity of belatacept dosing and the actual mean trough concentrations of cyclosporine achieved during the 36-month duration of the Phase 3 trials.
3. In the original BLA submission, the sponsor's PD-response analysis focused on Month 12 immunoglobulin (i.e., IgG, IgM, IgA) concentration data, and only two clinical endpoints (i.e., serious infections and malignancies). The reviewer's exploratory PD-response analyses included both Month 6 and Month 12 immunoglobulin data and additional clinical endpoints. The reviewer decided to focus on IgG data at Month 6 as the main PD parameter because of the following reasons:
 - i. In belatacept patients, the reduction in IgG (not IgM and IgA) distinguished belatacept LI from belatacept MI (Table 7, Figure 3A).
In belatacept MI, the onset of HGG was earlier (before Month 3) than in belatacept LI and CsA (at or after Month 3); the duration of HGG was also longer in MI than in LI and CsA. After Month 3, the baseline IgG levels were restored at a faster rate in CsA patients than in belatacept LI and MI patients.
 - ii. IgG appears to be more sensitive than IgM and IgA to belatacept therapy (Figures 3A to 3C). Belatacept did not reduce IgM and IgA concentrations as much as it did IgG concentrations throughout the 36-month study period.
 - iii. IgG offers most plausible biological association to belatacept-related events because belatacept is a derivative of human IgG.
 - iv. IgG can be used potentially as a global biomarker of the level of total immunosuppression because CsA did not significantly reduce IgM concentrations from baseline, and neither belatacept nor CsA significantly reduced IgA concentrations from baseline (Figures 3A to 3C).
 - v. Stronger PD-response associations were observed when using IgG concentrations/levels at Month 6 versus Month 12. This observation is expected given the higher intensity of immunosuppression in patients during the first 6 months post-transplant.

Figure 3A. Time course of IgG concentrations, by treatment group

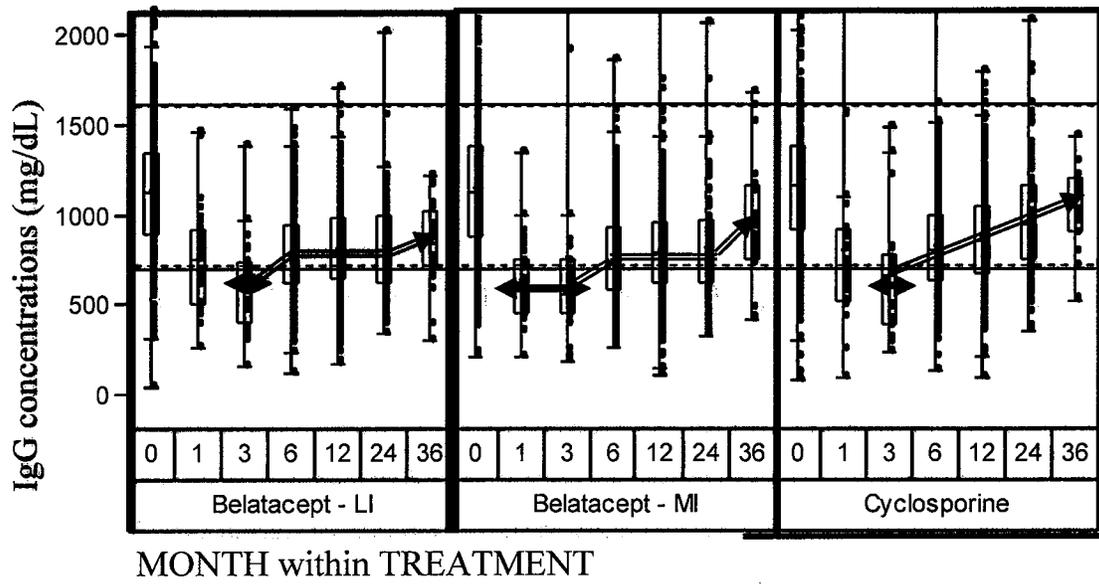


Figure 3B. Time course of IgM concentrations, by treatment group

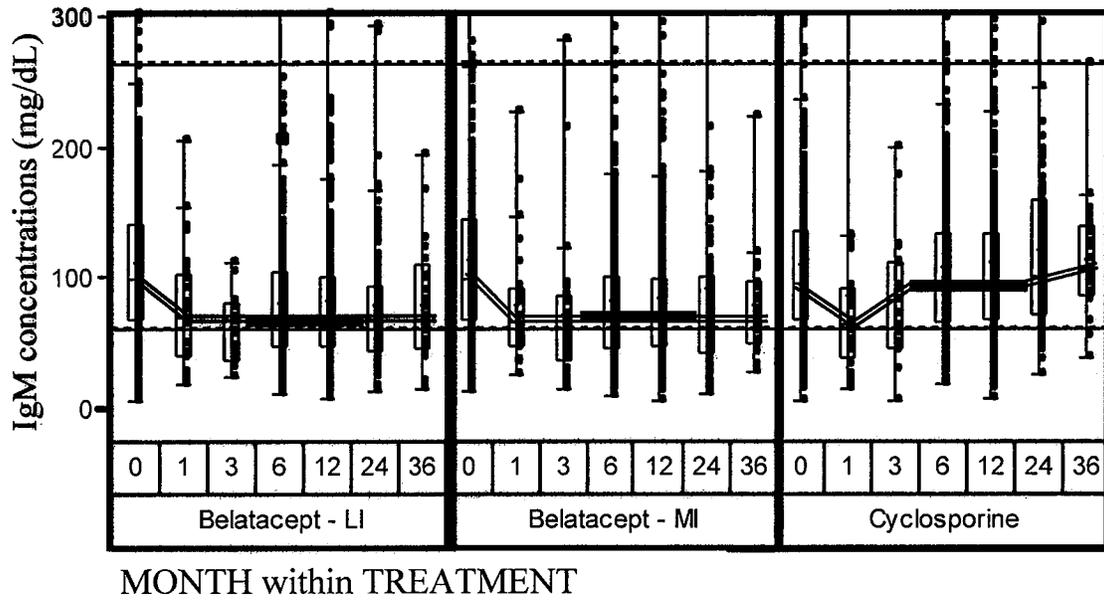
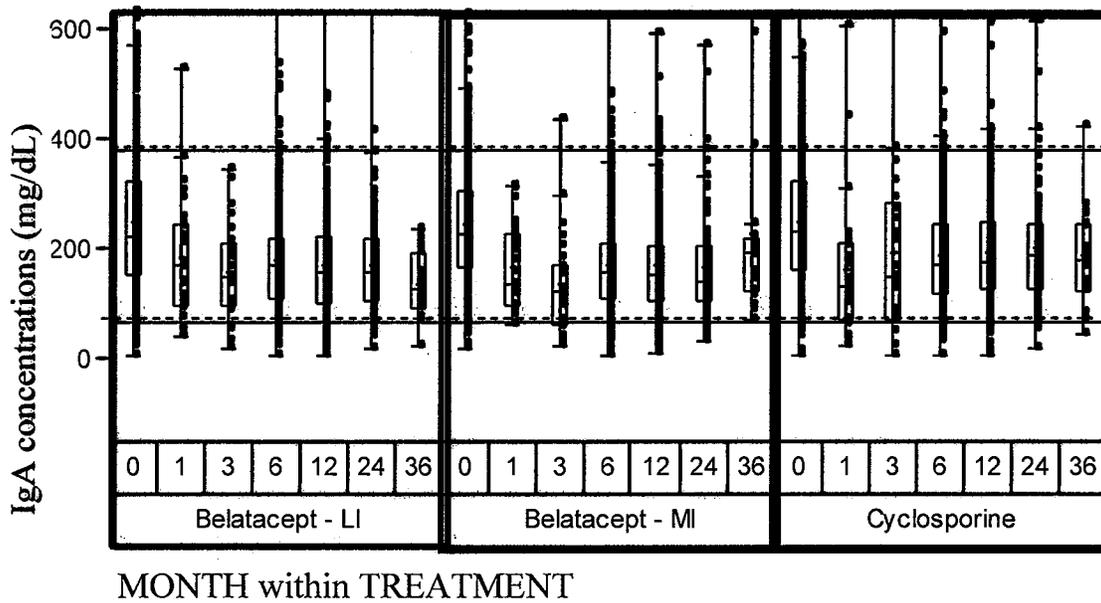


Figure 3C. Time course of IgA concentrations, by treatment group



The broken horizontal lines represent the normal limits of Ig concentrations.

Box and Whiskers plot: The horizontal line within the box represents the median value; the ends of the box represent the 25th and 75th percentiles. Data points outside the whiskers are outliers.

The numbers of patients included in the Ig concentration-time plots are shown in the table below.

Month	Number of patients included at each timepoint (n)		
	Belatacept LI	Belatacept MI	Cyclosporine
0	390	381	386
1	27	26	25
3	24	26	21
6	328	323	318
12	337	339	328
24	110	104	103
36	24	22	20

- The reviewer compared the three treatments and the various demographic and baseline characteristic subgroups within treatment, in terms of the incidence of hypogammaglobulinemia (HGG; IgG < 694 mg/dL). Table 8 shows the findings of univariate analysis for factors contributing to HGG at Month 6. Gender was not a significant covariate of HGG whereas there was a consistently (at least numerically) higher rate of HGG in Study 27 (versus Study 08), Whites (versus non-Whites), age > 60 years (versus age ≤ 60 years), EBV-seronegatives (versus EBV-seropositives), and CMV-seronegatives (versus CMV-seropositives). Of all the three treatments, belatacept MI is generally associated with the highest HGG rates. When considering the Chi-square p-values between the subgroups, belatacept LI was statistically comparable to cyclosporine, except with respect to the following subgroups: age > 60 years, CMV-negatives, and LDT-users. Additional analysis using multivariate modeling was performed; the factors included in the best-fit models are shown in Table 8A. Based on the Likelihood Ratio Test p-values, the following factors can be considered significant risk factors of HGG: Whites, CMV negative serostatus, and age > 60 years but not LDT use (for Bela LI);

Whites, Study ID, and EBV negative serostatus (for Bela MI); Whites (for cyclosporine)
 Note: The reviewer's covariate analyses findings were not provided to the sponsor.

Table 8. Incidence of Hypogammaglobulinemia (IgG<694 mg/dL) at Month 6 in Subgroups, by Treatment (% , n/N)

Covariate		Belatacept LI	Chi- square p-value	Belatacept MI	Chi- square p-value	Cyclosporine	Chi- square p-value
Phase 3 Study	IM103027	40 51/127	0.0075	48 63/132	0.0455	35 43/122	(NS)
	IM103008	26 44/172		34 55/161		26 43/164	
Race	Whites	40 76/191	<0.0001	51 89/176	<0.0001	35 67/189	0.0040
	Others	18 19/108		25 29/117		20 19/97	
Age (years)	> 60	49 27/55	0.0023	51 38/75	(NS)	39 27/70	(NS)
	≤ 60	28 68/244		37 80/218		27 59/216	
EBV serostatus	EBV- positive	32 84/266	(NS)	39 103/262	(NS)	30 75/252	(NS)
	EBV- negative	33 11/33		50 15/30		32 11/34	
CMV serostatus	CMV- positive	26 59/225	0.0009	38 84/220	(NS)	28 57/201	(NS)
	CMV- negative	49 36/73		47 34/72		34 29/85	
Lymphocyte Depleting Therapy Use	No	30 85/281	0.0254	40 105/265	(NS)	32 79/250	(NS)
	Yes	56 10/18		46 13/28		19 7/36	
Gender	Males	32 (66/206)	(NS)	41 (85/205)	(NS)	27 (57/210)	(NS)
	Females	31 (29/93)		38 (33/88)		38 (29/76)	

Table 8A. Multivariate Risk Factor Assessment for Hypogammaglobulinemia (HGG), by Treatment^a

TREATMENT	Source ^b	Likelihood Ratio Chi-Square	Likelihood ratio Prob>Chi Square
Belatacept LI	White	9.3989	0.0022*
	CMV negative serostatus ^c	10.7995	0.0010*
	Age > 60 years	7.5466	0.0060*
	LDT use	0.2435	0.6217
	White * LDT Use	3.7934	0.0515
Belatacept MI	White	19.6295	<0.0001*
	Study 27	3.8577	0.0495*
	EBV-negative serostatus ^c	3.9205	0.0477*
Cyclosporine	White	8.0235	0.0046*

^a JMP 9 Modeling, Personality: Nominal Logistic

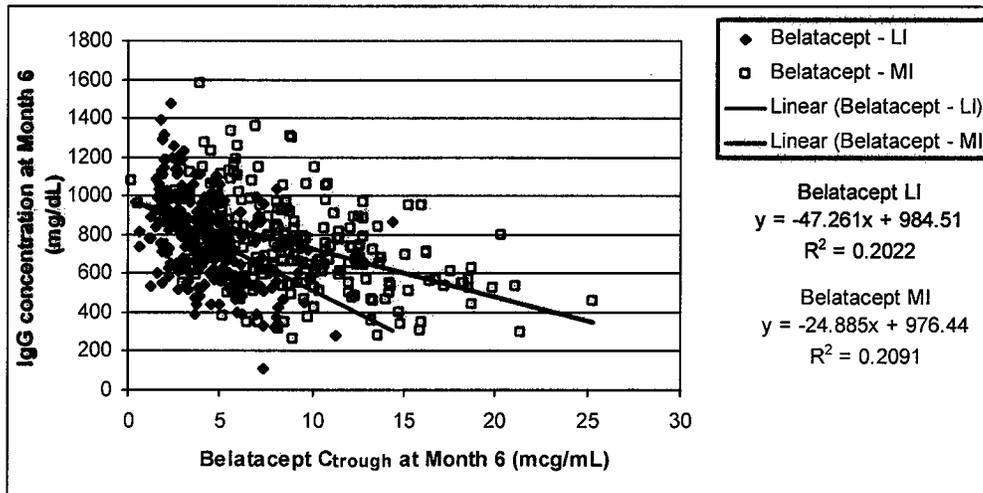
^b Factors included in the Best-Fit Model (model with the lowest objective function value)

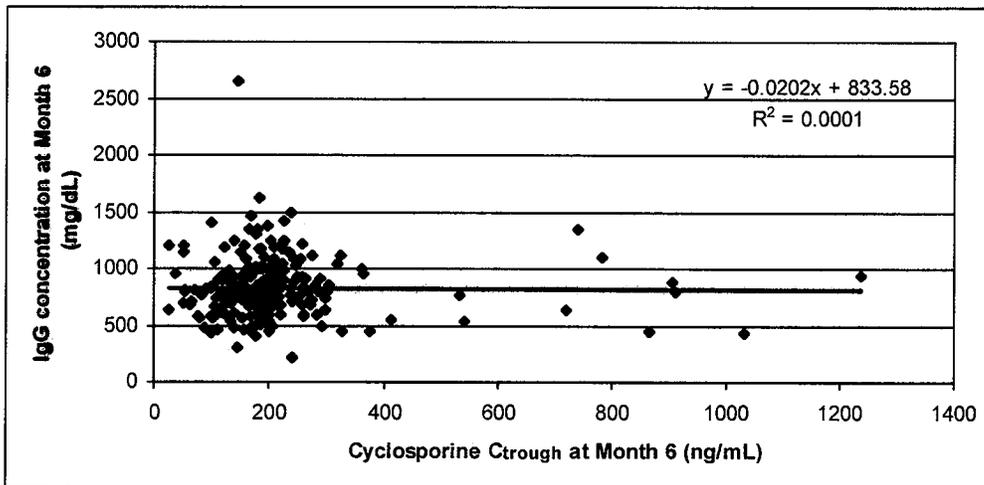
^c patients with unknown serostatus excluded

* p-value <0.05

5. Figure 4A and Figure 4B are linear plots of individual patient IgG concentrations at Month 6 as a function of belatacept trough concentrations at Month 6, and cyclosporine trough concentrations at Month 6, respectively. The reviewer's PK-PD plots suggest that with belatacept but not cyclosporine, there is a trend of decreasing IgG concentrations at Month 6 with decreasing trough concentrations at Month 6. Note: The reviewer's PK-PD findings were not provided to the sponsor.

Figures 4A and 4B. Linear plots of IgG concentrations at Month 6 as a function of belatacept or cyclosporine trough concentrations at Month 6 in Phase 3 trials





6. The three tables sent to the sponsor on 01 October 2010 were based on the reviewer's analyses including 711 patients with PK, IgG, and clinical response data. The PK (trough concentrations at Month 6) and the PD (IgG concentrations at Month 6) of belatacept and cyclosporine were considered along with the efficacy and safety endpoints up to Month 36 (or in the case of CNS events, up to database lock). To allow for a fair comparison with the sponsor's analysis findings, the reviewer performed further exploratory PD-response analyses on a larger population consisting of 878 patients who do not necessarily have belatacept trough concentrations at Month 6. Note that the results discussed in this review are those based on these subsequent analyses. Note also that the reviewer's analyses excluded patients with IgG < LLN at baseline because these patients have HGG prior to introduction of immunosuppressants, and it was assumed that they would be more susceptible to the adverse events associated with immunosuppressive therapy.
7. The reviewer envisions (low) IgG concentrations/level to be useful as a *pharmacodynamic (PD) biomarker* of the level of aggregate immunosuppression, not a surrogate endpoint of adverse events.
8. The reviewer acknowledges that it is difficult to find surrogate endpoints of death and other serious adverse events in kidney transplant patients because of multiple confounding factors that contribute to the AE. However, confidence on the predictive potential of low IgG concentrations/level as a PD biomarker should not be diminished by its low PPV because for events with low prevalence (<10%):
 - (a) a low PPV and a high NPV is expected, and
 - (b) the FDA Biomarkers group at the Office of Clinical Pharmacology gives more weight to other parameters, i.e., "sensitivity" and "specificity", when evaluating predictive potential of the biomarker.

Furthermore, the reviewer notes that based on the sponsor's proposed Nulojix® USPI, the PPVs of EBV-seronegative status as a prognostic biomarker of PTLD and CNS-PTLD are low, i.e., 7.7% and 5.5%, respectively.

9. The predictive potential of "low IgG" as a surrogate biomarker of adverse events could be further improved by combining with "low IgM" and "low IgA" (Table 9).

Table 9. Predictive Parameters of Biomarkers of CNS Events in Belatacept-Treated Patients^a

Biomarker	PPV	NPV	Sensitivity	Specificity	Likelihood Ratio (LR ^b)
a) EBV-negative	5.4% (5/93)	99% (574/581)	42% (5/12)	90% (574/639)	4.2
b) Low IgG	2.8% (7/251)	99% (395/400)	58% (7/12)	62% (395/639)	1.5
e) Low IgG & IgM	5.1% (7/137)	99% (509/514)	58% (7/12)	80% (509/639)	2.9
f) Low Ig G,A,&M	7.4% (2/27)	98% (614/624)	17% (2/12)	96% (614/639)	4.3

^a does not exclude patients with low Ig concentrations at baseline

^b LR= (sensitivity)/(1-specificity)

10. For each clinical endpoint of interest, the reviewer presents the following data to summarize the findings of the exploratory PD-response analysis for belatacept: a) logistic regression plot of the event with a binary outcome (absent or present; 0 or 1) as a function of the IgG concentrations at Month 6, or linear regression plot of continuous variable (e.g., GFR) as a function of IgG concentrations, and b) table summarizing the event rates in HGG versus NGG subgroups.

a. Acute Rejection (AR)

In the reviewer's analysis, AR was associated with decreased IgG concentrations (Figure 5). There was about a 2-fold higher incidence of acute rejections in the HGG group than in the NGG group (Table 10). Majority of these acute rejection episodes occurred prior to Month 6. Because the protocol did not specify the collection of Ig concentrations between Months 0 and 6, it was not possible for the reviewer to perform time-dependent analyses to verify any direct causal association of HGG to acute rejections. However, further exploratory analysis was performed to evaluate the influence of concomitant use of supplementary immunosuppressive products for the treatment of acute rejection on IgG concentrations. Figure 6 shows that belatacept patients who were treated with concomitant pulse steroids and lymphocyte depleting therapy during the first 6 months post-transplant to treat their acute rejection episodes had lower IgG concentrations at Month 6 than those patients who did not receive concomitant therapy, considering a similar range of belatacept trough concentrations at Month 6 between the two groups. Thus, the observed association between acute rejections and IgG concentrations at Month 6 could be explained, at least in part, by the use of supplementary immunosuppressive products to treat acute rejection. This separation of PK-PD profiles according to use of concomitant therapy for acute rejection was not similarly observed in the cyclosporine arm, although it is important to note that the incidence of acute rejections was about 50% lower in the cyclosporine arm than in the belatacept arms.

Figure 5. Acute Rejection as a function of log-transformed IgG concentrations at Month 6

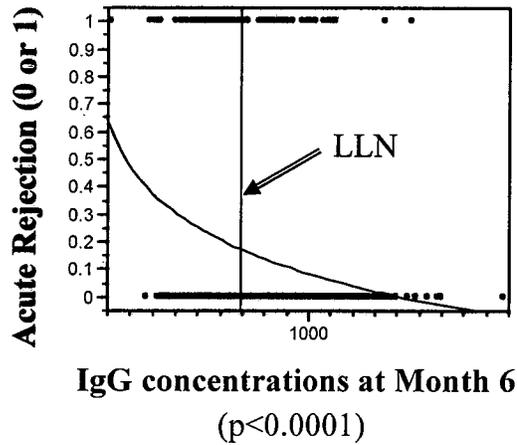
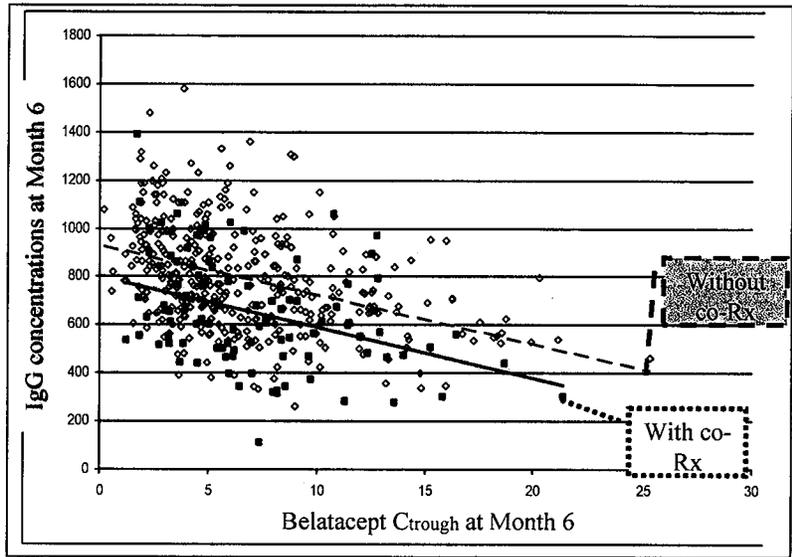


Table 10. Proportion of Patients with Acute Rejection up to Month 36 – n/N (%)

TREATMENT	HGG (IgG<694 mg/dL)	NGG (IgG =694-1618 mg/dL)	Reviewer's HGG/NGG ratio	Sponsor's HGG/NGG ratio
Bela LI	19/95 (20%)	20/204 (10%)	2.0	(Not determined)
Bela MI	29/118 (25%)	22/174 (13%)	1.9	(Not determined)
CsA	14/86 (16%)	15/198 (8%)	2.0	(Not determined)

Figure 6. IgG concentrations as a function of Belatacept trough concentrations (Month 6)



Co-Rx (Co-therapy): pulse steroids and/or lymphocyte-depleting therapy used during 1st 6 month post-transplant

b. CNS Events

In the reviewer’s analysis, decreasing IgG concentrations at Month 6 were associated with increasing incidence of CNS PTLD, PML and other CNS infections (Figure 7). The incidence of these CNS events in the belatacept LI and MI arms was higher in the HGG group than in the NGG group (Table 11). In the sponsor’s analysis, there was an impact of HGG in belatacept MI but not in LI because the sponsor considered CNS events up to Month 36 only whereas the reviewer considered events up to database lock; the sponsor has only 1 case of CNS Event in the HGG group whereas the reviewer has 2 cases.

Figure 7 . CNS Events as a function of log-transformed IgG concentrations at Month 6

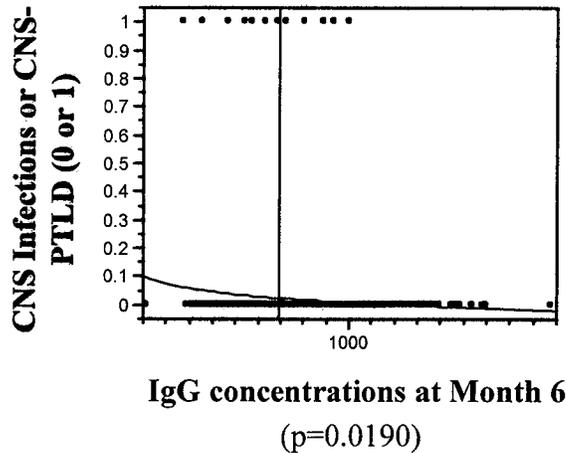


Table 11. Proportion of Patients with CNS Events up to database lock (or Month 36) – n/N (%)

TREATMENT	HGG (IgG<694 mg/dL)	NGG (IgG =694-1618 mg/dL)	Reviewer's HGG/NGG ratio	Sponsor's HGG/NGG ratio
Bela LI	2/95 (2.1%)	2/204 (1.0%)	2.1	1.0
Bela MI	5/118 (4.2%)	3/174 (1.7%)	2.5	3.1
CsA	0/86 (0%)	0/198 (0%)	(Not determined)	(Not determined)

In a similar analysis of CNS events including CNS-PTLD and PML only, similar conclusions regarding the impact of low IgG concentrations can be made (Figure 7A and Table 11A).

Figure 7A . CNS PTLD and PML as a function of log-transformed IgG concentrations at Month 6

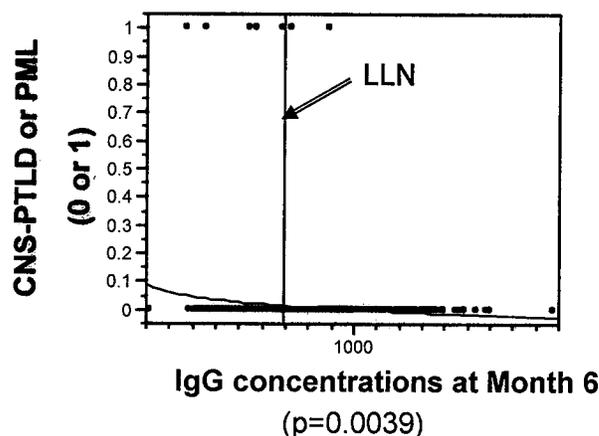


Table 11A. Proportion of Patients with CNS PTLD and PML up to database lock – n/N (%)

TREATMENT	HGG (IgG<694 mg/dL)	NGG (IgG =694-1618 mg/dL)	Reviewer's HGG/NGG ratio
Bela LI	1.1 (1/95)	0.5 (1/204)	2.2
Bela MI	3.4 (4/118)	0.6 (1/174)	5.9
CsA	0 (0/86)	0 (0/198)	-

Table 12 provides a comparison of HGG versus NGG subgroups in each treatment, by type of CNS event. Based on the findings summarized in this table, EBV-seronegative status is an independent risk factor of CNS-PTLD. The data also demonstrate that reductions in IgG below the LLN, with or without corresponding reductions in IgM and IgA, could contribute to the development of CNS-PTLD and CNS infections in kidney transplant patients receiving belatacept-based immunosuppressive therapy. Individual IgG concentration-time profiles of the patients who developed CNS-PTLD or PML during belatacept therapy are shown in Figures 8A to 8C. Of note, the lone case of PML had what appears to have been persistent panhypogammaglobulinemia, i.e., IgG, IgA, IgM <LLN at both Months 6 and 12 posttransplant; at Month 24, IgG and IgM concentrations were <LLN whereas the IgA concentration (70 mg/dL) was still very close to LLN (68 mg/dL). It is also important to note for this PML case that at baseline, both IgG and IgM were already either close to or <LLN. However, the reviewer's logistic regression analysis does not suggest that IgG concentration at baseline is associated with the incidence of CNS-PTLD and PML events in belatacept treated patients.

Table 11. Proportion of Patients with PTLD, CNS-PTLD, and CNS infections in Phase 3 trials - n/N (%)

Treatment Group	IgG Level at Month 6	PTLD	CNS-PTLD	PML	CNS Infections ^d
Belatacept Less-Intensive (LI) and More-Intensive (MI)	Normal Range (694 – 1618 mg/dL)	0.5 (2/378)	0.5 (2/378)	0 (0/378)	0.8 (3/378)
	Below LLN (< 694 mg/dL)	2.3 (5/213)	1.9 (4/213)	0.5 (1/213)	1.4 (3/213)
	Above ULN (> 1618 mg/dL)	0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)
Belatacept Less-Intensive (LI)	Normal Range (694 – 1618 mg/dL)	0.5 (1/204) ^e	0.5 (1/204) ^e	0 (0/204)	0.5 (1/204) ^m
	Below LLN (< 694 mg/dL)	2.1 (2/95) ^{f,g}	1.1 (1/95) ^f	0 (0/95)	1.1 (1/95) ⁿ
	Above ULN (> 1618 mg/dL)	-	-	-	-
Belatacept More-Intensive (MI)	Normal Range (694 – 1618 mg/dL)	0.6 (1/174) ^h	0.6 (1/174) ^h	0 (0/174)	1.1 (2/174) ^{o,p}
	Below LLN (< 694 mg/dL)	2.5 (3/118) ^{ij,k}	2.5 (3/118) ^{ij,k}	0.9 (1/118) ^l	1.7 (2/118) ^{l,q}
	Above ULN (> 1618 mg/dL)	0 (0/1)	0 (0/1)	0 (0/1)	0 (0/1)
Cyclosporine	Normal Range (694 – 1618 mg/dL)	0 (0/198)	0 (0/198)	0 (0/198)	0 (0/198)
	Below LLN (< 694 mg/dL)	0 (0/86)	0 (0/86)	0 (0/86)	0 (0/86)
	Above ULN (> 1618 mg/dL)	0 (0/2)	0 (0/2)	0 (0/2)	0 (0/2)

LLN: Lower Limit of Normal Range; ULN: Upper Limit of Normal Range

^a Post-Transplant Lymphoproliferative Disease

^b CNS-associated Post-Transplant Lymphoproliferative Disease

^c Progressive Multifocal Leukoencephalopathy

^d CNS infections including PML

^e CNS-PTLD: EBV-positive patient; Normal but low IgG (=712 mg/dL) at Month 6; also, IgM<LLN at Month 6 (27-101-10093)

^f CNS-PTLD: EBV-negative patient; IgG and IgM<LLN at Months 6 & 9 (27-138-10593)

^g PTLD: EBV-positive patient; IgG<LLN at Month 6 (8-122-20256)

^h CNS-PTLD: EBV-negative patient (8-142-20548)

ⁱ CNS-PTLD: EBV-positive patient; IgG and IgM<LLN at Month 6 (8-76-20734)

^j CNS-PTLD: EBV-positive patient; IgG, IgM, and IgA<LLN at Month 6; IgG and IgM<LLN at Month 12 (27-35-10185)

^k CNS-PTLD: EBV-negative; IgG and IgM<LLN at Months 6 & 9 (27-70-10447)

^l lone case of PML: EBV-negative patient; IgG, IgM, and IgA<LLN at Months 6 and 12 (27-15-10045)

^m Cryptococcal meningitis (fungal infection) at Week 72: EBV-positive patient; Normal IgG at Month 6 but IgG<LLN at Month 19 (day 535); IgM <LLN at Month 6 and Month 12 (8-73-20006)

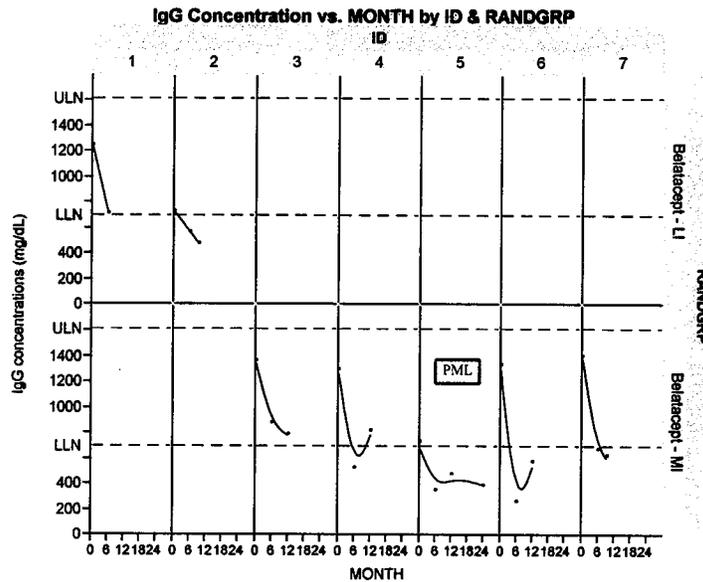
ⁿ unspecified CNS infection: EBV-negative patient; IgG<LLN at Month 6; IgM<LLN at Months 6 and 12 (27-124-10466)

^o Chagas meningoencephalitis at Week 74, cryptococcal meningitis at Week 80 (protozoal and fungal infections): EBV-positive patient; Normal IgG at Month 6 but IgG and IgM <LLN at Month 12 (8-46-20152)

^p Meningitis with unspecified pathogen at Week 24: EBV-positive patient (8-73-20192)

^q Cerebral aspergillosis at Week 84: EBV-positive patient; IgG and IgM<LLN at Months 6 and 12 (27-13-10047)

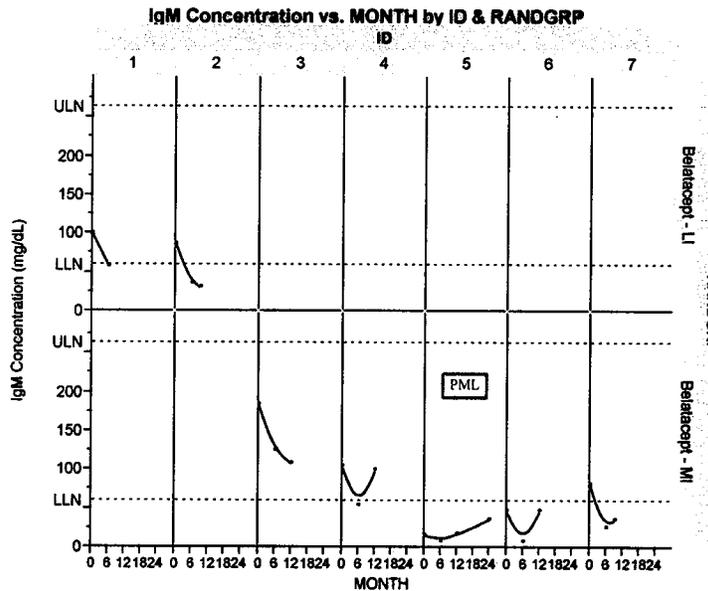
Figure 8A. Individual IgG concentration-time profiles of Phase 3 trial patients who developed CNS-PTLD or PML up to database lock



NOTES (IgG):

- LLN: Lower Limit of Normal Range (694 mg/dL); ULN: Upper Limit of Normal (1618 mg/dL)
- Only Patients #1 and #2 received belatacept LI; the remaining 5 patients received belatacept MI.
- Patient #5 was the lone case of PML in the belatacept Phase 3 trials. This patient had IgG close to LLN at baseline and persistent hypogammaglobulinemia during belatacept MI therapy, i.e., IgG <LLN at Months 6, 12 and 24 post-transplant.
- Although Patient #3 did not develop IgG <LLN at Months 6 and 12 post-transplant, this patient was EBV-seronegative at baseline.
- Patient ID: 1 (8-142-20548); 2 (8-76-20734); 3 (27-101-10093); 4 (27-138-10593); 5 (27-15-10045); 6 (27-35-10185); 7 (27-70-10447)

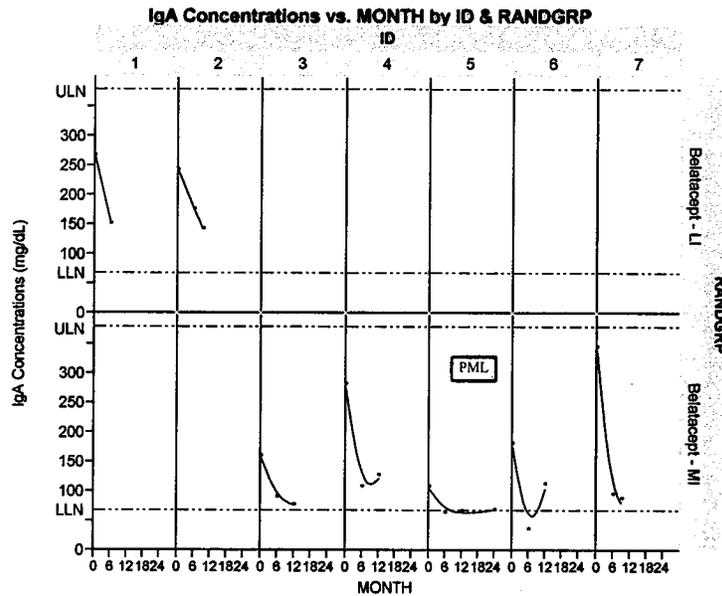
Figure 8B. Individual IgM concentration-time profiles of Phase 3 trial patients who developed CNS-PTLD or PML up to database lock



NOTES (IgM):

- LLN: Lower Limit of Normal Range (60 mg/dL); ULN: Upper Limit of Normal (263 mg/dL)
- Only Patients #1 and #2 received belatacept LI; the remaining 5 patients received belatacept MI.
- Patient #5 was the lone case of PML in the belatacept Phase 3 trials. This patient had IgM <LLN status starting at baseline and during belatacept MI therapy.
- Although Patient #3 did not develop IgM <LLN at Months 6 and 12 post-transplant, this patient was EBV-seronegative at baseline.
- Patient ID: 1 (8-142-20548); 2 (8-76-20734); 3 (27-101-10093); 4 (27-138-10593); 5 (27-15-10045); 6 (27-35-10185); 7 (27-70-10447)

Figure 8C. Individual IgA concentration-time profiles of Phase 3 trial patients who developed CNS-PTLD or PML up to database lock

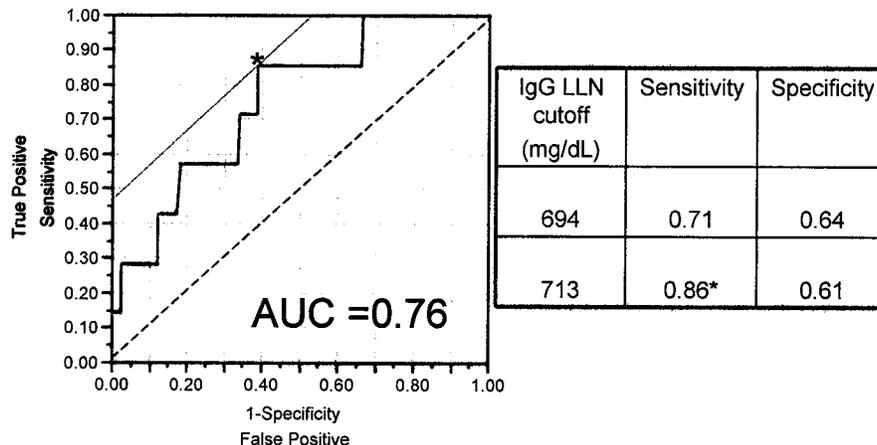


NOTES (IgA):

- LLN: Lower Limit of Normal Range (68 mg/dL); ULN: Upper Limit of Normal (378 mg/dL)
- Only Patients #1 and #2 received belatacept LI; the remaining 5 patients received belatacept MI.
- Patient #5 was the lone case of PML in the belatacept Phase 3 trials. This patient had IgA close to LLN during belatacept MI therapy.
- Patient ID: 1 (8-142-20548); 2 (8-76-20734); 3 (27-101-10093); 4 (27-138-10593); 5 (27-15-10045); 6 (27-35-10185); 7 (27-70-10447)

Given that belatacept will be contraindicated in patients with EBV-negative or unknown serostatus at baseline, it is important to note that of the four CNS-PTLD cases in this analysis who were EBV-seropositive at baseline, three had IgG < 694 mg/mL at Month 6; the 4th of 4 cases had IgG concentration (712 mg/mL) close to the protocol-specified LLN. Consequently, the reviewer's Receiver Operating Characteristics (ROC) analysis results suggest that a more appropriate cutoff for LLN of IgG concentrations as a predictive parameter of PTLD or CNS-PTLD is 713 mg/dL rather than 694 mg/dL (Figure 9).

Figure 9. Receiver Operating Characteristic Curve for Low IgG Concentrations as a Predictor of CNS-PTLD and PML



c. Malignancies

In belatacept patients, decreasing IgG concentrations at Month 6 were associated with increasing incidence of malignancies (Figure 10). In all three treatments, the incidence of malignancies was higher in the HGG group than in the NGG group (Table 13). In the belatacept LI group, the difference in the Reviewer's and the Sponsor's HGG/NGG ratios could be explained by the higher number of malignancy cases in the NGG group of the reviewer (n=8) versus that of the sponsor's (n=4).

Figure 10. Malignancies as a function of log-transformed IgG concentrations at Month 6

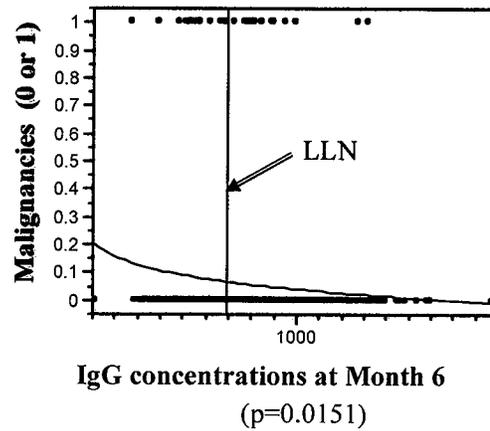


Table 13. Proportion of Patients with Malignancies up to Month 36 – n/N (%)

TREATMENT	HGG (IgG<694 mg/dL)	NGG (IgG =694-1618 mg/dL)	Reviewer's HGG/NGG ratio	Sponsor's HGG/NGG ratio
Bela LI	6/95 (6.3%)	8/204(3.7%)	1.6	3.8
Bela MI	14/118 (11.9%)	8/174 (4.6%)	2.6	2.3
CsA	10/86 (10.5%)	12/198 (6.1%)	1.7	1.3

d. Serious Infections

The incidence of serious infections increased with decreasing IgG concentrations at Month 6 (Figure 11). The Reviewer's and the Sponsor's HGG/NGG ratios were comparable (Table 14). That there was only a $\leq 50\%$ higher incidence of serious infections in the HGG group versus the NGG group could be explained by the use of protocol-specified chemoprophylactic antimicrobials in the Phase 3 trials.

Figure 11. Serious Infections as a function of log-transformed IgG concentrations at Month 6

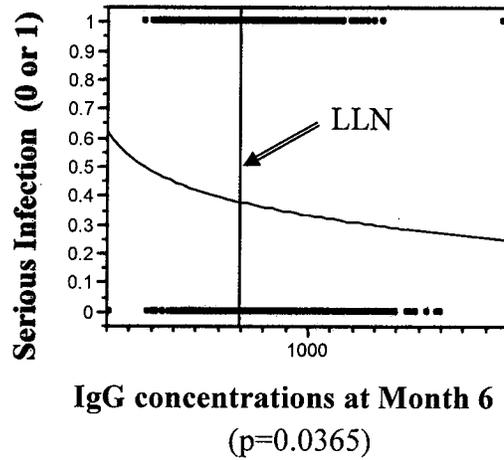


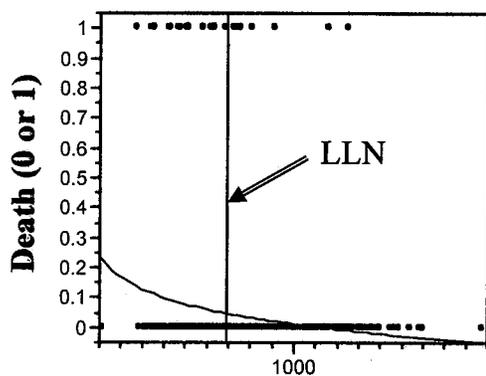
Table 14. Proportion of Patients with Serious Infections up to Month 36 – n/N (%)

TREATMENT	HGG (IgG < 694 mg/dL)	NGG (IgG = 694-1618 mg/dL)	Reviewer's HGG/NGG ratio	Sponsor's HGG/NGG ratio
Bela LI	38/95 (40%)	61/204 (30%)	1.3	1.4
Bela MI	55/118 (47%)	63/174 (36%)	1.3	1.5
CsA	39/86 (45%)	(74/198 (36%))	1.2	1.2

e. Death

In belatacept patients, decreased IgG concentrations at Month 6 were associated with a higher incidence of death (Figure 12). The Reviewer's and the Sponsor's HGG/NGG ratios were comparable; the incidence of death in all three treatment arms were higher in the HGG group than in the NGG group (Table 15). The reviewer acknowledges the sponsor's conclusion that the causal relationship between HGG and death would be very difficult to establish because of the multiple factors that could have contributed to this adverse outcome. However, the reviewer notes that about 52% (12/23) of the deaths in the Phase 3 trials were adjudicated to be primarily due to infections, malignancies or endocarditis (sepsis); the corresponding rates were 57% (4/7) for LI, 56% (5/9) for MI, and 43% (3/7) for CsA.

Figure 12. Death as a function of log-transformed IgG concentrations at Month 6



IgG concentrations at Month 6
($p < 0.0001$)

Table 15. Proportion of Patients who Died up to Month 36 – n/N (%)

TREATMENT	HGG (IgG < 694 mg/dL)	NGG (IgG = 694-1618 mg/dL)	Reviewer's HGG/NGG ratio	Sponsor's HGG/NGG ratio
Bela LI	8/95 (8.4%)	3/204 (1.5%)	5.7	5.5
Bela MI	7/118 (6%)	5/174 (3%)	2.1	2.0
CsA	4/86 (5%)	9/198 (4%)	1.0	1.6

f. Graft Loss

The reviewer did not find an association between graft loss and HGG. Infection or malignancy was the primary cause of death in 16% (13/83) of graft loss cases up to Month 36 in Phase 3 trials.

g. Renal Function (as change from baseline calculated GFR at Month 12; delta cGFR)

In the reviewer's analysis, lower renal function at Month 12 was associated with lower IgG concentrations at Month 6 (Figure 13). The renal function was lower in the HGG group versus the NGG group in the belatacept LI and MI arms but not in the cyclosporine treatment arm (Table 16). The lack of an impact of HGG on cyclosporine could probably be explained by CsA-associated nephrotoxicity. The sponsor did not explore the relationship between HGG at Month 6 and renal function because GFR is not a binary outcome variable.

A potential link between lower GFR and HGG is BK virus-associated nephropathy (BKVAN) or polyomavirus-associated nephropathy (PVAN). BK virus has tropism for renal epithelial cells, and BKVAN or PVAN is a known contributory factor to deteriorating renal function in kidney transplant patients. In the small number (n=13) of belatacept patients who were reported to have developed PVAN, 7 had IgG concentrations measured at Month 6. There was a trend of decreasing times to PVAN in patients with decreasing IgG concentrations at Month 6 (Figure 14). Furthermore, the mean/median time to PVAN was shorter in the HGG group than in the NGG group (Table 17).

Figure 13. Change from baseline calculated GFR at Month 12 as a function of IgG concentrations at Month 6

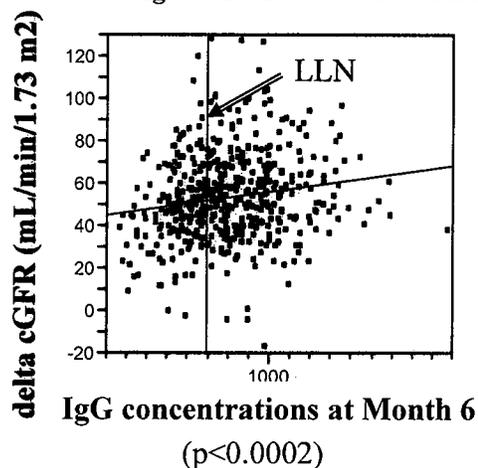


Table 16. Mean \pm SD (Median) Change from Baseline Calculated GFR at Month 12 (mL/min/1.73 m²)

TREATMENT	HGG (IgG<694 mg/dL) n=72	NGG (IgG =694-1618 mg/dL) n=172	Reviewer's HGG/NGG difference	Sponsor's HGG/NGG difference
Bela LI	50 \pm 16 (48)	55 \pm 20 (55)	-5 (-7)	(Not determined)
Bela MI	47 \pm 21 (48)	56 \pm 22 (55)	-9 (-7)	(Not determined)
CsA	42 \pm 18 (43)	42 \pm 18 (40)	0 (+1)	(Not determined)

Figure 14. Time to BK Virus Associated Nephropathy (BKVAN) as a function of IgG concentrations at Month 6

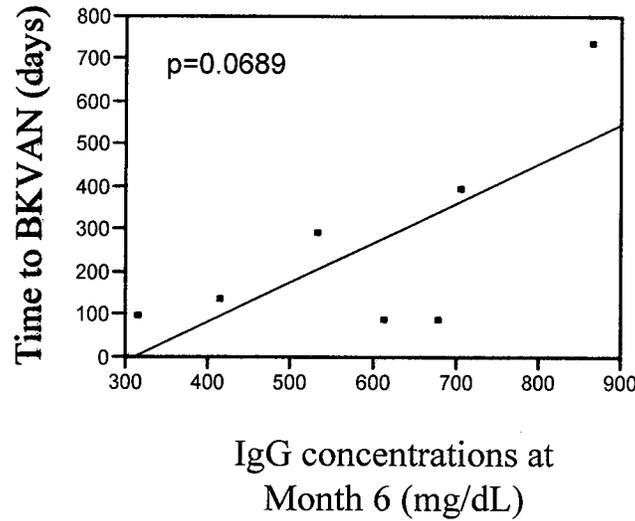


Table 17. Time to BK Virus Associated Nephropathy, by HGG status

	Time to BKVAN (days)		
	n	Mean ± SD	Median
HGG	5	137 ± 87	95
NGG	2	562 ± 24	562

To further explore the link between renal function and HGG, the effect of serious infections on renal function was evaluated. The mean change from baseline cGFR-MDRD at Month 12 was lower by 7 – 10 mL/min/1.73 m² in patients with serious infections than those who did not develop serious infections within the first 12 months of therapy. The corresponding mean cGFR-MDRD values for HGG versus NGG were 48 versus 56 mL/min/1.73 m² in LI, 45 versus 55 mL/min/1.73 m² in MI, and 38 versus 45 mL/min/1.73 m² in CsA.

The following table compares the incidence of hypogammaglobulinemia at Month 6 in patients with CNS events or other types of serious infections or malignancies versus those patients who did not experience these adverse events.

Table 18. Proportion of Patients with Low IgG¹ at Month 6, by Adverse Event Status (% , n/N)

	Adverse Event Status (0 or 1) ²	Low IgG (% , n/N)		
		Belatacept Non-Recommended ³ Regimen	Belatacept Recommended Regimen	Cyclosporine
CNS event ⁴ or other Serious Infection/Malignancy	0	35 (57/164)	28 (54/191)	26 (42/162)
	1	48 (61/128)	38 (41/108)	36 (44/122)
CNS Event only	0	40 (113/284)	32 (93/295)	30 (86/284)
	1	63 (5/8)	50 (2/4)	0
Serious Infection only (includes PML and other CNS infections)	0	36 (63/174)	29 (57/200)	27 (47/173)
	1	47 (55/118)	38 (38/99)	35 (39/111)
Malignancy only (includes CNS-PTLD)	0	39 (104/270)	31 (89/285)	29 (77/263)
	1	64 (14/22)	43 (6/14)	43 (9/21)

¹ IgG < 694 mg/dL

² 0: did not experience the adverse event; 1: experienced the adverse event

³ regimen with higher cumulative dose and more frequent dosing than the recommended NULOJIX regimen

⁴ CNS event includes CNS-PTLD, PML, and other CNS infections up to database lock

B. Regarding the Impact of Concomitant Immunoglobulin Use on Belatacept PK, Efficacy and Safety in the Phase 3 Trials:

1. In response to the Clinical Pharmacology reviewer's information request, the sponsor conducted exploratory analyses to evaluate the impact of concomitant use of immunoglobulin antibody products on belatacept trough concentrations and on belatacept efficacy and safety. According to the sponsor, thymoglobulin was the most frequently (~75%) used concomitant antibody product in Phase 3 trials.
2. Sponsor's Figures 2A and 2B show that concomitant use of immunoglobulin products did not affect belatacept trough concentrations in the Phase 3 trials.
3. Sponsor's Table 5 shows that although the frequency of serious infections was not influenced by concomitant use of thymoglobulin (in all three treatments), for those who received thymoglobulin there was an increased frequency of CNS events (in belatacept MI) and malignancies (in belatacept LI), events associated with over-immunosuppression. Additionally, although the sponsor recognizes that there was a lower mean and median GFR and a higher frequency of death and graft loss in patients who used thymoglobulin, the sponsor suggests that these associations could be explained by the observed impact of acute rejections on renal function and graft survival. The sponsor concluded that definitive interpretation of the findings of this exploratory analysis (e.g., in the context of death) is precluded by the small numbers of events and numerous confounding variables such as other concomitant therapies and co-morbidities (e.g., diabetes, hypertension, and infections). The reviewer notes that ~50% of the deaths in each of the three treatments in the Phase 3 trials were adjudicated to be caused primarily by infections, malignancies, and cardiovascular sepsis.
4. The sponsor did not explore the impact of concomitant therapy with intravenous immunoglobulins (IVIg) on the efficacy and safety of belatacept, likely because of the low number (n=5) of patients who used IVIg exclusively for the treatment of their acute rejection episodes. The reviewer notes that none of these 5 patients developed CNS-associated PTLD or infections.

III. REVIEWER'S CONCLUSIONS:

1. In addition to the main immunosuppressive regimen, several baseline (e.g., age >60 years) and post-transplant factors (e.g., LDT use for treatment of acute rejection) could contribute to low Ig concentrations in kidney transplant patients treated with belatacept.
2. IgG concentration is a potential pharmacodynamic biomarker of the level of aggregate immunosuppression in belatacept-treated patients.

Lines of Evidence:

- a) Greater reduction from baseline in mean IgG concentrations and greater proportion of patients with shift to IgG<LLN in MI than LI at Month 6
- b) IgG-time profile reflects the time course of belatacept dosing, i.e., highest IgG concentration at Month 0, lowest between Months 1-3.

- c) Trend of decreasing IgG concentration with increasing belatacept trough concentrations at Month 6
 - d) Lower IgG concentrations in belatacept patients who received co-treatment with thymoglobulin/steroids than those who did not receive supplementary immunosuppressives
3. IgG level may be a useful pharmacodynamic marker for identifying belatacept treated patients who are over-immunosuppressed, i.e., at risk for opportunistic infections, malignancies, and complications (e.g. death). That IgG concentrations/levels could also influence the adverse event rates in transplant patients receiving cyclosporine and other immunosuppressive regimens should be further explored.
 4. The benefits of pre-emptive Ig replacement therapy (e.g., with IVIg) in alleviating the risks of HGG in belatacept-treated patients is not known.

IV. REVIEWER'S RECOMMENDATIONS:

1. The Nulojix® USPI should describe the potential of belatacept to decrease immunoglobulin (i.e., IgG, IgA, IgM) concentrations relative to cyclosporine. The labeling should also provide a factual representation of the impact of IgG reductions on the therapeutic outcomes in Phase 3 trials, with the appropriate caveats. As an alternative to describing the impact of low IgG on the incidence of adverse events, the incidence of low IgG could be compared in patients with and without adverse events.
2. Based on several lines of preliminary evidence from the reviewer's exploratory analyses, IgG concentration is a potential pharmacodynamic biomarker of the level of total or aggregate immunosuppression in belatacept treated patients. The sponsor should collect additional information in ongoing/future clinical trials to better understand the impact of low IgG concentrations on the risk of PTLD/CNS-PTLD and other serious adverse events in belatacept treated patients.

B. Clinical Pharmacology Review of the Protocol of Sponsor's Proposed Post-Marketing Study IM103075ST (SN-063 submitted 13 December 2010)

I. PROTOCOL SYNOPSIS

Title of Study: Belatacept and risk of PTLD in US Renal Transplant Recipients

Department: Global Pharmacovigilance and Epidemiology

Study Objective(s):

Primary Objectives:

(1) to estimate the incidence rate of post-transplant lymphoproliferative disorder (PTLD) in adult kidney-only transplant recipients treated with belatacept at the time of transplantation, (2) to estimate the incidence rate of PTLD in adult kidney-only transplant recipients treated with calcineurin inhibitors (CNI)-based regimens at the time of transplantation, and (3) to compare the PTLD incidence rate in patients treated with belatacept to the rate in similar patients treated with CNI-based regimens at the time of transplantation.

(b) (4)

Study Design: The study will be a prospective observational study that utilizes data from the United Network for Organ Sharing (UNOS).

(b) (4)

(b) (4)

(b) (4)

II. REVIEWER'S RECOMMENDATION:

In this observational post-marketing study, the type and the duration of antibody induction medications and other concomitant anti-rejection and maintenance immunosuppressive medications will be recorded. The type and the duration of antiviral and other antimicrobial prophylaxis used in the study should be also recorded. The assessment of these concomitant therapies as independent risk factors of PTLD and CNS-PTLD development should be included as an official secondary study objective of the protocol.

Clinical Pharmacology Review

BLA: STN 125288	Submission Date(s): 01 July 2009
Brand Name (proposed)	Nulojix™
Generic Name	Belatacept
Clinical Pharmacology Reviewer(s)	Gerlie Gieser, Ph.D.; Seong H. Jang, Ph.D.
Clinical Pharmacology Team Leader	Philip Colangelo, Pharm.D., Ph.D.
Pharmacometrics Reviewer	Jiang Liu, Ph.D.; Seong H. Jang, Ph.D.
Pharmacometrics Team Leader	Pravin Jadhav, Ph.D.
Pharmacogenomics Reviewer	Shashi Amur, Ph.D.; Li Zhang, Ph.D.
Pharmacogenomics Team Leader	Issam Zineh, Pharm.D., MPH
OCP Division	Division of Clinical Pharmacology IV
Clinical Division	Division of Special Pathogen and Transplant Products
Sponsor	Bristol-Myer Squibb
Relevant IND(s)	BB-IND 009,418
Submission Type; Code	NME, Standard Review
Formulation; Strength(s)	Lyophilized Powder for IV infusion (250 mg single use vial) for reconstitution to 25 mg/mL
Proposed Indication	Prophylaxis of organ transplant rejection and preservation of functioning allograft in adult renal transplant recipients
PDUFA Date	01 May 2010

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1. Executive Summary

Belatacept is a genetically engineered fusion protein that consists of the functional binding domain of modified cytotoxic T-lymphocyte antigen-4 (CTLA-4) and the Fc domain of human monoclonal immunoglobulin of the IgG₁ subclass. Belatacept is a selective costimulation blocker with a proposed indication of prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving kidney transplants. Belatacept has been studied as a replacement for the calcineurin inhibitor, cyclosporine, to be used in combination with an interleukin-2 (IL-2) receptor antagonist (e.g., basiliximab), mycophenolic acid (MPA; e.g., mycophenolate mofetil (MMF)), and corticosteroids.

1.1. Recommendations

Overall, the clinical pharmacology information presented in this BLA is acceptable to support the approval of belatacept for the proposed indication of prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving kidney transplants.

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.

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 trials 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 antiviral 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. It should be noted that this recommendation is not a Post-Marketing Requirement at this time because a Complete Response (CR) action will be taken for BLA 125288 for belatacept during this review cycle.

1.2. Post Marketing Requirement/Commitment

In light of the Complete Response (CR) action for BLA 125288 for belatacept during this review cycle, 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. We note that the sponsor has already proposed a post marketing trial to study PTLT in belatacept-treated kidney transplant patients (Protocol No: IM103075ST). We recommend the sponsor evaluate the impact of CMV serostatus on PTLT risk in belatacept-treated patients as a secondary objective in the

proposed post marketing trial.

1.3 Clinical Pharmacology Findings

The clinical development program of belatacept included 21 clinical trials with clinical pharmacology information for both the belatacept less intensive (LI) and more intensive (MI) regimens (see **Dose Selection** below). Five of these studies were not reviewed because they evaluated a (b) (4) dosage form, or evaluated a different (b) (4) (b) (4) or involved a (b) (4) that was different from that being proposed for FDA approval. Two pivotal Phase 3 clinical trials, IM103008 using standard criteria kidney donors (SCD) and IM103027 using extended criteria kidney donors (ECD), are pivotal in demonstrating the efficacy and safety of the LI regimen of intravenous belatacept in the prevention of organ rejection and preservation of the functioning allograft in kidney transplant recipients. In addition, the Phase 2 clinical trial (IM103100) is considered pivotal in assessing the safety of belatacept dosage regimens, particularly with respect to PTLD risk. Because of a higher incidence of subclinical rejection observed in Phase 2 with the LI regimen, the LI regimen was modified in the Phase 3 trials to include an additional 10 mg/kg dose on Day 5 post transplant.

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 1 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 (V_{ss}) of belatacept in kidney transplant patients were also comparable to those in healthy subjects. Likewise, the mean estimates of belatacept half-life ($T_{1/2}$) 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 1. Pharmacokinetic parameters (Mean \pm 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}) [$\mu\text{g/mL}$]	300 \pm 77 (190-492)	139 \pm 28 (80-176)	247 \pm 68 (161-340)
AUC ^a [$\mu\text{g}\cdot\text{h/mL}$]	26398 \pm 5175 (18964-40684)	14090 \pm 3860 (7906-20510)	22252 \pm 7868 (13575-42144)
Terminal half-life ($T_{1/2}$) [days]	9.8 \pm 2.8 (6.4-15.6)	8.2 \pm 2.4 ^b (3.1-11.9)	9.8 \pm 3.2 (6.1-15.1)
Systemic clearance (CL) [mL/h/kg]	0.39 \pm 0.07 (0.25-0.53)	0.51 \pm 0.14 ^b (0.33-0.75)	0.49 \pm 0.13 (0.23-0.70)
Volume of distribution (V_{ss}) [L/kg]	0.09 \pm 0.02 (0.07-0.15)	0.12 \pm 0.03 ^b (0.09-0.17)	0.11 \pm 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

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 weight-based dosing. 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.

Design Features of The Pivotal Clinical Studies: Two Phase 3 clinical trials, IM103008 and IM103027, evaluated the efficacy and safety of the more intensive (MI) and less intensive (LI) dosing regimens of belatacept in *de novo* renal transplant patients, in comparison to cyclosporine A (CsA). Both Phase 3 trials are multicenter, randomized, blinded with respect to belatacept regimen. The patients in IM103008 received kidneys from standard-criteria donors (SCD), whereas those in IM103027 received kidneys from extended-criteria donors (ECD). The adjunctive immunosuppressive therapy used in the belatacept treatment and CsA control arms consisted of basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids.

Dose Selection: 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, the sponsor is seeking approval for the belatacept LI regimen studied in the Phase 3 trials for kidney transplantation.

As shown in Table 2, 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 IV dose of 5 mg/kg every 4 weeks (\pm 5 days).

Table 2. 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 MI regimen in the Phase 3 studies IM103008 and IM103027 consisted of belatacept 10 mg/kg IV administration on Day 1 (the day of transplantation, prior to implantation), and on Days 5, 14, 28, 42, 56, 70, and 84; then every 4 weeks through 6 months after transplantation. Starting at Month 7 after transplantation, belatacept in the MI regimen was administered at the maintenance IV dose of 5 mg/kg every 4 weeks (\pm 5 days). The belatacept MI regimen differed from the LI regimen in the period between Month 2 and Month 6 post transplant.

In the pivotal Phase 3 studies IM103008 (SCD) and IM103027 (ECD), the LI regimen was either non-inferior or superior to the comparator (cyclosporine) in terms of the following efficacy endpoints: patient and graft survival, preservation of renal function, and chronic allograft nephropathy. However, the belatacept LI regimen was inferior to cyclosporine in terms of acute rejection (AR); the AR rates in Phase 3 trials at 12 months were 17.5% (70/401) for belatacept LI and 10.4% (42/405) for cyclosporine. As compared to the LI regimen, the MI regimen did not demonstrate a therapeutic benefit and was associated with more safety concerns.

Belatacept Trough Concentrations Observed in Phase 3 Studies: The Phase 3 trials IM103008 and IM103027 were designed to administer fixed mg/kg doses of belatacept, with no target trough concentration range specified to be attained by therapeutic drug monitoring with dose adjustment. These fixed dosing regimens were chosen based on the overall efficacy findings of the Phase 2 trial IM103100, which included measurement of belatacept trough concentrations. Table 3 summarizes the belatacept threshold trough concentrations for Phase 3 trials IM103008 and IM103027 that were shown to be effective in Phase 2 trial IM103100.

Table 3. Proposed Belatacept Threshold Trough Concentrations for Studies IM103008 and IM103027

Threshold Trough Concentration^a	Less Intensive (LI) Regimen	More Intensive (MI) Regimen
20 μ g/mL	Month 1	Months 1-3
5 μ g/mL	Months 2-4	Months 4-6
2 μ g/mL	Months 5-12	Months 7-12

^a Based on Phase 2 trial IM103100

In the Phase 3 trials IM103008 and IM103027, the observed belatacept trough concentrations were higher than the threshold trough concentrations at each of the measured time points in approximately 80% of the patients receiving the LI and MI regimens (Figure 1). There was substantial between-patient variability in trough concentrations in the belatacept LI and MI regimens; the percent coefficient of variation (%CV) at Month 1 was lowest at (44%), while %CV was 52% to 70% from Months 2 to 12.

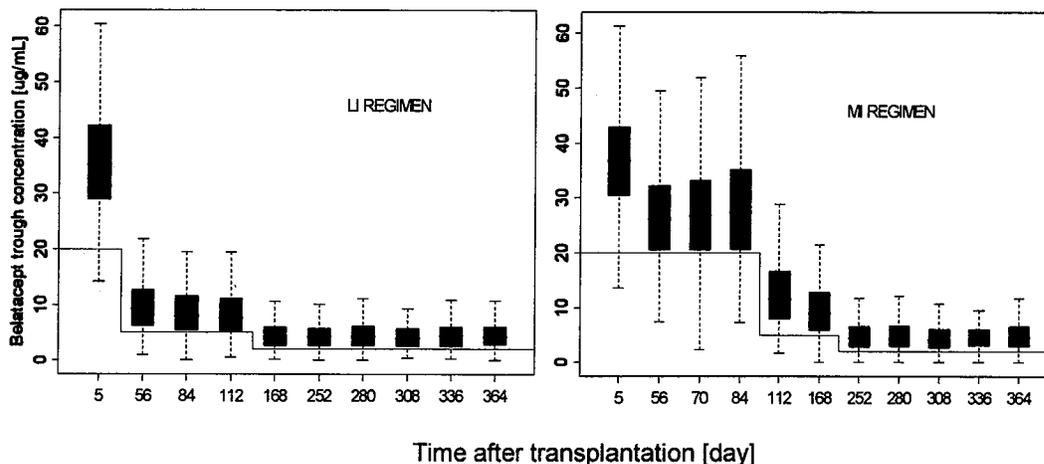


Figure 1. Belatacept Trough Concentrations in *de novo* Kidney Transplant Patients Receiving the LI Regimen (left panel) and the MI Regimen (right panel). Data from the Phase 3 trials were combined. The bottom and top of each box represent the inter quartile range (i.e., 25th and 75th percentiles, respectively). The bar inside each box represents the median trough concentration. The whiskers represent 5th and 95th percentiles, respectively. The horizontal reference lines represent the threshold trough concentration as outlined in Table 3.

Exposure-Response Relationships for Efficacy: The relationship between exposure (belatacept trough concentrations) and response (acute rejection (AR), and renal function) was assessed and the results are summarized below. The incidence of patient and graft loss was too low to conduct a meaningful exposure-response analysis.

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 approximately 1/3 of the total AR episodes. Overall, no apparent relationship of belatacept trough concentrations with AR was observed in Phase 3 trials IM103008 and IM103027.

Renal Function: In Phase 3 trials IM103008 and IM103027, renal impairment was defined as a measured GFR (mGFR) < 60 mL/min/1.73 m² at Month 12 or a decrease in mGFR \geq 10 mL/min/1.73 m² 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 (Table 4).

Table 4. Relationship between Belatacept Trough Concentrations (Median; 10-90th percentile) and Proportion of Patients with a Decrease in Measured GFR ≥ 10 mL/min/1.73 m² from Month 3 to Month 12. Data from the LI and MI regimens in IM103008 and IM103027 were combined for the quartile analysis.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Month 1^a				
Median (10-90 th 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 (10-90 th 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)
\geq Months 6				
Median (10-90 th 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 (10-90 th 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 m² from Month 3 to Month 12

Exposure-Response Relationships for Safety: The relationship between exposure (belatacept trough concentrations) and response (Post-transplant lymphoproliferative disorder (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., \leq 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]] (Table 5), suggesting that CMV negative serostatus should be considered as an additional risk factor when considering belatacept as a treatment option.

Table 5. 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.

Therapeutic Drug Monitoring (TDM) of Belatacept: Current data obtained from Phase 3 trials, where fixed mg/kg belatacept dosing regimens were used, are not sufficient to evaluate whether monitoring belatacept C_{trough} may be needed for dose adjustment in de novo kidney transplant patients. However, the findings from analyses of data from Studies IM103008 and IM103027 (i.e., (a) large between-subject variability of belatacept C_{trough}, (b) a trend for improvement of renal function (mGFR) associated with belatacept C_{trough} in recipients of standard criteria kidney donors, and (c) the incidence of some viral infections (BK virus and herpes virus) may be higher with higher belatacept C_{trough}) would suggest that there may be a need to further evaluate the need for TDM of belatacept C_{trough} in de novo kidney transplant patients through additional clinical experience, or additional clinical trials, or both.

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.

Mycophenolate Mofetil (MMF) Dosing and Mycophenolic Acid (MPA) Exposure Observed in Phase 3 Trials:

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 (Table 6). 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.

Table 6. Percent of Patients who Received MMF 2 g/day at Given Times in Phase 3 Trials 008 and 027

	Study 103008			Study 103027		
	Month 3	Month 6	Month 12	Month 3	Month 6	Month 12
Belatacept MI	74%	75%	68%	67%	66%	56%
Belatacept LI	71%	71%	67%	71%	66%	58%
CsA	70%	65%	64%	68%	60%	57%

Cyclosporine (CsA) inhibits enterohepatic recirculation of MPA, the active form of MMF, and, consequently, lowers MPA exposure. Belatacept does not interact with MPA. Thus, systemic exposure to MPA would 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 C_{max} 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.

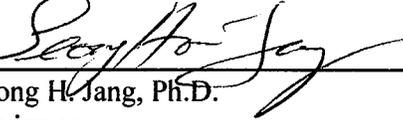
QT/QTc Evaluation: Because belatacept is a large fusion protein (401 amino acids) with a high specificity for its molecular target, a thorough QT study was not recommended. In the Phase 2 and 3 clinical trials, belatacept did not cause QT prolongation in renal transplant patients.

Product Comparability: (b) (4) belatacept was used in the two pivotal Phase 3 trials and is also the formulation intended for commercial purposes. Only the PK parameters of (b) (4)

belatacept will be described in the proposed label.



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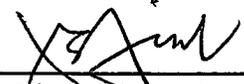
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2. Question Based Review

2.1. General Attributes

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Chemistry and Physical-Chemical Properties:

Belatacept is a genetically engineered fusion protein that consists of the functional binding domain of modified cytotoxic T-lymphocyte antigen-4 (CTLA-4) and the Fc domain of human monoclonal immunoglobulin of the IgG₁ subclass. Belatacept consists of two polypeptide chains with 357 amino acids and exists as covalent homodimer (referred to as belatacept "monomer") linked through an inter-chain disulfide bond. Belatacept has an average mass of approximately 90,619 Da as determined by mass spectrometry.

Formulation:

Belatacept for injection is a single use, sterile, (b) (4) lyophilized powder for intravenous (IV) administration after its constitution with either sterile water for injection (SWFI), 0.9% sodium chloride injection (NS) or 5% dextrose solution (D5W) to obtain a solution with a protein concentration of 25 mg/mL and subsequent dilution to concentrations between (b) (4) mg/mL and 10 mg/mL with either NS or D5W.

When reconstituted, belatacept is a clear to opalescent, colorless to pale yellow solution which contains ~ 25 mg of belatacept/mL in (b) (4) sodium phosphate and (b) (4) sodium chloride, pH 7.5.

2.1.2. What are the proposed mechanisms of action and therapeutic indications?

Mechanism of Action:

Belatacept represents a class of potential therapeutic agents that target the blockade of CD28-B7 (CD80, CD86), signaling key co-stimulatory signals required for T-cell activation.

Full activation of T-cells requires two signals provided by the antigen presenting cells (APCs). One of the signals occurs with the interaction between CD28 on the T-cells and B7-1 and B7-2 (CD80 and CD86, respectively) on the APCs. This specific interaction initiates a signal transduction mechanism, which includes the production of cytokines, T-cell activation and proliferation. Belatacept selectively blocks full activation of T-lymphocytes by binding specifically to B7-1 and B7-2 on the APC, and inhibiting the co-stimulatory pathway.

Belatacept had been shown to inhibit the production of cytokines (IL-2, IL-4, TNF- α , and IFN- γ) *in vitro*. Of note, IFN- γ is an endogenous antiviral and antitumor cytokine and is known to prevent EBV-induced B cell transformation.

• *Proposed Indication:*

Belatacept is a selective costimulation blocker with the proposed indication of prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal

transplants. Belatacept has been used in combination with an interleukin-2 (IL-2) receptor antagonist (e.g., basiliximab), mycophenolic acid (MPA; as mycophenolate mofetil (MMF)), and corticosteroids.

2.1.3. What are the proposed dosage and route of administration?

Proposed Dose and Route of Administration:

For adult renal transplant recipients, belatacept should be prepared based on actual body weight and administered as a 30-minute intravenous infusion with the dosing recommendations in Table 7.

Table 7. Dosing of belatacept for renal transplant recipients

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
Months 2 and 3 after transplantation	10 mg/kg every 4 weeks
Maintenance Phase:	
Month 4 after transplantation and afterwards	5 mg/kg every 4 weeks

Dose Adjustments:

Dose modification of belatacept is not recommended:

- During episodes of acute rejection.
- For a change in body weight of less than 10%.

Patients do not require premedication prior to administration of belatacept.

Therapeutic drug monitoring (TDM) of trough concentrations is not required with belatacept.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Two Phase 3 clinical trials, IM103008 and IM103027 evaluated the efficacy and safety of the more intensive (MI) and less intensive (LI) dosing regimens of belatacept in *de novo* renal transplant patients, in comparison to cyclosporine. Both Phase 3 trials are multicenter, randomized, and were blinded with respect to belatacept regimen. The patients in IM103008 received kidneys from standard-criteria donors (SCD), whereas those in IM103027 received kidneys from extended-criteria donors (ECD). The adjunctive immunosuppressive therapy used in the belatacept treatment and cyclosporine control arms consisted of basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids.

Although the following two belatacept regimens were evaluated in Phase 3 trials, the less-intensive (LI) regimen is being proposed for approval.

- The MI regimen of 10 mg/kg of belatacept given IV on Day 1 (the day of transplantation, prior to implantation), Day 5, 14, 28, 42, and 56, and then every 4 weeks through 6 months after

transplantation. Starting at Month 7 after transplantation, belatacept was administered at 5 mg/kg IV monthly.

- The LI regimen of 10 mg/kg of belatacept given IV on Day 1 (the day of transplantation, prior to implantation), Days 5, 14, 28, Month 2 and Month 3, and then at 5 mg/kg IV monthly starting at Month 4 after transplantation. Note: Because there was a relatively higher rate of subclinical rejection observed with the LI regimen in previously completed Phase 2 trials, the LI regimen was modified in these Phase 3 trials by adding a 10 mg/kg dose on Day 5 post-transplant.

Table 8 provides a summary of the clinical pharmacology and clinical studies that provided supportive information in the **Dosage and Administration**, **Drug Interactions**, **Immunogenicity** and **Clinical Pharmacology** sections of the belatacept labeling.

Table 8. Studies 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) vs C; 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	<p>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</p> <p>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</p> <p>Background meds (all subjects): basiliximab induction, MMF + corticosteroids</p>	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	<p>Belatacept MI regimen: same as IM103008</p> <p>Belatacept LI regimen: same as IM103008</p> <p>CsA: same as IM103008</p> <p>Background meds (all subjects): same as IM103008</p>	MI, 183 LI, 174 CsA, 179

2.2.2. What is the basis of the dose selection?

The overall efficacy of belatacept was similar between the less intensive (LI) and more intensive (MI) dosing regimens, with some suggestion of a more favorable safety profile with the LI dosing regimen. Therefore, the LI dosing regimen is the recommended dosing regimen for belatacept.

2.2.3. What are the clinical endpoints used to assess efficacy in the pivotal clinical efficacy study? What is the clinical outcome in terms of safety and efficacy?

Efficacy:

The co-primary efficacy endpoints were (1) the composite of patient and graft survival at 12 months, and (2) the composite of renal impairment as assessed by measured GFR <60 mL/min/1.73 m² at Month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73 m² from Month 3 to Month 12, and (3) the incidence of acute rejection (AR) at 12 months (Study IM103027 only). Incidence of AR was a secondary endpoint in Study IM103027. Mean calculated GFR at Month 12 post transplant and incidence of chronic allograft nephropathy (CAN) were also secondary endpoints in both studies.

The primary endpoints of patient and graft survival and of AR were assessed for non-inferiority, whereas the endpoint of composite renal impairment was assessed for superiority. In IM103008 and IM103027, both MI and LI regimens of belatacept were non-inferior to the cyclosporine regimen as assessed by the primary endpoint of patient and graft survival at 1 year (Table 9).

Table 9. 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)	

The belatacept MI regimen was superior to CsA in terms of composite renal impairment (GFR) at Month 12 in IM103008 and IM103027; the LI regimen was superior to CsA, but did not meet statistically significant superiority in Study IM103027 (Table 10).

Table 10. Composite Measured GFR Endpoint

Study		Belatacept MI	Belatacept LI	CsA
008	Composite endpoint	(n=219) 125 (57.1)	(n=226) 128 (56.6)	(n=221) 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	Composite endpoint	(n=184) 132 (71.7)	(n=175) 135 (77.1)	(n=184) 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	

In IM103008, the proportion of patients with acute rejection (AR) at Month 12 was higher in the belatacept MI and LI groups compared with the cyclosporine group. In IM103027, the proportion of patients with AR at Month 12 was comparable among the groups. In both trials, a larger proportion of patients in both belatacept regimens had episodes of higher-grade AR than in the cyclosporine group (Table 11).

Table 11. 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)	

There were no substantial differences in the efficacy of belatacept, as assessed by patient and graft survival, renal function, and AR, between elderly, diabetic, and black/African-American subgroups vs. the overall study population.

Safety.

In Phase 2 and 3 clinical trials, the most serious adverse reactions reported with belatacept were post transplant lymphoproliferative disorders (PTLD), serious infections (e.g., TB, BK virus, herpes virus), and other malignancies. The incidence of PTLD was higher in belatacept-treated patients (13/949; 1.4%) than in cyclosporine-treated patients (2/476; 0.4%). Eight of 13 cases of PTLD in belatacept-treated patients presented in the CNS and half of these were fatal. One fatal case of progressive multifocal leukoencephalopathy (PML) was reported after year 1 of treatment in a patient receiving belatacept MI in clinical studies.

The most commonly reported adverse reactions occurring in $\geq 20\%$ of patients treated with belatacept were anemia, constipation, urinary tract infection, peripheral edema, diarrhea, hypertension, graft dysfunction, nausea, pyrexia, and hypophosphatemia. The adverse reactions resulting in clinical intervention (interruption or discontinuation of belatacept) in $\geq 1\%$ of patients were renal vein thrombosis and CMV infection.

2.2.4. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship? (if yes, refer to 2.6.6 Analytical Section; if no, describe the reasons)

Yes, see Section 2.6.6, Analytical Section.

2.2.5. Belatacept Trough Concentrations (C_{trough}) Observed in Phase 3 Trials

Phase 3 trials IM103008 and IM 103027 were designed to administer fixed mg/kg doses of belatacept, with no target C_{trough} range specified to be attained by therapeutic drug monitoring with dose adjustment. Table 12 summarizes the belatacept threshold C_{trough} for Phase 3 trials IM103008 and 103027 which were shown to be effective in Phase 2 Study IM103100 of *de novo* kidney transplantation.

Table 12. Belatacept threshold trough concentrations for Phase 3 Trials IM103008 and 103027

Threshold Trough Concentration ^a	Less Intensive (LI) Regimen	More Intensive (MI) Regimen
20 $\mu\text{g/mL}$	Month 1	Months 1-3
5 $\mu\text{g/mL}$	Months 2-4	Months 4-6
2 $\mu\text{g/mL}$	Months 5-12	Months 7-12

^a: Based on Phase 2 Study IM103100.

In the two Phase 3 studies, belatacept trough serum concentrations were measured at nominal Days 5, 56, 70 (MI only), 84, 112, 168, 252, 280, 308, 336 and 364. In these trials, belatacept C_{trough} were higher than the threshold C_{trough} at each of the measured time points in $\sim 80\%$ of the patients receiving the LI and MI dosing regimens (Figure 2). There was substantial between-patient variability in C_{trough} in the belatacept LI and MI regimens; the %CV at Month 1 was lowest at $< 50\%$, while %CV was $> 60\%$ after Month 1 (Table 13).

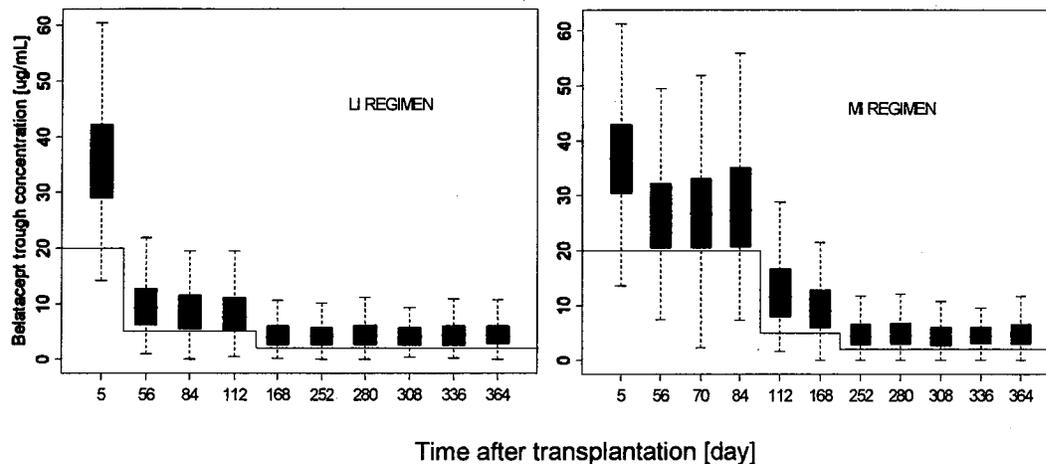


Figure 2. Belatacept C_{trough} in *de novo* kidney transplant patients receiving the LI regimen (left panel) and the MI regimen (right panel). Data from Phase 3 trials IM103008 and 103027 were combined. The bottom and top of each box represent the inter quartile range (i.e., 25th and 75th percentiles, 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 threshold C_{trough} as outlined in Table 12.

Table 13. Mean and SD of belatacept C_{trough} in *de novo* kidney transplant patients receiving the LI regimen and the MI regimen in Phase 3 Studies IM103008 and IM 103027

Time (Days)	Study 103008				Study 103027			
	Belatacept LI		Belatacept MI		Belatacept LI		Belatacept MI	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
5	37.33	22.03	36.76	11.71	37.95	11.80	41.45	22.60
56	9.42	4.57	27.05	15.89	11.17	6.70	28.28	11.34
84	8.27	4.47	28.10	10.62	10.46	8.70	30.89	19.68
112	7.85	4.12	12.63	8.36	9.52	5.40	14.44	6.67
168	4.10	2.44	9.46	6.24	5.24	2.97	10.54	4.84
252	4.38	3.55	4.54	2.71	4.69	2.42	5.72	3.48
280	4.21	2.91	4.74	3.78	5.28	4.09	5.45	2.99
308	4.05	2.60	4.28	2.42	5.24	3.22	5.24	2.88
336	4.46	3.04	4.53	2.24	5.11	2.86	5.13	2.71
364	4.35	2.97	4.63	2.50	5.06	2.97	5.24	2.75

2.2.6. Cyclosporine Trough Concentrations Observed in Phase 3 Trials

Patients randomized to the CsA arm in Phase 3 trials IM103008 and IM103027 received CsA twice daily to achieve protocol-specified target trough CsA concentrations of 150 to 300 ng/mL during the first month post transplant and then 100 to 250 ng/mL thereafter. The CsA troughs observed in the Phase 3 trials, however, tended to be higher than the protocol-specified CsA targets during the first 2 to 3 months post transplant (Figure 3). For the first two months, trough

CsA concentrations were attained within the protocol-specified target range in approximately 50 to 60% of patients. In approximately 40% of patients, trough CsA concentrations attained for the first two months were higher than the protocol-specified target range. After Month 3 post transplant, trough CsA concentrations were attained within the protocol-specified target range in approximately 70 to 80% of patients. After the two week time point, the majority of trough CsA concentrations outside of the protocol-specified target range were above the upper limit of the target range rather than below the lower limit of the target range.

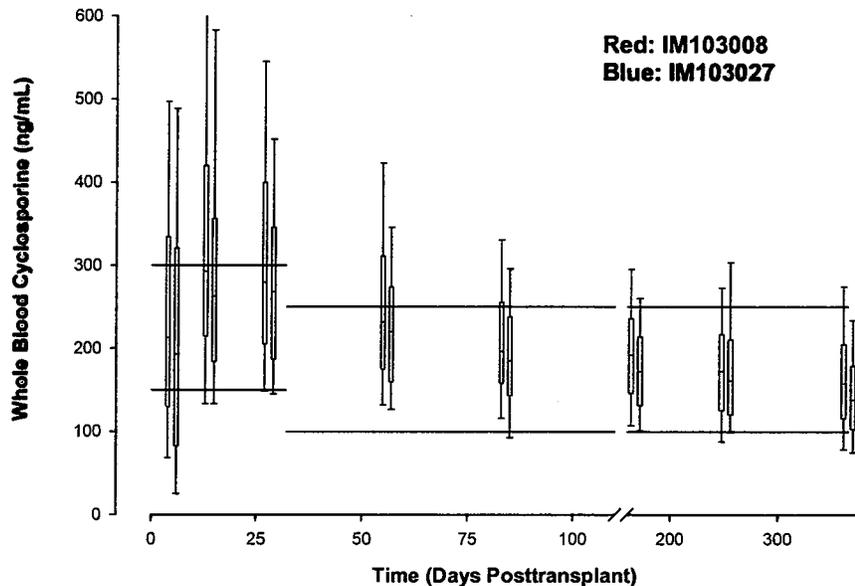


Figure 3. Whole Blood Trough Concentrations of CsA in Patients Randomized to CsA in the Phase 3 Studies IM103008 (red, left-side bars at each day) and IM103027 (blue, right-side bars at each day)

2.2.7. Mycophenolate Mofetil (MMF) Dosing and Mycophenolic Acid (MPA) Exposure Observed in Phase 3 Trials:

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 (Table 14). 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.

Table 14. Percent of Patients who Received MMF 2 g/day at Given Times in Phase 3 Trials 008 and 027

	Study 103008			Study 103027		
	Month 3	Month 6	Month 12	Month 3	Month 6	Month 12
Belatacept MI	74%	75%	68%	67%	66%	56%
Belatacept LI	71%	71%	67%	71%	66%	58%
CsA	70%	65%	64%	68%	60%	57%

Unlike belatacept, cyclosporine (CsA) inhibits enterohepatic recirculation of 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 C_{max} 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. Based on the assessment of Dr. Patrick Archdeacon (Medical Officer), despite this belatacept-associated increased exposure to MPA, there was not a greater frequency of MMF-related toxicities, such as gastrointestinal adverse events (AEs) or leukopenia, in belatacept- versus CsA-treated subjects.

2.2.8. Exposure-Response

2.2.8.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The exposure-response relationships for efficacy of belatacept were explored with the incidence of acute rejection and renal function estimated by measured GFR as a function of belatacept C_{trough} in Phase 3 Studies IM103008 and IM103027. The incidence of patient and graft loss was too low to conduct a meaningful exposure-response analysis.

Acute Rejection (AR): Higher belatacept C_{trough} on Day 5 appeared to be related to a lower incidence of AR during Month 1 post transplant (Figure 4). However, the incidence of AR during Month 1 post transplant only accounts for approximately 1/3 of total AR. No apparent relationship of belatacept C_{trough} with AR was observed after Month 1 post transplant in Phase 3 trials IM103008 and 103027 (see Pharmacometrics Review in Appendix). In the Phase 3 trials, 97% (147/152) of the belatacept-treated patients with reported AR episodes experienced the event within 6 months of transplantation.

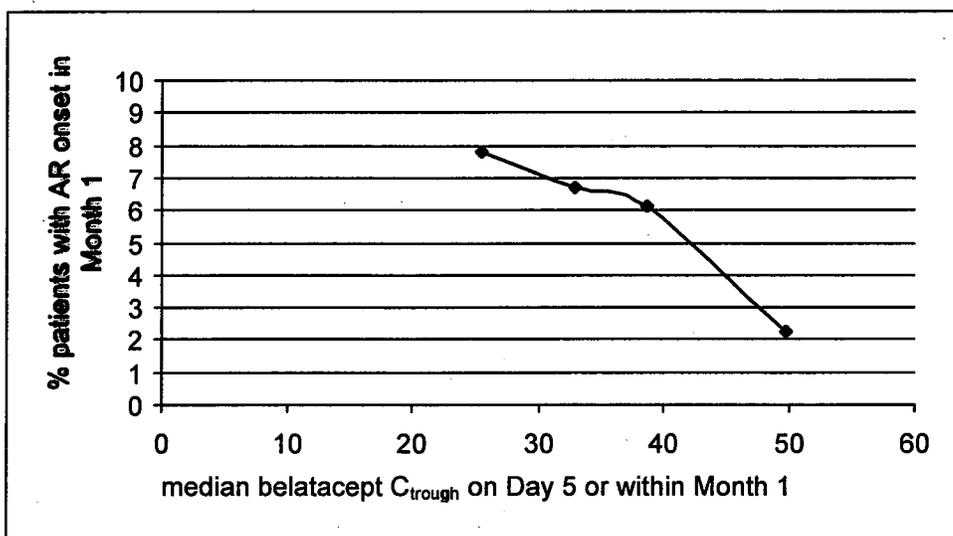


Figure 4. Percent of patients with acute rejection (AR) occurring within Month 1 of belatacept therapy, as a function of median belatacept C_{trough} on Day 5 or Month 1 (Quartile analysis). Data obtained from Phase 3 Studies IM103008 and IM103027 were combined.

Improvement in GFR: In Phase 3 trials IM103008 and IM103027, renal impairment was defined as a measured GFR (mGFR) <60 mL/min/1.73 m² or a decrease in measured GFR ≥ 10 mL/min/1.73 m² from Month 3 to Month 12 (mGFR10). In those studies, GFR were estimated at Month 3 and Month 12 by measurement of the clearance of a true glomerular filtration marker (non-radiolabeled iothalamate). 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 C_{trough} in Studies IM103008 and IM103027 (Table 15).

Table 15. Relationship between belatacept average C_{trough} (median; 10-90th percentile) and proportion of patients with a decrease in mGFR ≥ 10 mL/min/1.73 m² from Month 3 to Month 12 (mGFR10). Data from de novo transplant patients who received the LI or MI regimens in Phase 3 trials IM103008 and IM103027 were combined for the quartile analysis.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Month 1^a				
Median (10-90 th percentile) belatacept C_{trough} ($\mu\text{g/mL}$)	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 (10-90 th percentile) belatacept C_{trough} ($\mu\text{g/mL}$)	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)
\geq Months 6				
Median (10-90 th percentile) belatacept C_{trough} ($\mu\text{g/mL}$)	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 (10-90 th percentile) belatacept C_{trough} ($\mu\text{g/mL}$)	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

Additional analyses were conducted to evaluate the relationship between renal function (i.e., mGFR10) and belatacept C_{trough} (i.e., average of C_{trough} from Month 3 to Month 12 in each patient) as a function of belatacept dosing regimen in each Phase 3 study. In Study IM103008 in the transplant recipients of standard criteria donor kidneys, the percent of patients with mGFR10 decreased with increasing belatacept C_{trough} in both the belatacept LI and MI treatment groups (Table 16). It should be noted that the percent of patients with mGFR10 in the lower quartile of belatacept C_{trough} among the patients who received the LI regimen (39%) was numerically greater than that in the CsA treatment group (28%, 60/221).

Table 16. Percent of patients with a decrease in mGFR ≥ 10 mL/min/1.73 m² from Month 3 to Month 12 (mGFR10) (n/N, %) as a function of average C_{trough} for the same periods (Study IM103008)

LI Regimen		MI Regimen	
Average C_{trough} Quartiles (Range)	Patients with mGFR10 (n/N, %)	Average C_{trough} Quartiles (Range)	Patients with mGFR10 (n/N, %)
Q1 (<3.24 $\mu\text{g/mL}$)	17/44 (39%)	Q1 (<6.75 $\mu\text{g/mL}$)	13/41 (32%)
Q2 (3.24-5.03 $\mu\text{g/mL}$)	9/43 (21%)	Q2 (6.75-9.34 $\mu\text{g/mL}$)	10/41 (24%)
Q3 (5.03-6.5 $\mu\text{g/mL}$)	9/43 (21%)	Q3 (9.34-12.3 $\mu\text{g/mL}$)	10/41 (24%)

Q4 (>6.5 µg/mL)	10/44 (23%)	Q4 (>12.3 µg/mL)	7/40 (18%)
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In Study IM103027 in the transplant recipients of extended criteria donor kidneys, the relationship between the percent of patients with mGFR10 and belatacept C_{trough} does not appear to be as clear as in Study IM103008 (Table 16). The baseline kidney function among the patients who received kidneys from extended-criteria donors (Study IM103027) may be more variable than among the patients who received kidney from standard-criteria donors (Study IM103008). This may be a possible reason for the different observation between Studies IM103008 and IM103027.

Table 17. Percent of patients with a decrease in mGFR ≥ 10 mL/min/1.73 m² from Month 3 to Month 12 (mGFR10) (n/N, %) as a function of average C_{trough} for the same periods (Study IM103027)

LI Regimen		MI Regimen	
Average C_{trough} Quartiles (Range)	Patients with mGFR10 (n/N, %)	Average C_{trough} Quartiles (Range)	Patients with mGFR10 (n/N, %)
Q1 (<3.92 µg/mL)	10/30 (33%)	Q1 (<7.32 µg/mL)	7/30 (23%)
Q2 (3.92-6.03 µg/mL)	13/28 (46%)	Q2 (7.32-9.88 µg/mL)	9/29 (31%)
Q3 (6.03-8.14 µg/mL)	6/30 (20%)	Q3 (9.88-13.2 µg/mL)	3/30 (10%)
Q4 (>8.14 µg/mL)	8/29 (28%)	Q4 (>13.2 µg/mL)	5/29 (17%)

Chronic Allograft Nephropathy (CAN): The clinical pharmacology reviewer's exposure-response analysis showed that the incidence of CAN measured at Month 12 significantly decreased with an increase in belatacept average C_{trough} from Month 6 to Month 12 in Study IM103008 (Figure 5). However, no apparent relationship between the incidence of CAN and belatacept average C_{trough} was observed in Study 103027, where patients received kidneys from extended-criteria donors (data not presented). In Study 103027, the incidence of CAN measured at Month 12 may have been confounded with the baseline (i.e., pre-transplant) kidney pathological status. For these analyses, data from the LI and MI treatment groups were combined. Average C_{trough} from Month 6 to Month 12 were used because the belatacept doses during this period were same between the LI and MI regimens, in addition to the presumed relatively stable clinical status of the patient after Month 6 of renal transplantation. It should be noted that (a) the presence of CAN at Month 12 was assessed as a secondary endpoint, using protocol biopsies in an attempt to assess differences in structural changes across the treatment groups, (b) CAN was developed as a term to describe histopathologic findings on biopsy associated with progressive renal dysfunction not attributable to a more specific diagnosis, and (c) although the observation of CAN reflects structural findings, the understanding of its clinical relevance remains rather uncertain.

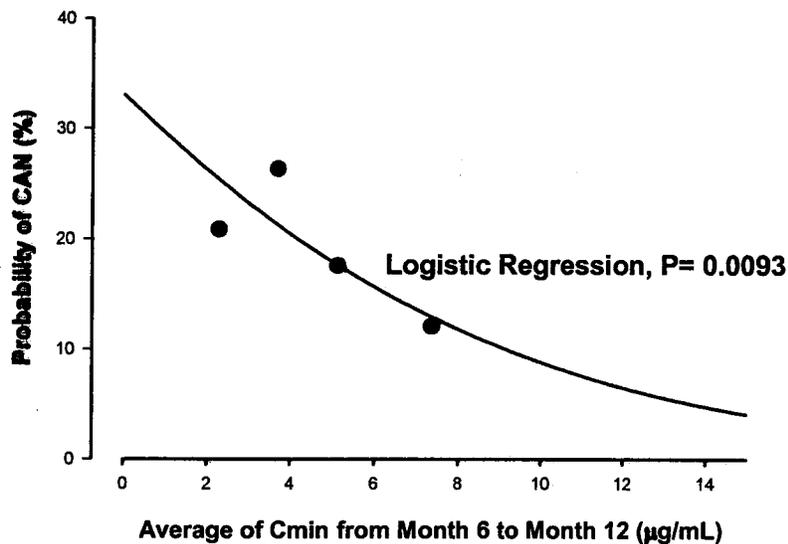


Figure 5. Incidence of CAN at Month 12 as a function of average C_{trough} from Month 6 to Month 12 (Study IM103008). Data from the LI and MI treatment groups were combined. Logistic regression was performed using average C_{trough} from Month 6 to Month 12 per patient as a continuous variable and the incidence of CAN as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the response rates in each of the 4 quartiles of C_{trough} (closed circles) are plotted to assess the goodness-of-fit.

Reviewer's comments: There is speculation that the observed better renal function (i.e., lower proportion of patients with $mGFR_{10}$) and lower incidence of CAN in the belatacept treatment groups as compared with the CsA treatment group is confounded by the potential of CsA to induce renal toxicity in contrast to belatacept. However, the findings of exposure-response analysis for the proportion of patients with $mGFR_{10}$ and the incidence of CAN may suggest that belatacept indeed has beneficial effects in terms of increasing renal function in kidney transplant patients.

The reviewer also notes that the term chronic allograft nephropathy (CAN) is no longer used, but rather the more current terminology is chronic allograft injury (CAI) or Interstitial Fibrosis/Tubular Atrophy (IF/TA). However, at the time of the conduct of the Phase 3 studies and the analysis of the data by the sponsor, the older CAN term was still in use.

2.2.8.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) or non-exposure-related factors for safety?

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

Post transplant lymphoproliferative disorder (PTLD): There are 13 belatacept PTL D (8 MI

and 5 LI) cases in the 3 core studies (3 in IM103100, 5 in IM103008, and 5 in IM103027). Up to Month 12, the incidence of PTLD was similar in the belatacept LI and MI groups (4 [0.8%] subjects in each group). Based on visual inspection of graphical analyses comparing belatacept C_{trough} in patients with PTLD, belatacept trough concentrations in patients with PTLD were not substantially different from that in patients without PTLD. The number of clinical cases was not adequate to derive meaningful exposure-response relationships. 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 $\mu\text{g}/\text{mL}$) whereas no PTLD (0/312) occurred in the patients with lower C_{trough} (i.e., ≤ 4.4 $\mu\text{g}/\text{mL}$) (Table 18).

Table 18. Relationship between belatacept C_{trough} (median; 10-90th percentile) and proportion of patients with PTLD and CNS-PTLD in Phase 3 trials^{a,b}.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Month 1				
Median (10-90 th percentile) belatacept C_{trough} ($\mu\text{g}/\text{mL}$)	25.5 (18.9 – 28.8)	32.9 (30.5 – 35.5)	38.7 (36.5 – 41.8)	49.8 (43.4 – 62.8)
Percentage of patients with PTLD (%; n/N)	0 (0/179)	0 (0/179)	0 (0/179)	0 (0/178)
Percentage of patients with CNS-PTLD (%; n/N)	0 (0/179)	0 (0/179)	0 (0/179)	0 (0/178)
Months 2 to 4				
Median (10-90 th percentile) belatacept C_{trough} ($\mu\text{g}/\text{mL}$)	5.2 (3.1 – 7.3)	10.4 (8.3 – 12.8)	16.9 (13.8 – 20.4)	27.1 (22.3 – 38.3)
Percentage of patients with PTLD (%; n/N)	0 (0/182)	1.1 (2/182)	1.1 (2/182)	0 (0/180)
Percentage of patients with CNS-PTLD (%; n/N)	0 (0/182)	0 (0/182)	0 (0/182)	0 (0/180)
Months 6 to 12				
Median (10-90 th percentile) belatacept C_{trough} ($\mu\text{g}/\text{mL}$)	2.1 (1.0 – 2.8)	3.7 (3.0 – 4.3)	5.1 (4.5 – 5.8)	7.3 (6.2 – 10.1.9)
Percentage of patients with PTLD (%; n/N)	0 (0/156)	0 (0/156)	0.6 (1/156)	0.6 (1/155)
Percentage of patients with CNS-PTLD (%; n/N)	0 (0/156)	0 (0/156)	0.6 (1/156)	0.6 (1/155)

^a Only Phase 3 patients were included in the analysis because the three Phase 2 patients who developed PTLD had either a Q 8wk or an unknown dosing schedule during the maintenance phase, i.e., belatacept was administered Q 4wk after Month 6 post-transplant in Phase 3 trials. The patients randomized to the original LI regimen evaluated in the Phase 2 trial were excluded in the analysis.

^b With the exception of Patient IM103008-142-30548, all 10 patients who developed PTLD in the Phase 3 trials had belatacept C_{trough} data. Three (3) of the 10 patients were reported to have developed PTLD after Month 12 of belatacept therapy.

Based on the sponsor's analysis of data up to database lock, renal transplant patients with CNS-PTLD and other CNS infections, including the one transplant patient with progressive multifocal lekoencephalopathy (PML) tended to have higher cumulative exposure in the peri-transplant period compared with patients who did not have these events (Figure 6).

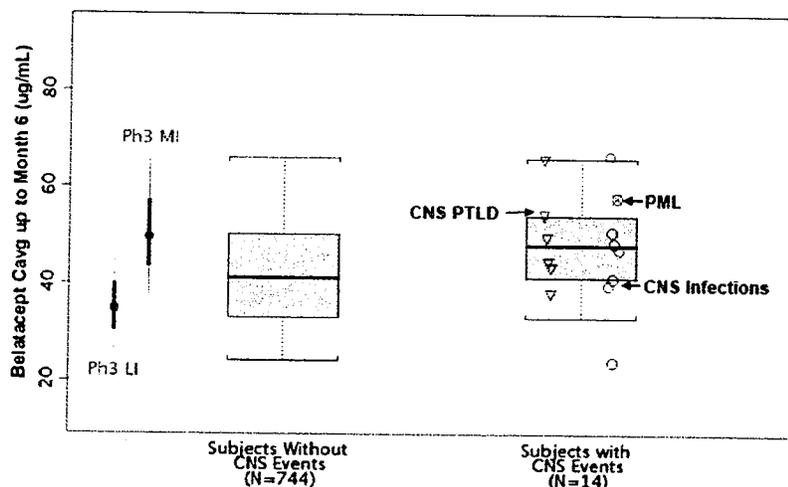


Figure 6. Box and whiskers plots are the distribution of belatacept average concentrations (Cavg) up to 6 months after transplantation (Cavg = total cumulative AUC divided by time) in subjects treated with belatacept with and without CNS events in Phase 2 and 3 Studies IM103100, IM103008, and IM103027 (Adapted from the sponsor's Advisory Committee briefing book).

An additional FDA analysis suggests that joint consideration of Epstein-Barr Virus (EBV) and cytomegalovirus (CMV) status may provide additional information regarding PTLD. Specifically, among EBV positive patients, those patients with CMV negative serology were more likely to develop PTLD than those patients with CMV positive serology (see below).

Non-exposure-related risk factors of PTLD in belatacept-treated patients: There are 13 belatacept PTLD (8 MI and 5 LI) cases in the 3 core studies (3 in IM103100, 5 in IM103008, and 5 in IM103027) up to database lock and an additional PTLD case was found in a transplant recipient on belatacept LI regimen after the database lock. ROC and chi-square analyses were conducted to identify predictive risk factors for PTLD in belatacept-treated patients. Our results agree with those of the sponsor that EBV serostatus is the most significant risk factor for PTLD and that EBV negative serostatus is a strong risk factor for PTLD. However, EBV positive transplant recipients are also at considerable risk for PTLD (6/13 cases of PTLD were found in EBV positive transplant recipients). Our analyses suggest that joint consideration of EBV and CMV serostatus is more informative than consideration of EBV alone. Specifically, among EBV positive patients, those patients with CMV negative serology were more likely to develop PTLD than those patients with CMV positive serology (see below).

Figure 7 and Table 19 show the ROC analysis results using data from Studies IM103100, IM103008 and IM103027 to identify potential factors associated with PTLD risk in belatacept-treated patients. EBV negative serostatus was the strongest risk factor, followed by CMV negative serostatus. The predictive value of the combination of these two factors for PTLD was very similar to that obtained with the combination of EBV serostatus and CMV infection prior to detection of PTLD as well as to NRISK, a combination of potential risk factors, age category, EBV status, use of T cell depleting agents and CMV infection prior to detection of PTLD.

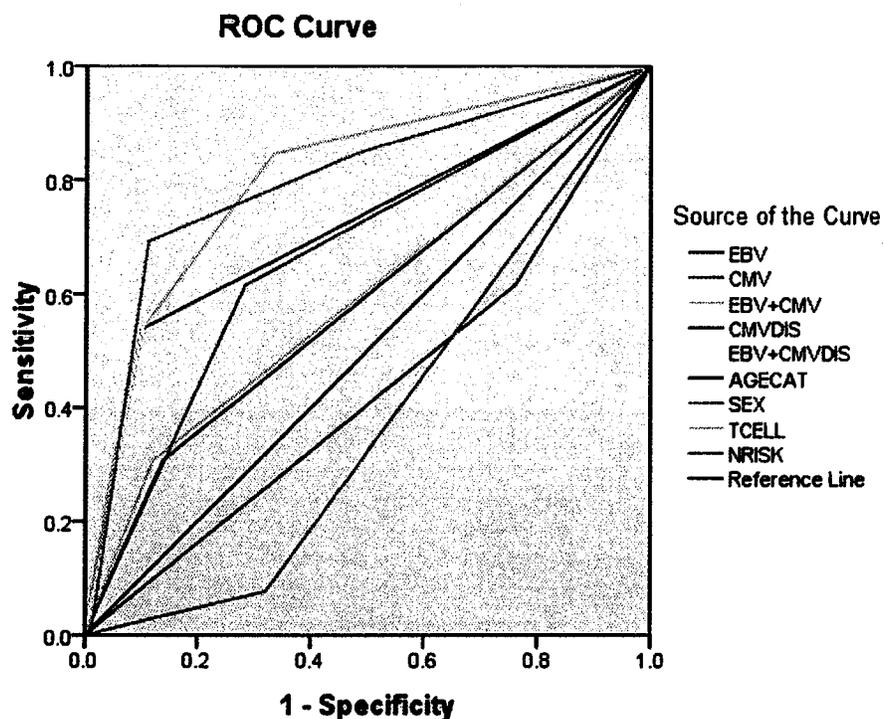


Figure 7. Correlates of PTLD Risk in Belatacept-Treated Patients. EBV: Epstein-Barr virus serostatus; CMV: Cytomegalovirus serostatus; CMVDIS: CMV infection prior to PTLD diagnosis; AGECAT: Age category (below or above 60 years); SEX: Female/Male; TCELL: Lymphocyte depletion prior to PTLD through treatment with T-cell depleting agents; NRISK: A combination of risk factors; AGECAT, EBV, TCELL and CMV DIS.

The results of the chi-square analysis using data from Studies IM103100, IM103008 and IM103027 are summarized in Table 20. Joint consideration of EBV and CMV serostatus provided additional information regarding PTLD. 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], Table 20). Similar imbalance, although to a lesser extent, was seen for PTLD manifested in the CNS (data not shown).

Table 19. Results of the ROC Analyses to Identify Potential Factors Associated with PTLD Risk in Belatacept-Treated Patients

Test Result Variable(s)	Area	Std. Error	P-value
EBV	.719	.085	.007
CMV	.666	.079	.039
EBV+CMV	.806	.065	<.0001
CMVDIS	.584	.087	.296
EBV+CMVDIS	.794	.070	<.0001
AGECAT	.428	.084	.370
SEX	.378	.065	.132
TCELL	.593	.087	.247
NRISK	.799	.071	<.0001

Table 20. 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

The analysis found EBV serostatus (EBV negative recipients) to be the highest risk predictor of PTLD in belatacept-treated patients. In addition, CMV (CMV negative recipients) was also identified as a risk factor for PTLD. In combination with EBV, CMV was identified as an important risk factor for PTLD in belatacept-treated patients on the basis of ROC analyses and on the imbalance of PTLD in EBV seropositive, CMV negative individuals. The results suggest that CMV negative serostatus should be considered as an additional risk factor in EBV seropositive individuals when considering belatacept as a treatment option.

While EBV serostatus is a well appreciated risk factor for PTLD in patients receiving post transplant immunosuppressants, the role of CMV serology to date has been equivocal. Reports from two trials conducted outside of the United States (Germany and the UK) do not substantiate the role of CMV status in PTLD risk whereas data from three trials in the United States support the hypothesis that CMV status (serostatus or mismatch) is a risk factor for PTLD. The risk factors for PTLD may be different depending on the organ transplanted, age of the patients, co-medications, number of acute rejection episodes, etc. The risk factors for PTLD may be different in the context of the drug/biologic also. Based on the data in the BLA submission for belatacept, and some support from the literature, EBV and CMV serostatus appear to be important risk factors for PTLD in kidney transplant patients.

Infections: Serious infections occurred more frequently in the first 6 months following transplantation. From Month 2 to Month 6, belatacept C_{trough} 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 (Figure 8).

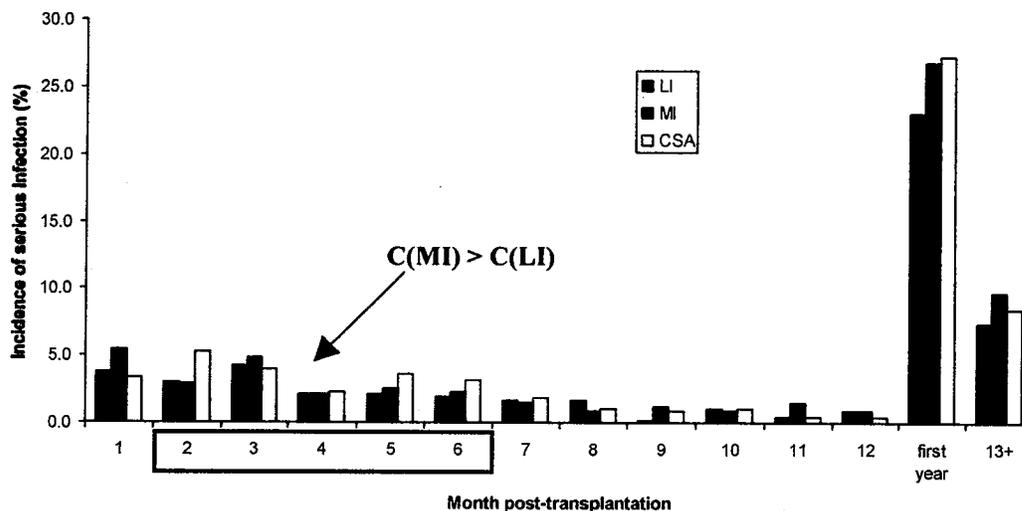


Figure 8. Comparison of incidence of serious infection among treatments by months post transplant. Data from Phase 3 Studies IM103008 and IM103027 were combined. From Month 2 to Month 6, belatacept C_{trough} were substantially higher in the MI regimen compared with in the LI regimen.

Reviewer's comments: (1) The incidence of serious infections tended to be higher for the first six months post transplant compared with after Month 6 post transplant in both the LI and MI treatment groups. Coincidentally, the belatacept C_{trough} were also higher first six months post transplant in the MI treatment group and for the first four months in LI treatment group because the maintenance dose of belatacept (i.e., 5 mg/kg every month) started at Month 6 in the MI treatment group and at Month 4 in the LI treatment group. This may indirectly suggests that the incidence of serious infections may be associated with belatacept C_{trough} (i.e., the higher incidence of serious infections, the higher belatacept C_{trough}). However, it is not clear at this time whether the higher incidence of serious infections during the first 6 months post-transplant could have been influenced by other factors (e.g., the higher propensity of patients to contract infections in the early post-surgery period).

(2) The incidence of CNS-PTLD and other CNS infections were reported to be higher in the belatacept MI regimen (1.3 to 1.5%) than in the LI regimen (0.2 to 0.6%).

BK virus infection: The incidence of BK virus infection tends to be higher in patients with higher belatacept C_{trough} . There was an apparent association between the percentage of patients with BK virus infection and belatacept C_{trough} at Month 2 and at later months but not during

Month 1. During Months 2 to <6, there was a trend for the percentage of patients with BK virus infection to increase with increasing belatacept average C_{trough} during Months 2 to 6 (Table 19). During Months 6 to 12, the incidence of BK virus infection was too low to conclude a definitive relationship with belatacept C_{trough} (Table 21).

Table 21. Relationship between belatacept C_{trough} (median; 10-90th percentile) and proportion of patients with BK viral infection

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Months 2 to 4				
Median (10-90 th percentile) belatacept C _{trough} (µg/mL)	5.3 (3.1 – 7.3)	10.6 (8.4 – 12.9)	17.3 (13.9 – 20.8)	27.7 (23 – 42.8)
Percentage of patients with BKV (%; n/N)	1.6 (3/182)	1.6 (3/182)	3.8 (7/182)	5.6 (10/180)
Months 6 to 12				
Median (10-90 th percentile) belatacept C _{trough} (µg/mL)	2.1 (1.0 – 2.8)	3.7 (3.1 – 4.3)	5.2 (4.5 – 5.9)	7.7 (6.4 – 13.9)
Percentage of patients with BKV (%; n/N)	0.6 (1/156)	1.3 (2/156)	1.3 (2/156)	1.3 (2/155)

Herpes virus infection: The incidence of herpes virus infection tends to be higher in patients with higher belatacept C_{trough} during Months 6 to 12. Exposure-response associations during Month 1 and during Months 2 to 4 were not observed (Table 22).

Table 22. Relationship between belatacept C_{trough} (median; 10-90th percentile) and proportion of patients with herpes.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Month 1				
Median (10-90 th 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 herpes (%; n/N)	0 (0/179)	1.1 (2/179)	0 (0/179)	1.1 (2/178)
Months 2 to 4				
Median (10-90 th percentile) belatacept C _{trough} (µg/mL)	5.3 (3.1 – 7.3)	10.6 (8.4 – 12.9)	17.3 (13.9 – 20.7)	27.6 (23.0 – 4.8)
Percentage of patients with herpes (%; n/N)	5.5 (10/182)	1.6 (3/182)	3.8 (7/182)	2.8 (5/180)
Months 6 to 12				
Median (10-90 th percentile) belatacept C _{trough} (µg/mL)	2.1 (1.0 – 2.8)	3.7 (3.1 – 4.3)	5.2 (4.5 – 5.9)	7.7 (6.4 – 13.9)
Percentage of patients with herpes (%; n/N)	2.6 (4/156)	2.6 (4/156)	4.5 (7/156)	7.1 (11/155)

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.

2.2.8.3. Is there a need for therapeutic drug monitoring (TDM) with belatacept LI regimen?

Current data obtained from Phase 3 trials, where fixed mg/kg belatacept dosing regimens were used, are not sufficient to evaluate whether therapeutic drug monitoring of belatacept C_{trough} may be needed for dose adjustment in de novo kidney transplant patients. However, some of the findings from the exposure-response analyses of data from Studies IM103008 and IM103027, as noted in the various sections above, would suggest that there may be a need to further evaluate the utility of TDM of belatacept C_{trough} in de novo kidney transplant patient through additional clinical experience, or additional clinical trials, or both.

A retrospective analysis of data obtained from Phase 3 Studies IM103008 and IM103027 showed that the percent of patients with mGFR10 increased as the number of belatacept C_{trough} samples per patient that were $<4 \mu\text{g/mL}$ increased (Figure 9), partially substantiating that TDM with belatacept LI regimen may provide better clinical outcome, at least, in terms of improvement of GFR in kidney transplant patients. In this analysis, a threshold C_{trough} of $4 \mu\text{g/mL}$ was estimated as approximately 25 percentile C_{trough} in patients who received the LI belatacept regimen (Tables 15 and 16). It is important to note that the beneficial effect of increasing belatacept C_{trough} to improve clinical efficacy will need to be further evaluated via additional clinical experience, additional clinical trials, or both, along with the assessment of the impact of maintaining these higher target trough concentrations on safety (e.g., PTLD and other malignancies, serious infections). For the incidence of patient/graft survival and AR, no apparent relationships with the number of belatacept C_{trough} samples per patient that were $<4 \mu\text{g/mL}$ were observed in the same retrospective analysis of data obtained from Phase 3 Studies IM103008 and IM 103027.

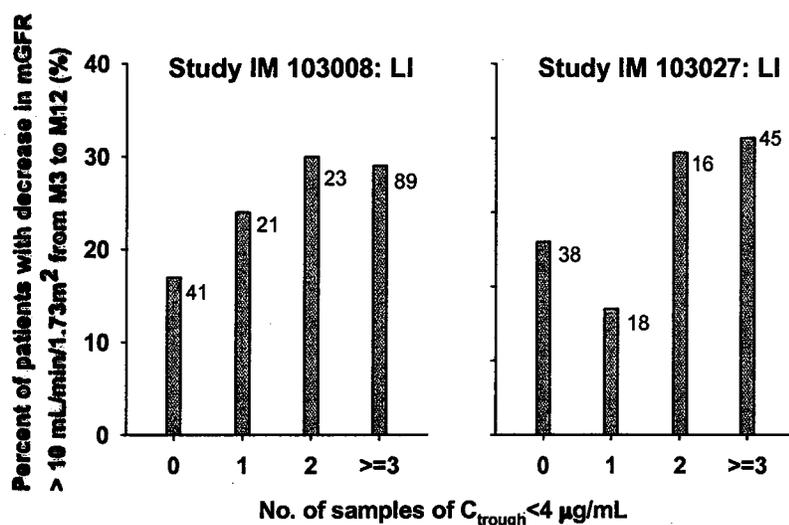


Figure 9. Percent of patients with decrease in mGFR $> 10 \text{ mL/min/1.73m}^2$ from Month 3 to Month 12 as a function of the sample numbers of belatacept $C_{trough} < 4 \mu\text{g/mL}$ during the same period. Four $\mu\text{g/mL}$ was estimated as approximately 25 percentile C_{trough} in patients who received the LI belatacept regimen. The numbers beside each bar represent the total number of patients with those sample numbers of belatacept $C_{trough} < 4 \mu\text{g/mL}$.

2.2.9. Does this drug prolong the QT or QTc interval?

A thorough QT study was not conducted for belatacept because it is a large molecular protein ^{(b) (4)} and it has high specificity for its molecular targets. Nonclinical studies did not detect QTc interval changes. In the two Phase 3 studies (IM103008 and IM103027), belatacept had no effect on prolongation of the QTc interval. The proportion of subjects with a prolonged QTc interval $> 30 \text{ msec}$ or $> 60 \text{ msec}$ compared with baseline and $> 450 \text{ msec}$ was similar across the belatacept treatment and the comparator (CsA) groups.

2.2.10. Pharmacokinetic characteristics of the drug and its major metabolites

2.2.10.1. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Healthy Subjects: The pharmacokinetic parameters of belatacept were linear over a range of escalating IV doses from 1 to 20 mg/kg. A higher than dose-proportional increase in mean AUC and a shorter elimination $t_{1/2}$ was observed from 0.1 to 1.0 mg/kg.

Renal Transplant Patients: The mean estimate of systemic clearance (CL) and volume of distribution (V_{ss}) of belatacept following multiple IV doses of 5 mg/kg and 10 mg/kg every 4 weeks in renal transplant patients were comparable. (Table 21 in Section 2.2.6.3).

2.2.10.2. Do PK parameters change with time following chronic dosing?

Following once monthly IV infusions of 10 mg/kg and 5 mg/kg, i.e., starting from Month 2 of the Belatacept LI regimen, there was minimal systemic accumulation (10-20%) of belatacept in renal transplant patients. In Phase 3 trials, the mean belatacept trough concentrations were relatively stable during monthly IV dosing.

2.2.10.3. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The pharmacokinetics (PK) of belatacept are linear and plasma exposures (C_{max} and AUC) increase dose proportionally in healthy subjects following single escalating IV infusion doses from 1 to 20 mg/kg (Figure 10 and Table 23). The terminal half-life ($T_{1/2}$) of belatacept is approximately 8 to 10 days in healthy subjects.

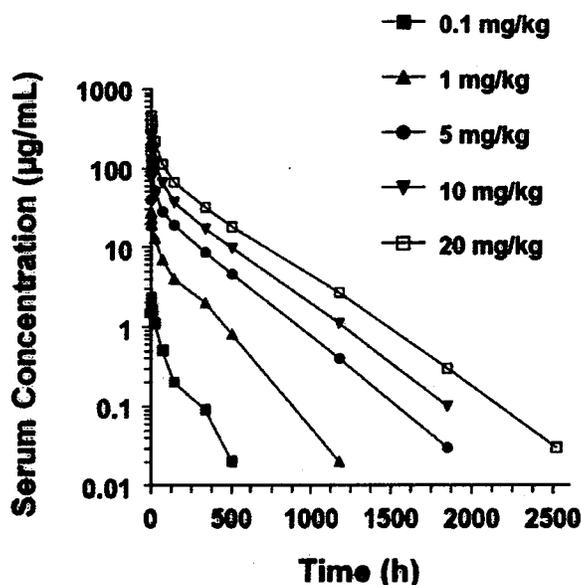


Figure 10. Mean serum concentration-time profiles of belatacept following single intravenous dose administration of belatacept.

Table 23. Mean pharmacokinetic parameters of belatacept in healthy subjects following a single intravenous infusion (n = 6/dose)

PK Parameter	BMS-224818 Dose Level				
	0.1 mg/kg	1 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg
C_{max}^a ($\mu\text{g/mL}$)	2.32 (13.6%)	28.2 (20.2%)	126 (14.9%)	260 (9.9%)	466 (10.3%)
$AUC(INF)^a$ ($\mu\text{g}\cdot\text{h/mL}$)	143 (14.4%)	2232 (16.0%)	10341 (21.8%)	22049 (15.1%)	41380 (4.4%)
T_{max}^b (h)	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.5 (1.0, 2.0)
T_{-HALF}^c (h)	86.4 (14.7)	137 (24.3)	176 (25.8)	197 (36.6)	222 (37.1)
CLT^c (mL/h/kg)	0.71 (0.12)	0.45 (0.07)	0.49 (0.11)	0.46 (0.07)	0.48 (0.02)
VSS^c (mL/kg)	80.2 (14.8)	79.6 (19.1)	102 (15.4)	98.8 (10.1)	117 (12.6)

- ^a Geometric mean (CV)
- ^b Median (minimum, maximum)
- ^c Arithmetic mean (SD)

Table 24 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 ($T_{1/2}$) were similar between kidney transplant patients (approximately 8 to 10 days) and healthy subjects. The between subject variability in the PK estimates from Table 4 (as %CV) is less than 30% in healthy subjects (range 18-28%), and is slightly higher in kidney transplant patients (range 27-35%).

Table 24. Pharmacokinetic parameters (Mean \pm SD [Range]) in Healthy Subjects and *de novo* 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}) [$\mu\text{g}/\text{mL}$]	300 \pm 77 (190-492)	139 \pm 28 (80-176)	247 \pm 68 (161-340)
AUC ^a [$\mu\text{g}\cdot\text{h}/\text{mL}$]	26398 \pm 5175 (18964-40684)	14090 \pm 3860 (7906-20510)	22252 \pm 7868 (13575-42144)
Terminal half-life ($T_{1/2}$) [days]	9.8 \pm 2.8 (6.4-15.6)	8.2 \pm 2.4 ^b (3.1-11.9)	9.8 \pm 3.2 (6.1-15.1)
Systemic clearance (CL) [mL/h/kg]	0.39 \pm 0.07 (0.25-0.53)	0.51 ^b (0.33-0.75)	0.49 \pm 0.13 (0.23-0.70)
Volume of distribution (V_{ss}) [L/kg]	0.09 \pm 0.02 (0.07-0.15)	0.12 ^b (0.09-0.17)	0.11 \pm 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

2.2.10.4. Is this a high extraction ratio or a low extraction ratio drug?

Not applicable.

2.2.10.5. Does mass balance study suggest renal or hepatic the major route of elimination?

A mass balance study 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.

2.3. Intrinsic Factors

2.3.1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Pharmacokinetics in Specific Populations: No dedicated studies were conducted in subjects with hepatic impairment, renal impairment or in geriatric and pediatric populations.

There was a trend toward higher clearance 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. In Phase 3 trials, the average belatacept C_{trough} over the first 12 months of therapy was comparable between males and females (16.2 ± 9.3 versus 16.7 ± 10.3 mcg/ml).

Therapeutic Endpoints in Specific Populations: The subgroup analysis of elderly, African-American and diabetic subgroups in Phase 3 trials did not demonstrate inconsistency with the overall study population in terms of the following therapeutic endpoints: acute rejection, renal function, patient survival and graft survival.

2.3.2. Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

None.

2.3.2.1. What pregnancy and lactation use information is there in the application?

Pregnancy Category. C

Belatacept was shown to cross the placenta of rats and rabbits. Belatacept should be used in pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In a Phase 1 single dose study, two pregnancies were reported in belatacept-treated subjects. Both females had been reported to have given birth to normal newborns.

Nursing Mothers:

Belatacept is known to be excreted in rat milk. It is not known whether belatacept is excreted in human milk or absorbed systemically after ingestion by a nursing infant. No patient is known to have breast-fed during any study. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from belatacept in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

2.3.3. Immunogenicity

2.3.3.1. What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

Based on the reviewer's confirmatory analysis, a total of 34 of 857 patients (4.0%) developed antibodies during treatment with intravenous belatacept in two Phase 3 trials and during the

long-term extension (LTE) phase of 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. The incidence of anti-belatacept antibodies at baseline is as follows: 6.2% (49/796) and 10.5% (10/95) in Phase 3 trials and in the LTE-phase of the key Phase 2 trial, respectively. The clinical pharmacology reviewer's calculated rates of anti-belatacept antibody formation are similar to that reported by the sponsor (Table 25). However, note that due to immunogenicity assay sensitivity limitations (i.e., interference at > 10 mcg/mL belatacept concentrations), some serum samples were labeled "indeterminate" for the production of anti-belatacept antibodies, which could explain at least in part what appears to be higher than expected rates of anti-belatacept antibodies at baseline than during and after therapy. Such indeterminate samples could have also resulted in the underestimation of immunogenicity rates during the initial phase of belatacept therapy, when belatacept concentrations were expected to be higher and when more patients had immunogenicity tests done prior to therapy discontinuation, than during the maintenance phase, i.e., the long-term extension phase of the key Phase 2 trial.

Table 25. Reviewer's calculated proportion (% and n/N) of patients who developed anti-belatacept antibodies in Phase 2 and 3 trials

Studies included	Baseline	During Treatment	After Discontinuation of Treatment ^c
Phase 3 only^a	6.1 (49/806)	3.5 (28/806)	5.6 (7/124)
Phase 2 (LTE)^b	10.5 (10/95)	16.8 (16/95)	20.0 (1/5)
Phase 3 + Phase 2-(LTE)- 4 weeks and 8 weeks	6.5 (59/901)	4.9 (44/901)	6.2 (8/129)
Phase 3 + Phase 2-(LTE)- 4 weeks only	6.3 (54/857)	4.0 (34/857)	5.6 (7/124)
Phase 2(LTE)- 4 weeks only	9.8 (5/51)	11.8 (6/51)	- (0/0)
Phase 2(LTE)- 8 weeks only	11.4 (5/44)	22.7 (10/44)	20 (1/5)
Belatacept Less-Intensive ^d	7.5 (32/428)	4.9 (21/428)	3.2 (2/62)
Belatacept More-Intensive ^d	5.1 (22/429)	5.4 (23/429)	8.1 (5/62)

^a Studies IM103008 and IM103027

^b Long-term extension phased of Study IM103100 with 5 mg/kg every 4 weeks and every 8 weeks regimens

^c Within 7 belatacept half-lives after discontinuation of therapy, and not seropositive previously

^d Phase 3 + Phase 2 (LTE) 4 weeks regimen

Overall, the proportion of anti-belatacept antibody seropositive individuals was lower in *de novo* renal transplant patients than in: (a) healthy subjects (100% in the single dose study IM103046) who were immunocompetent and not receiving additional immunosuppressive agents, (b) a few patients with functioning grafts after the complete elimination of immunosuppression, and (c) in the 8-week cohort of the LTE phase of the key Phase 2 trial. These findings indicate that concomitantly administered immunosuppressive agents likely attenuated the capability of renal transplant patients to produce anti-belatacept antibodies. Additionally, it appears that after discontinuation of belatacept therapy, the Belatacept More-Intensive regimen is associated with a higher incidence of anti-belatacept antibody response than the Less-Intensive regimen.

In the Phase 3 trials, the median (range) time to first seroconversion was about 103 (1 to 728) days. In the two Phase 3 trials, immunogenicity samples were collected at baseline, Months 3, 6, and 12 during Year 1 post-transplantation; thus, **the specific time of a subject's seroconversion** could not be accurately assessed. However, samples were collected anytime that a subject experienced a suspected acute rejection. In the long-term extension phase (but not in the first 12 months) of the Phase 2 trial, immunogenicity samples were collected initially, at 6-month visits, and then at yearly interval visits.

Of those patients who seroconverted during belatacept treatment and after discontinuation of therapy, 50% and 71.4%, respectively, had persistent antibodies. Persistence is defined as the presence of anti-belatacept antibodies on at least two consecutive occasions or during the time of **the patient's last immunogenicity assessment**. Table 26 summarizes the clinical pharmacology

reviewer's calculated proportions of patients with persistent anti-belatacept antibodies. It appears that at least after discontinuation of belatacept therapy, there was a trend of a lower seroconversion rate but a higher persistent antibody rate in the less-intensive (LI) regimen than in the more-intensive (MI) regimen. However, the antibody titers at any given time during or after belatacept appear to be relatively low (range 5 to 320).

Table 26. Reviewer's calculated proportion (% and n/N) of patients who had persistent anti-belatacept antibodies in key Phase 2 and 3 trials

Studies included	Persistent anti-belatacept antibodies (%, n/N)	
	During Treatment ^e	After Discontinuation of Treatment ^{e,f}
Phase 3 only ^a	50 (14/28)	71.4 (5/7)
Phase 2 (LTE) ^b	56 (9/16)	0 -
Phase 3 + Phase 2-(LTE)- 4 weeks and 8 weeks	52.3 (23/44)	71.4 (5/7)
Phase 3 + Phase 2-(LTE)- 4 weeks only	50 (17/34)	71.4 (5/7)
Phase 2(LTE)- 4 weeks only	50 (3/6)	0 -
Phase 2(LTE)- 8 weeks only	60 (6/10)	0 -
Belatacept Less-Intensive ^d	58.8 (10/17)	100 (2/2)
Belatacept More-Intensive ^d	41.2 (7/17)	60 (3/5)

^a Studies IM103008 and IM103027

^b Long-term extension phase of Study IM103100 with 5 mg/kg every 4 weeks and every 8 weeks regimens

^c Within 7 belatacept half-lives after discontinuation of therapy

^d Phase 3 + Phase 2 (LTE) 4 weeks regimen

^e Total N (denominator) equals the number of patients who seroconverted

^f Total N (denominator) equals the number of patients who seroconverted after therapy discontinuation

2.3.3.2. Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

Impact of Immunogenicity on PK: According to the sponsor's analysis, the Bayesian-predicted clearance of belatacept from population PK analysis was similar in seronegative, seropositive, and indeterminate subjects (Figure 11).

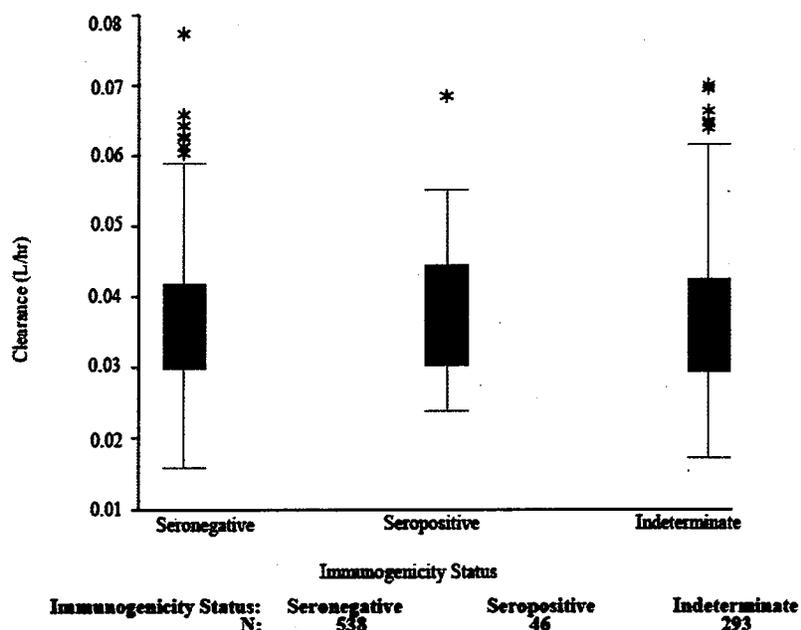


Figure 11. Population PK predicted belatacept clearance, by seroconversion status

The descriptive statistics of belatacept clearance by immunogenicity status are summarized in **Table 27**. Based on the reviewer's analysis, there is no significant difference in belatacept clearance among the three groups.

Table 27. Belatacept clearance as a function of seroconversion status

Seroconversion Status	Number of Subjects	Bayesian-predicted Belatacept Clearance (L/h)			
		Mean \pm SD	Min	Max	Median
indeterminate	204	0.0376 \pm 0.0067	0.0172	0.0699	0.036
seronegative	544	0.0364 \pm 0.0092	0.0159	0.0773	0.0357
seropositive	33	0.0362 \pm 0.0083	0.0221	0.0543	0.0365

2.3.3.3. Do the anti-product antibodies have neutralizing activity?

Of the 19 patients with confirmed binding to the CTLA-4 region of belatacept, 6 (31.6%) patients were shown to possess neutralizing antibodies. The clinical pharmacology reviewer's calculated rate of neutralizing antibodies (27.3%; 6/22) was similar to that reported by the sponsor (Table 28). All 6 patients who developed NAB against belatacept were participants of the Phase 3 trial, IM103027, with equal proportions in the less-intensive and more-intensive belatacept regimens. Note however that the development of neutralizing antibodies (NAB) could have been underestimated because of drug interference of the NAB assay at > 1 mcg/mL belatacept concentrations.

Table 28. Reviewer's calculated proportion (% and n/N) of patients who developed Neutralizing Antibodies (NAB) against belatacept in key Phase 2 and 3 trials

Studies included	NAB (%, n/N)
Phase 3 only ^a	33.3 (6/18)
Phase 2 (LTE) ^b	14.3 (2/14)
Phase 3 + Phase 2-(LTE)- 4 weeks and 8 weeks	25 (8/32)
Phase 3 + Phase 2-(LTE)- 4 weeks only	27.3 (6/22)
Phase 2(LTE)- 4 weeks only	0 (0/4)
Phase 2(LTE)- 8 weeks only	20 (2/10)
Belatacept Less-Intensive ^d	25 (3/12)
Belatacept More-Intensive ^d	30 (3/10)

^a Studies IM103008 and IM103027

^b Long-term extension phase of Study IM103100 with 5 mg/kg every 4 weeks and every 8 weeks regimens

^c Within 7 belatacept half-lives after discontinuation of therapy

^d Phase 3 + Phase 2 (LTE) 4 weeks regimen

Table 29 compares the belatacept clearance of the 6 NAB-positive patients with those patients who were either not tested for NAB status due to lack of confirmed reactivity to CTLA4, NAB-negative, NAB-indeterminate due to assay limitations. There is no significant difference in belatacept clearance among the two groups.

Table 29. Belatacept clearance as a function of neutralizing antibody (NAB) status

Seroconversion Status	Number of Subjects	Bayesian-predicted Belatacept Clearance (L/h)			
		Mean ± SD	Min	Max	Median
NAB-(+)	6	0.0393 ± 0.0112	0.0247	0.0543	0.0416
Others ^a	778	0.0367 ± 0.0095	0.0159	0.0773	0.0358

^a includes patients who were not tested for neutralizing antibodies (NAB) due to lack of confirmed reactivity to CTLA4, and those who were not NAB-positive

2.3.3.4. What is the impact of anti-product antibodies on clinical efficacy?

Table 30 compares the incidence of efficacy-related events in Phase 2 and 3 clinical trials, by seroconversion status. It appears that there is a trend of a higher incidence of death, graft loss, and acute rejection in those patients who were positive or indeterminate for the development of anti-belatacept antibodies than those who were negative. However, causal and temporal association with anti-belatacept antibody development cannot be established due to either the

complexity of the clinical cases or the limited data available on the antibody titers and belatacept concentrations around the time of the event.

Table 30. Incidence of death, graft loss, and acute rejection in key Phase 2 and 3 trials, by seroconversion status

	Death (%; n/N)	Graft Loss (%; n/N)	Acute Rejection (%; n/N)
Seropositive	3.1 (1/32)	12.5 (4/32)	28 (7/32)
Seronegative	1.5 (7/481)	2.1 (10/481)	14.1 (68/481)
Indeterminate	8.5 (24/283)	10.2 (29/283)	26.9 (76/283)

Impact of anti-drug antibodies on graft loss:

Based on the sponsor's summary Phase 3 data through database lock, the rates of graft loss in anti-belatacept antibody seropositive patients and indeterminate patients were higher [12.5% (4/32) and 10.2% (29/283), respectively] than in seronegative patients [2.1% (10/481)] which suggests a potential association between immunogenicity and graft loss. A similar trend was also observed when including the data from the key Phase 2-LTE-4 weeks regimen, i.e., 10.5% (4/38), 1.9% (10/514), and 10.5% (31/295) for seropositive, seronegative and indeterminate patients, respectively.

The sponsor did not conclude a causal association between graft loss and immunogenicity because all the 4 reported cases of graft loss during Year 1 in anti-belatacept antibody seropositive patients were due to primary graft thrombosis or technical causes, and occurred within 8 days of transplant. The reviewer notes that the reported times to sero-conversion in these 4 patients ranged from 7 to 364 days but in 2 of these 4 patients, the antibody titers around the dates of graft loss were below the LLQ of the assay. Immunogenicity assessments were not adequate for the other two patients to allow for the evaluation of a temporal association between seroconversion/NAB-positivity and graft loss, although the anti-belatacept antibody titers for these patients with inadequate immunogenicity data were both >LLQ, i.e., 20.

Impact anti-drug antibodies on patient survival:

Based on the sponsor's summary Phase 3 data through database lock, there was a trend of higher death rates in anti-belatacept antibody seropositive patients [3.1% (1/32)] and indeterminate patients [8.5% (24/283)] as compared to seronegative patients [1.5% (7/481)], suggesting a potential association between death and immunogenicity. The difference between seropositive and seronegative patients was lower [2.6% (1/38) versus 1.8% (9/514)] when including the data from the key Phase 2 study-LTE-4 week regimen. There was no apparent difference in the rates of "death with functioning graft" between seropositive and seronegative patients (0% versus 0.8 to 1.2%); however the corresponding rate in indeterminate patients was substantially higher [7.5 to 7.8%].

The sponsor did not conclude a causal association between death and immunogenicity because the single case of death in an anti-belatacept antibody seropositive patient was characterized with a complicated transplantation procedure and post-operative course. The reviewer notes that this

patient was reported to have suffered from graft loss on day 3 and died on day 96 but the only time that immunogenicity was evaluated in this seropositive patient was on day 58 (NAB +).

Impact of anti-drug antibodies on acute rejection (AR):

Based on the sponsor's summary Phase 3 data through database lock, there was trend of higher AR incidence in anti-belatacept antibody seropositive patients (28%; 7/32) and indeterminate patients (26.9%; 76/283) than in seronegative patients (14.1%; 68/481), suggesting a potential association between immunogenicity to belatacept and AR.

The sponsor did not conclude an association between AR and immunogenicity because the incidence (7/25; 28%) of acute rejection in anti-belatacept antibody seropositive patients was comparable to the overall rate of AR of 20% in the two Phase 3 trials. The reviewer notes that 8 seropositive patients had at least 1 acute rejection episode at 4 to 128 days post-transplant. In 5 of these 8 patients with immunogenicity evaluations around the time of the acute rejection, the anti-belatacept antibody titers were > LLQ, i.e., 5 to 20, and the belatacept trough concentrations did not appear to be abnormally low compared to the population values.

Impact of neutralizing antibodies (NAB) on death, graft loss, and acute rejection:

Of note, 3 of the 6 patients who developed neutralizing antibodies against belatacept had acute rejection, graft loss and/or death. However, the lack of immunogenicity data surrounding the time of the event, the low antibody titers, and the low number of cases preclude the reviewer from attributing any of these events to the production of NAB against belatacept.

2.3.3.5. What is the impact of anti-product antibodies on clinical safety? (e.g., infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)?

Based on the reviewer's analysis of key Phase 2 and Phase 3 immunogenicity and adverse event data, there was a trend of a higher percentage of patients with acute infusional and peri-infusional adverse events in anti-belatacept antibody seropositive than in seronegative patients, suggesting a potential association between the development of anti-belatacept antibodies and these adverse events. Table 31 provides a comparison of these adverse events in the various seroconversion subgroups. The sponsor did not conclude a causal association between immunogenicity and serious infusional or hypersensitivity reactions because only 1 of the anti-belatacept antibody seropositive subjects developed a serious reaction and was also described with a complicated post-operative course and multiple events with onset on Day 1.

Table 31. Acute Infusional and Peri-Infusional Adverse Events By Seroconversion Status

	Acute Infusional Adverse Events (%; n/N)	Peri-Infusional Adverse Events (%; n/N)
Seropositive	13.7 (7/51)	60.8 (31/51)
Seronegative	3.7 (23/614)	50.5 (310/614)
Indeterminate	5.3 (12/226)	42.9 (97/226)

The sponsor's reported rates of autoimmune events in seropositive and indeterminate patients were 3.1% (1/32) and 0.71% (2/283), respectively. The sponsor did not conclude a causal association between immunogenicity and autoimmune events because the one seropositive patient who developed Guillain-Barré syndrome was seronegative prior to and immediately following the event.

2.3.3.6. What is the impact of the cross-reactivity of the neutralizing anti-product antibodies to endogenous protein on clinical outcome?

There appears to be no significant association between clinical outcome and the cross-reactivity of anti-belatacept antibodies with abatacept (used as the surrogate of the endogenous CTLA4). Out of the 8 NAB-positive patients in the three key clinical trials, two patients (IM103027-84-10034 and IM103100-30-00001) who showed cross-reactivity to abatacept did not show any negative clinical consequence, i.e., death, graft loss, acute rejection, acute-infusional and on-treatment peri-infusional adverse events.

2.3.3.7 What is the impact on acute rejection of anti-donor (HLA) antibodies?

Impact of anti-donor human leukocyte antigen (HLA) antibodies on acute rejection (AR):

Table 32 compares patients with acute rejection versus without acute rejection by Month 12 in terms of the proportion of patients who developed, possibly developed, or did not develop anti-donor HLA antibodies by Month 12 of therapy. The data indicate that patients without acute rejection by Month 12 do not normally change from a seronegative status at baseline, regardless of treatment. On the other hand, unlike belatacept-treated patients, cyclosporine-treated patients with acute rejection have a higher probability of changing from a seronegative status at baseline to a positive/possible seropositive status at Month 12.

Overall, the findings suggest that in Phase 3 trials, the incidence of antibody-mediated rejections observed in the Phase 3 trials was lower following treatment with belatacept than with cyclosporine.

**Table 32. Anti-donor HLA antibody status of patients by Month 12 post-transplant:
With Acute Rejection versus Without Acute Rejection**

Treatment	Seroconversion status	Proportion of patients (%)		Change from baseline
		Baseline or Pre-transplant	Month 12 Post-transplant (Unadjusted)	
With Acute Rejection				
Belatacept MI		N=77	N=78	
	Positive	3.9	5.1	
	Possible	6.5	5.1	
	Negative	89.6	89.7	No change
Belatacept LI		N=66	N=68	
	Positive	6.1	1.5	
	Possible	4.5	7.4	
	Negative	89.4	91.2	No change
Cyclosporine		N=40	N=39	
	Positive	5.0	15.4	
	Possible	12.5	17.9	
	Negative	82.5	66.7	↓ 19%
Without Acute Rejection				
Belatacept MI		N=300	N=306	
	Positive	5.7	3.6	
	Possible	7.0	5.6	
	Negative	87.3	90.8	No change
Belatacept LI		N=313	N=315	
	Positive	5.1	2.9	
	Possible	5.8	6.7	
	Negative	89.1	90.5	No change
Cyclosporine		N=326	N=325	
	Positive	7.1	6.8	
	Possible	8.9	8.6	
	Negative	84.0	84.6	No change

2.4. Extrinsic Factors

2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Concomitant use with mycophenolate mofetil (MMF): Consistent with the ability of cyclosporine (but not belatacept) to inhibit the enterohepatic recirculation of mycophenolic acid

glucuronide (MPAG) to mycophenolic acid (MPA), the belatacept-treated patients who participated in a PK substudy were shown to have about a 41% higher MPA AUC and 22% higher MPA Cmax, as compared to the cyclosporine-treated patients.

Lymphocyte depleting agents (LDT, e.g., thymoglobulin) and PTLD: Based on the sponsor's analysis, the PTLD event rate was higher in those patients who used lymphocyte-depleting therapy (LDT) in the belatacept MI group but not in the belatacept LI group. For the MI group, the PTLD rates for those who did not use LDT and those who did were 1% (4/408) and 5.8% (4/69), respectively; the corresponding rates for the LI group were 1.2% (5/423) versus 0% (0/49). A review of the individual patient profiles of those who developed PTLD in the Phase 2 and Phase 3 trials indicate that only the belatacept MI patients were given LDT to treat their acute rejection episodes. Because LDT is a known risk factor of PTLD, the potential contribution of LDT use and PTLD development in belatacept MI is possible; the direct influence of LDT use on PTLD development in belatacept LI is less clear at this time.

Table 33 compares the descriptive statistics of belatacept C_{trough} over the first 6 months in belatacept -treated patients who received LDT versus those who did not, by PTLD status. There was no substantial difference in the mean/median/range of belatacept C_{trough} in those patients who received LDT or did not receive LDT and development of PTLD.

Table 33. Comparison of Belatacept C_{trough} over the first 6 months in Phase 3 trial patients, by PTLD status and use of lymphocyte-depleting therapy (LDT)

LDT Use	PTLD	N	Mean ± SD (µg/mL)	Median	Range	10 th to 19 th Percentile
No	No	625	19.4 ± 8.8	17.6	1.8 – 63.5	9.6 – 30.8
	Yes	6	21.5 ± 8.2	19.8	13.4 – 34.9	13.4 – 34.9
Yes	No	61	21.1 ± 8.5	21.1	6.5 - 46.3	10.1 – 32.0
	Yes	3	23.9 ± 3.3	24.6	20.4 – 26.8	20.4 – 26.8

2.4.2. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None.

2.4.3. Drug-Drug interactions

2.4.3.1. Is there an in vitro basis to suspect in vivo drug-drug interaction?

It is not clear at the time of writing this review. 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. It should be noted that this recommendation is not a Phase 4 Commitment because a Complete Response (CR) action will be taken for BLA 125288 for belatacept during this review cycle.

2.4.3.2. Is the drug a substrate of CYP enzymes?

Not applicable.

2.4.3.3. Is the drug an inhibitor and/or an inducer of CYP enzymes?

Traditional *in vitro* and *in vivo* drug interaction studies were not conducted.

2.4.3.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Not applicable.

2.4.3.5. Are there other metabolic/transporter pathways that may be important?

No studies on the metabolism of belatacept have been performed in humans. Metabolism studies are not generally performed for proteins which are degraded into amino acids that are then recycled into other proteins, small peptides and individual amino acid. Therefore classical biotransformation studies as performed for pharmaceuticals are not needed. No *in vitro* drug-drug interaction studies have been performed since CYP450 enzyme system is not expected to play any role in belatacept biotransformation.

2.4.3.6. Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and if so, has the interaction potential between these drugs been evaluated?

In the pivotal Phase 3 trials, belatacept was used with basiliximab, mycophenolate mofetil, and corticosteroids. With the exception of the MPA/MPAG PK substudy that compared the MPA/MPAG exposures in the belatacept versus the cyclosporine treatment arms, traditional drug-drug interaction studies have not been conducted for belatacept and concomitant medications.

2.4.3.7. What other co-medications are likely to be administered to the target patient population?

In the clinical trials, the following non-therapy medications were also used to prevent viral infections (e.g., gancyclovir), and to treat acute rejections (e.g., lymphocyte-depleting agents).

2.4.3.8. Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

A PK substudy in these Phase 3 trials was conducted to determine whether MPA exposures were similar between the belatacept-based regimen and the cyclosporine-based regimen (comparator). (See also section 2.4.1.)

2.4.3.9. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

None.

2.4.3.10. Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

None.

2.5. General Biopharmaceutics

2.5.1. What is the relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative PK and PD?

Not applicable. Only (b) (4) belatacept, the proposed to-be-marketed formulation, was evaluated in the pivotal Phase 3 trials. Although some patients in the Phase 3 trials switched from the (b) (4) after Month 12, both preparations were reconstituted to the same strength (25 mg/mL) for further dilution. The sponsor's analysis indicates that the belatacept C_{trough} in values were comparable in these patients before and after the switch.

2.5.2. What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Not applicable.

2.5.3. If the formulations are not BE, what dosing recommendations should be made that would allow approval of the to-be-marketed formulation? (e.g., dosage adjustments may be made for injectables)

Not applicable.

2.5.4. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable. Belatacept is given via intravenous infusion.

2.5.5. When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.6. How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

Not applicable.

2.6. Analytical Section

2.6.1. How are the active moiety identified and measured in the serum in the clinical pharmacology and biopharmaceutics studies?

Enzyme-linked immunosorbent assay (ELISA) was used to measure serum and urinary belatacept concentrations in the clinical pharmacology and biopharmaceutics studies. Table 34 provides the assay validation parameters of the ELISA methods used in these studies.

Table 34. Summary of *in vitro* analytical methods used in biopharmaceutics and clinical pharmacology studies

Study No. ^a	Regression Model	Standard Curve Range	Assay Precision (%CV)		Accuracy (% Deviation)	Analyte Stability in Matrix	Document Control Number
			Inter-	Intra-			
Analyte: Belatacept (BMS-224818)			Sample Matrix: Human Serum			Method: ELISA	
IM103001	weighted	3.0-80.0	Within	Within	Within	Belatacept is stable in whole blood for up to 24 h at room temp, in human serum after five freeze-thaw cycles, up to 5 days at RT and approximately 4°C, up to 3 years 7 months at approximately -70°C, up to 120 days at approximately -20°C, and unaffected by 10% human serum from healthy subjects or subjects with psoriatic arthritis	910068401
IM103100	quadratic	ng/mL	± 2.32%	± 3.01%	± 1.38%		
IM103002	weighted quadratic	300-8000 ng/mL	Within ± 2.08%	Within ± 7.09%	Within ± 3.46%	Rheumatoid factor positive RA serum does not adversely affect the method when carried out in 0.1% serum	910074383
IM103008	weighted	3.0-80.0	Within	Within	Within	Belatacept is stable in human serum for up to 25h at RT and after 13 freeze-thaw cycles	930017013
IM103027	quadratic	ng/mL	± 7.42%	± 11.76%	± 9.78%		
IM103100							
IM103046							
IM103047	weighted	3.0-80.0	Within	Within	Within	Belatacept is stable in human serum for up to 25h at RT and after 13 freeze-thaw cycles	930007080
IM103024	quadratic	ng/mL	± 2.8%	± 5.5%	± 4.7%		
IM103029							
Analyte: Belatacept (BMS-224818)			Sample Matrix: Human Urine			Method: ELISA	
IM103047	Four parameter	3.0-80.0 ng/mL	Within ± 14.94% ^a	Within ± 11.92% ^a	Within ± 2.62%	Belatacept is stable in human urine up to for 26h at RT, after 3 freeze-thaw cycles, and for least 174 days at approximately -70°C and unaffected by 10% urine	930024243

^a IM103001 and IM103002 used the BMS manual method
 IM103008, IM103010, IM103027, IM103034, IM103045, IM103046 and IM103047 used the (b) (4) manual method
 IM103024 and IM103029 used the BMS automated method
 IM103100 used the BMS an (b) (4) manual method

2.6.2. Which metabolites have been selected for analysis and why?

Not applicable because belatacept is a protein.

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2.6.3. For all moiety measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Not applicable because belatacept is a protein.

2.6.3. What bioanalytical methods are used to assess therapeutic protein concentrations? Briefly describe the methods and summarize the assay performance.

Either the BMS Manual or the ^{(b) (4)} Manual ELISA method was used to quantify serum or urine belatacept concentrations in pivotal Phase 1, Phase 2 and Phase 3 trials (Table 34 in section 2.6.1). In all these clinical studies, both methods were reported to have the same range of reliable response (3.0 to 80 ng/mL), with a LLOQ of 3 ng/mL. The accuracy and (intra- and inter-) assay precision were also similar, i.e., not exceeding $\pm 10\%$ deviation and $\pm 15\%$, respectively, in all studies. The assay was not subject to interference with mycophenolate mofetil and basiliximab, or thymoglobulin. The ELISA method utilizes monoclonal antibodies specific to belatacept. A brief description of the assay follows.

Following dilution, the PK serum (or urine) samples is added to 96-well polystyrene microtiter plates coated with a monoclonal antibody (clone 7F8) capable of selectively binding belatacept in the serum samples. Non-specific binding was blocked by the addition of PTB buffer. After an incubation period, plates were washed with phosphate buffered saline, pH 7.4 and containing 0.05% Tween 20. The antibody-bound belatacept is detected using a biotinylated second monoclonal antibody (10A8) specific for belatacept. After another incubation period, the plates are washed again to remove unbound material and then a streptavidin-horseradish peroxidase (HRP) conjugate is added. After an additional incubation for 1 hour, unbound conjugate is removed in the plate washer, followed by the addition of 3, 3', 5, 5'- tetramethylbenzidine (TMB), which is a colorimetric substrate for horseradish peroxidase. The colored product following the reaction of TMB with HRP is then measured using a microtiter plate reader equipped with a 450 nm test and 620 nm reference filter.

2.6.3. What bioanalytical methods are used to assess the formation of the anti-product antibodies? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.6.3.1. What is the performance of the binding assay(s)?

Of the three generations of immunoassays that were employed to detect anti-belatacept antibodies, the most current and sensitive electro-chemiluminescence (ECL) assay (collectively referred to as Assay C) was used in the pivotal Phase 3 studies (IM103008, IM103027), as well as in the long-term extension of a key Phase 2 study (IM103100). All serum samples that tested positive in the screening assay (Tier 1) were subjected to a confirmatory assay (Tier 2), which determined antibody binding and titer to specific regions of the belatacept molecule. Table 35 summarizes the validation parameters for Assay C. The assay can detect up to 250 ng/mL of anti-drug antibodies in the presence of up to 10 mcg/mL of free belatacept. The

statistically determined assay cut point was utilized to identify the serum samples at a 5% false-positive rate.

Table 35. Summary of Validation Data for Assay C, an Electrochemiluminescence Assay for Screening, Titration, and Confirmation of Antibodies to Belatacept in Human Serum

Precision of Screening - Controls	
Inter-analyst Precision (%CV)	8.5 to 11.6%
Inter-run Precision (%CV)	10.8 to 25.0%
Intra-Assay Precision (%CV)	6.3 to 8.1%
Precision of Screening – Patient Samples	
Inter-donor Precision (%CV)	50.7 to 52.4%
Intra-donor Precision (%CV)	7.2 to 7.5%
Cut-Point	Ratio 1 Value = Mean RLU of Sample / Mean RLU of Diluent ≥ 1.29
Sensitivity	At least 12.5ng/mL with respect to the current lot of positive control antibody in normal and patient serum
Selectivity (Matrix Effect):	10/10 individuals unspiked classified as negative, and 10/10 individuals spiked with positive control antibody classified as positive
Specificity:	No cross-reactivity seen with human IgG1 or ovalbumin
Drug Interference	Assay can tolerate up to 10ug/mL free drug at 400ng/mL of positive control antibody
Consistency of Antibody Titration	Precision of antibody titration was found to be within one dilution
Confirmation of Positive Response	-Demonstrated greater than 90% inhibition of the positive control antibody with Belatacept or LEA29Y-T -Demonstrated less than 40% inhibition of the negative quality control with Belatacept or LEA29Y-T -Demonstrated less than 30% inhibition of individual patient sera with Belatacept or LEA29Y-T
Sample Stability	
Bench-top	23 hours
2-8°C	29 days
Freeze-Thaw	5 freeze-thaw cycles
Long-term storage at -70°C	30 day stability demonstrated

2.6.3.2. What is the performance of the neutralizing assay(s)?

In Tier 3 of Assay C, samples positive to the modified CTLA4 region were analyzed for neutralizing antibody (NAB). A cell-based bioassay was validated to identify whether the human serum samples possessed belatacept-specific NAB. Due to assay interference by belatacept, NAB was assessed only if the belatacept concentration was < 1 mcg/mL. Thus, 58% (14/24) of the samples tested for NAB were “NAB-indeterminate” because the belatacept concentrations in these samples exceeded 1 mcg/mL. Intra-sample precision estimates (%CV) for the belatacept responses at concentrations 50, 25, and 12.5 ng/mL were 26.84, 26.76, and 20.22%, respectively

and the overall accuracy estimates across the 3 concentrations were within $\pm 9\%$ of nominal level. The sensitivity of the assay in neat pooled RD serum with or without 100 ng/mL of drug was estimated to be 2.5 mcg/mL of neutralizing antibody. Significant neutralizing activity was reliably detected in 8 of 9 individual RD serum samples with belatacept-specific neutralizing antibody 7F8.

3. Proposed Labeling

(b)(4)

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

4. APPENDICES

4.1. Pharmacometrics Review

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**OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW**

Application Number	BLA 125,288
Submission Number (Date)	01 July 2009
Drug Name	Belatacept (Nulojix™)
Proposed Indication	Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants
Clinical Division	Division of Special Pathogens and Transplant Drugs
Primary CP Reviewer	Gerlie Gieser, Ph.D. & Seong Jang, Ph.D.
Primary PM Reviewer	Jiang Liu, Ph.D. & Seong Jang, Ph.D.
Secondary CP Reviewer	Philip Colangelo, Pharm.D., Ph.D.
Secondary PM Reviewer	Pravin Jadhav, Ph.D.
Sponsor	Bristol-Myers Squibb

1 SUMMARY OF FINDINGS

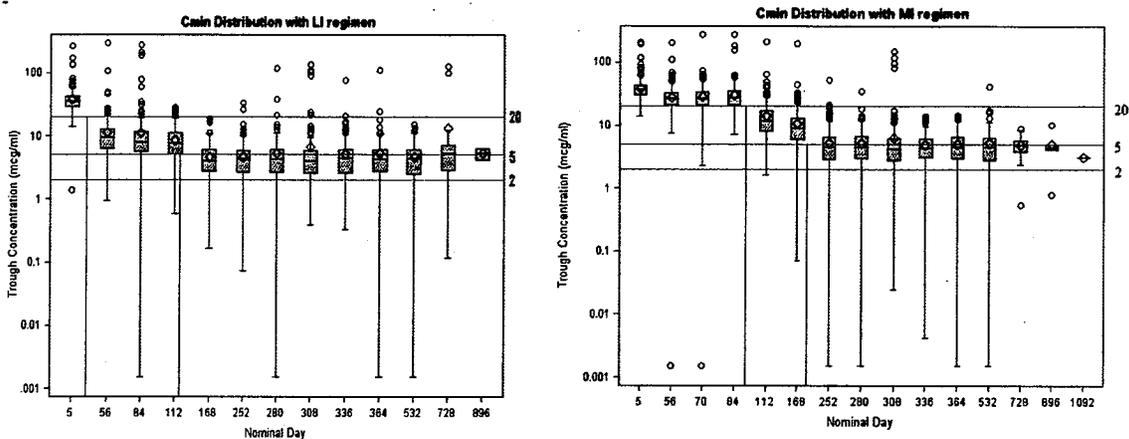
1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Did the proposed dose regimen achieve target belatacept concentration?

Yes, more than 80% of the patients receiving the LI and MI dosing regimens in pivotal studies achieved trough concentrations higher than the target concentration. The target was derived from in vitro experiments, pre-clinical studies and early phase studies. The trough concentrations of belatacept were similar in subjects on the LI or MI regimen on Day 5. The trough concentrations were higher in subjects on the MI regimen between Day 56 and 168 compared to those on the LI regimen. The trough concentrations were comparable after Day 168 (Figure 1 and Table 4). Belatacept has a consistent and predictable PK profile based on population PK analysis.

Figure 1. Belatacept dose regimens (LI regimen (left) and MI (right)) achieved target concentration



Note: the three reference lines represent the target trough concentrations in the 2 pivotal studies: 20 ug/mL (for Month 1 (LI) or Month 1-3 (MI)), 5 ug/mL (for Month 2-4 (LI) or Month 4-6 (MI)) and 2 ug/mL (Month 5 afterward (LI) or Month 7 afterward (MI))

1.1.2 Is there evidence of significant exposure-response relationship for efficacy?

- **Acute Rejection:** Higher belatacept C_{trough} on Day 5 was related with a lower incidence of acute rejection during Month 1 post-transplant. However, the incidence of acute rejection during Month 1 post-transplant accounted for only 1/3 of total acute rejection. Overall, no apparent relationship between belatacept C_{trough} and acute rejection was observed in pivotal studies, IM103008 and 103027.
- **Renal function:** The percent of patients with a decrease in measured GFR ≥ 10 mL/min/1.73 m² from Month 3 to Month 12 (mGFR10) decreased with increasing average belatacept C_{trough} for the same period.

1.1.3 Is there evidence of significant exposure-response relationship for safety?

There was no apparent relationship between belatacept exposure and incidence of safety endpoints.

- **Post transplant lymphoproliferative disorder (PTLD):** Belatacept C_{trough} levels in patients with PTLD were not substantially different from patients without PTLD. The conclusion was based on graphical analysis comparing belatacept exposure in patients with PTLD to overall exposures (Figure 4, Figure 10, Figure 14, and Figure 15). Due to low incidence of PTLD and lack of a suitable variable to describe the overall belatacept exposure, time-to-event analysis and logistic regression analysis were not intensively pursued. The known risk factors for PTLD, such as recipient EBV-negative status at the time of transplantation, CMV infection, and the use of T cell depleting therapy, were confirmed in belatacept-treated subjects (Figure 11). Also higher body weight was associated to higher average exposure and higher incidence of PTLD. But given the current study

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design and low incidence, the power to detect the exposure-response relationship for PTLD was low. The analysis also suggested that joint consideration of EBV status and CMV infection may provide additional information regarding PTLD (Figure 12). Additional analyses conducted by the Pharmacogenomics reviewers further suggested that among EBV positive patients, those with CMV negative serology were more likely to develop PTLD than those who are CMV positive (see Pharmacogenomic review).

- **Infections:** Serious infections occurred more frequently in the first 6 months of belatacept therapy. From Month 2 to Month 6, exposure in subjects on the MI regimen was generally higher than those on the LI regimen. However, the incidence of first serious infections did not appear to be substantially different between the MI regimen and the LI regimen in that period (Figure 13). The exposure-response analysis (logistic regression and quartile plot) using the serious infection (first occurrence) data up to Month 1 also confirmed lack of relationship between belatacept exposure and incidence of serious infection. The incidence of some infections, such as BK virus and Herpes virus infections, may be higher with higher belatacept C_{trough} . However, overall incidence of these infections was low to establish exposure-response relationship.

1.1.4 Is the belatacept LI regimen acceptable and is there a need for TDM?

Data obtained from pivotal trials, where fixed mg/kg belatacept dosing regimens were used, were not sufficient to evaluate whether monitoring belatacept C_{trough} may be needed for dose adjustment in de novo kidney transplant patients. However, the findings from analyses of data from Studies IM103008 and IM103027 (i.e., (a) large between-subject variability of belatacept C_{trough} , (b) a trend for improvement of renal function (mGFR) associated with belatacept C_{trough} in kidney transplant patients receiving standard criteria donor kidneys, and (c) the incidence of some viral infections (BK virus and herpes virus) may be higher with higher belatacept C_{trough}) would suggest that there may be a need to further evaluate the need for TDM of belatacept C_{trough} in de novo kidney transplant patients through additional clinical experience, or additional clinical trials, or both.

1.2 Recommendations

The LI dosing regimen is acceptable from clinical pharmacology perspective.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

2 PERTINENT REGULATORY BACKGROUND

This is the original submission that the sponsor is seeking approval of belatacept (BLA 125288) for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.

Belatacept represents a new class of therapeutic agent in transplant immunosuppression. It is a recombinant soluble fusion protein targets the blockade of CD28:CD80/CD86 interactions, key costimulatory signals required for T cell activation. Abatacept, the first-generation of this class of co-stimulation blocker fusion proteins, which differs from belatacept by 2 amino acids, was approved in the US for the treatment of rheumatoid arthritis and juvenile arthritis in adults. Belatacept was 3- to 11-fold more potent than abatacept in human.

The primary efficacy and safety data in support of belatacept comes from 3 similarly designed core studies in de novo renal transplant recipients: a Phase 2 study (IM103100) and two pivotal studies (IM103008 and IM103027). Study IM103008 received renal transplants from standard criteria donors (SCDs). Study received higher risk renal transplants from extended criteria donors (ECDs).

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Belatacept exposure of the proposed dose regimen

The 2 belatacept regimens studied in pivotal studies were:

- The LI regimen of 10 mg/kg of belatacept given IV on Day 1 (the day of transplantation, prior to implantation), Days 5, 14, 28, Month 2 and Month 3, and then at 5 mg/kg monthly starting at Month 4 after transplantation.
- The MI regimen of 10 mg/kg of belatacept given IV on Day 1 (the day of transplantation, prior to implantation), Day 5, 14, 28, 42, and 56, and then every 4 weeks through 6 months after transplantation. Starting at Month 7 after transplantation, belatacept was administered at 5 mg/kg monthly.

The LI and MI dosing regimens of belatacept investigated in the pivotal studies target tiered C_{trough} of belatacept over different periods post transplant. The dose rationale of belatacept was based on 3 sections:

1. In vitro pharmacodynamics of belatacept suggested 2-10 $\mu\text{g}/\text{mL}$ concentration of belatacept was needed to saturate CD86;
2. The primate transplant model suggested belatacept C_{trough} of approximately 3-30 $\mu\text{g}/\text{mL}$ would be needed during the initial phase post transplant, while C_{trough} of 0.005-1.5 $\mu\text{g}/\text{mL}$ might be needed during the later maintenance phase (after 3 months) to prevent acute rejection;
3. The efficacy results from the phase 2 Study IM103100 suggested that the targeted belatacept C_{trough} levels of 20, 5, and 2 $\mu\text{g}/\text{mL}$ were appropriate C_{trough} to achieve desired levels of immunosuppression during the initial and maintenance phases post transplant;

Majority of the patients receiving the LI and MI dosing regimens achieved targeted C_{trough} during both the initial and maintenance phases. Both the LI and MI dosing regimens provided >85% CD86 receptor occupancy by belatacept during Month 1 post-transplant while allowing gradual tapering of the CD86 receptor occupancy by belatacept, albeit at different schedule (Table 1).

Table 1. The observed trough concentration and expected CD86 receptor occupancy in pivotal studies

Time Post Transplant	Month 1	Month 2-4	Month 5-7	Month 7-12
LI Dosing Regimen				
Target C_{min} ($\mu\text{g/mL}$)	20	5	2	2
% of Patients Achieving C_{min}	>90%	>80%	>90%	>90%
Expected CD86 Receptor Occupancy	>85%	~68%	NA	NA
MI Dosing Regimen				
Target C_{min} ($\mu\text{g/mL}$)	20	20	5	2
% of Patients Achieving C_{min}	>90%	>79%	>80%	>90%
Expected CD86 Receptor Occupancy	>85%	~74%	68%	NA

NA = not available

Source: the sponsor's report, Summary of Clinical Pharmacology Studies, page 81.

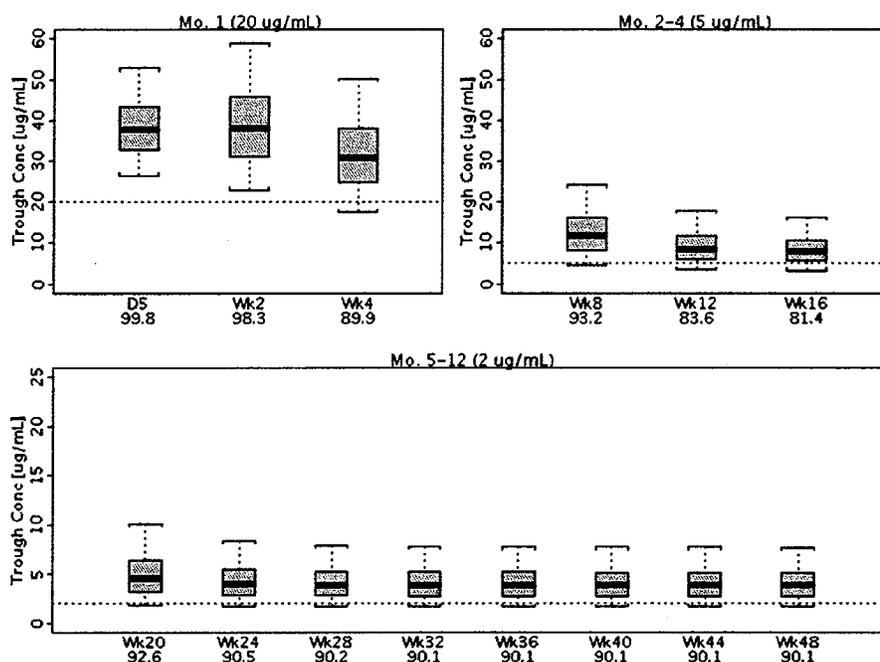
Reviewer's comments: The sponsor's population PK analyses (see appendix) indicated the PK of belatacept is linear and time-invariant across the therapeutic dose range of 5 to 10 mg/kg for healthy subjects and renal transplant recipients. Key belatacept PK parameters (CL and VC) increase with increasing baseline body weight, supporting a weight-based dose of belatacept. TDM was not applied in the drug clinical development program. The proposed dose approach is acceptable to achieve the target trough concentrations.

3.2 The Effect of Dose Rounding on Belatacept Trough Concentrations

The sponsor plans to market belatacept in 20-cc vials each containing 250 mg of belatacept lyophilized power. Belatacept 250 mg vials will be co-packaged in a 1:1 ratio with 10/12 mL silicone-free syringes graduated in 0.5 mL intervals through 12 mL. Belatacept is reconstituted to a concentration of 25 mg/mL by using the syringes

provided. When dosing, the total amount is calculated using the body weight of the patient and the dosing amount (in mg) for that day based on either a 5 or 10 mg/kg dosing target. The use of syringe provided in the commercial presentation of the product will render transfer of reconstituted drug to the nearest 12.5 mg. The worst case scenario would be consistently rounding up or rounding down each time. The maximum possible effect on belatacept exposure due to dose rounding to the nearest 0.5 mL (12.5 mg) was simulated using the PPK model (Figure 2) and suggested that dose rounding has minimal effect on belatacept exposure in RT patients.

Figure 2. Belatacept exposure with dose rounding down to nearest lower 0.5 mL for LI treatment in RT patients



The title is the time after the first dose and the target trough concentration for that time period. The first line of the x-axis label is the day of the trough; the second line is the percentage of subjects above the targeted trough. The dashed line is the targeted trough for each period for the LI regimen. The thick line in the middle of the box is the median, the box is the inter-quartiles, and the whiskers are the 5th and 95th percentiles.

Source: the sponsor's report, *Population Pharmacokinetics and Exposure-Response Report*, page 125.

Reviewer's comments: Dose rounding to the nearest 0.5 mL will cause ~6.25 mg absolute dose difference from the recommended dose for a RT patient. Since belatacept follows linear PK, the percentage change in exposure based on either a 5 or 10 mg/kg dosing target for an adult patient with normal body weight 60 kg is 2% or 1% respectively. From the PPK model, the inter-subject variability and intra-subject

variability are ~20% which is far beyond the error caused by dose rounding. Hence, we don't expect clinical important effect of dose rounding on belatacept exposure in RT patients on either the population level or the individual level.

3.3 Exposure-Response relationship for acute rejection

3.3.1 Method

A time-to-event E-R analysis was conducted to study relationship between belatacept exposure and AR using data from IM103008 and IM103027. The E-R for AR was characterized by a parametric hazard model which is comprised of the three components:

1. a baseline time varying hazard model: Gompertz baseline survival function (an exponential baseline hazard function $h_0(t) = \exp(-\beta-\lambda t)$ where $\lambda > 0$ to describe the declined risk of AR along time)
2. proportional hazard model that describes the relationship between belatacept exposure and total hazard (linear effect of time-varying belatacept serum concentration: $h_{base}(t) = \exp(-\beta_{base} - \lambda t - \alpha C(t))$)
3. covariate models: the effects of all pre-specified covariates (age, body weight, gender, race, study region, HLA mismatch, donor status, and study trails) on structural model parameters were evaluated during the model development

3.3.2 Results

HLA mismatches, the study region and baseline body weight were found to be the covariates affecting the hazard function. The covariate effect was modeled as following:

$$h(t) = \exp\left(-\beta_{base} - \lambda t - \alpha C(t) - \beta_{HLA} HLA - \beta_{REGION} REGION - \beta_{BBWT} \left(\exp\left(\frac{BBWT}{BBWT_{ref}} - 1\right) - 1\right)\right)$$

where $h_{base}(t)$ is the baseline hazard with no covariates included, β_{base} is the baseline constant, λ is the time constant, α is the exposure constant and $C(t)$ is the time-varying belatacept serum concentration. Table 2 contains the parameter estimates of the time-to-first AR model. The effect of belatacept concentration is relatively flat with the 95% CI of the estimated concentration effect includes zero. Hence there is no apparent exposure-response relationship at the studied dose range.

Table 2. Final AR model parameter estimates

Name [Units]	Estimate	Standard Error (RSE%) ^a	95% Confidence Interval ^b
β_{base}	10.1	0.883 (8.74)	9.23 - 11.3
λ [h ⁻¹]	0.000520	0.0000595 (11.4)	0.000413 - 0.000650
A	-0.00157	0.00217 (138)	-0.00496 - 0.00349
$\beta \sim$ HLA (ref = matched)	-1.08	0.868 (80.4)	-2.40 - -0.394
$\beta \sim$ REGION (ref = NA/EU)	0.603	0.225 (37.3)	0.198 - 1.11
$\beta \sim$ BBWT (ref = 75 kg)	-1.77	0.31 (17.5)	-2.43 - -1.17

Source: /global/pkms/data/IM/103/C02/prd/sz/er/nm/Final_Model

^a RSE% is the relative standard error (standard error as a percentage of estimate)

^b All confidence intervals are from 500 bootstrap runs

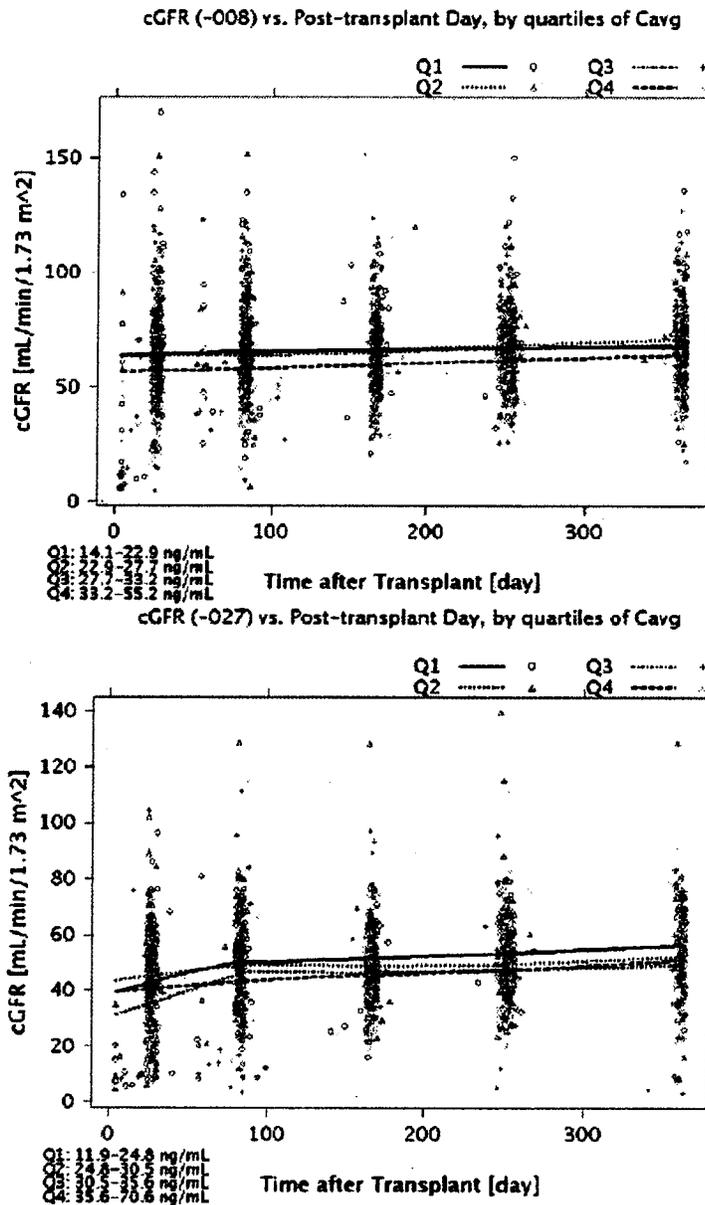
Source: *the sponsor's report, Population Pharmacokinetics and Exposure-Response Report, page 101.*

Reviewer's comments: Model evaluation was performed by visual predictive check and suggested that the model predictions are fairly consistent with the observed time-to-first AR. Reviewer's analyses also confirmed that the incidence of AR does not seem to be related with belatacept exposure at the doses studied.

3.4 Exposure-Response relationship for renal function

Based on the graphical analysis, there seems to be no relationship between exposure and cGFR. In Figure 3, cGFR was plotted separately for the Studies IM103008 and IM103027, as the difference in the organ types (SCD vs. ECD) from the 2 studies resulted in obvious differences between the cGFRs.

Figure 3. Measured cGFR on nominal study days by quartiles of C_{avg} (1 year after transplant)



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Source: the sponsor's report, Population Pharmacokinetics and Exposure-Response Report, page 113.

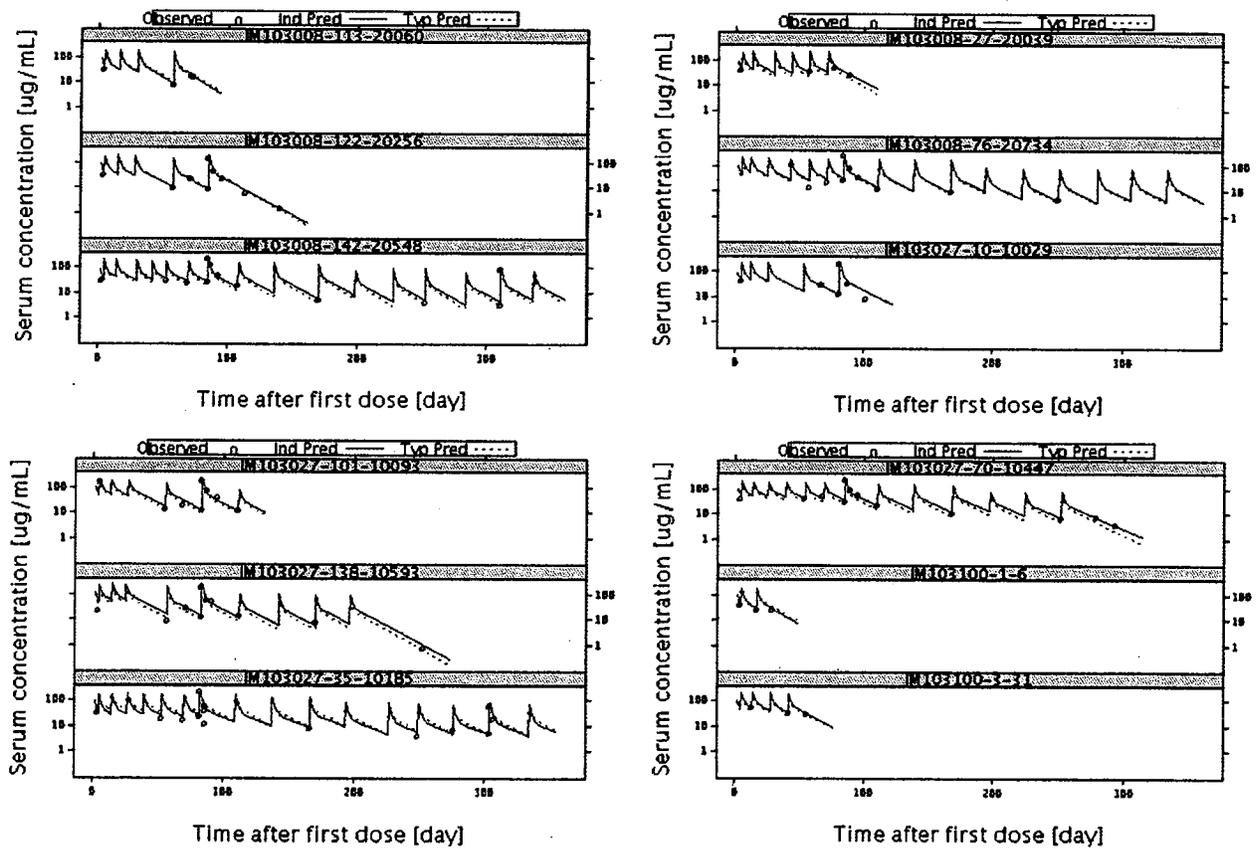
Reviewer's comments: The graphical analysis conducted by the sponsor does not appear to be sensitive to observe the exposure-response relationship for renal function. In pivotal studies IM103008 and IM103027, renal impairment was defined as a measured GFR (mGFR) <60 mL/min/1.73 m² or a decrease in measured GFR ≥ 10 mL/min/1.73 m²

from Month 3 to Month 12 (mGFR10). In those studies, GFR were estimated at Month 3 and Month 12 by measurement of the clearance of a true glomerular filtration marker (non-radiolabeled iothalamate). The baseline GFR values were substantially variable among patients. Thus, the exposure-response analysis may need to be conducted with mGFR10 because it is not influenced by the observed difference in baseline mGFR values in each patient.

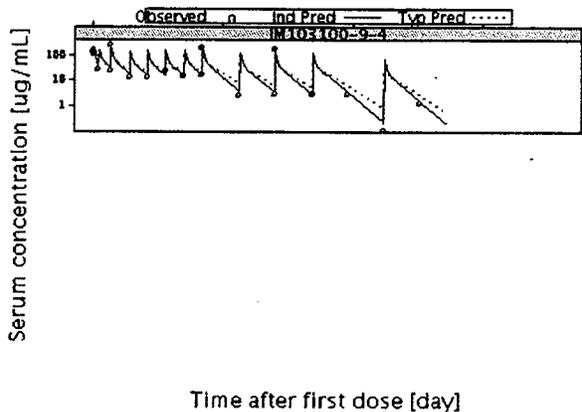
3.5 Exposure-Response relationship for PTLD

Given the special concern for PTLD, the individual predicted PK profiles of patients with PTLD are plotted. For PTLD subjects, each individual's predicted belatacept serum concentrations were similar to the typical predicted values, suggesting that there is no direct relationship between the PTLD events and belatacept exposure (Figure 4).

Figure 4. Observed and predicted (population and individual) belatacept serum concentrations for PTLD subjects



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Source: the sponsor's report, Population Pharmacokinetics and Exposure-Response Report, page 147.

Reviewer's comments: Given the low incidence of PTLD, the time-to-event analysis for exposure-response relationship will have very limited power. Comparing belatacept exposure between subjects with and without PTLD is a reasonable approach to detect extreme cases (such as concentrations in PTLD subjects are apparently higher than majority of the subjects). Reviewer's analysis also confirmed that the incidence of PTLD does not seem to be related with belatacept exposure at the doses studied.

4 REVIEWER'S ANALYSIS

4.1 Introduction

This is the original submission of belatacept, a new class of therapeutic agent in transplant immunosuppression. It is extremely difficult to find the optimal belatacept dosing regimen in the drug development program. During the course of the review, a number of efficacy and safety events appeared to be associated with belatacept treatment. A thorough review of the dosing strategy and exposure-response relationships for efficacy and safety is warranted.

4.2 Objectives

Analysis objectives are:

1. to investigate the ability of the (b) (4) LI and MI dose regimens to achieve target belatacept trough concentrations in pivotal studies
2. to explore the exposure-response relationship for efficacy to evaluate the proposed belatacept target trough concentrations
3. to explore the exposure-response relationship for safety to evaluate the proposed belatacept target trough concentrations

4. to evaluate the LI dose regimen versus the MI dose regimen and the need for TDM

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 3.

Table 3. Analysis Data Sets

Study Number	Name	Link to EDR
PPK_ER	pk-all.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0010\m5\datasets\poppk\analysis
PPK_ER	ER_AR.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0000\m5\datasets\poppk\analysis
PPK_ER	er_cmin.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0000\m5\datasets\poppk\analysis
PPK_ER	adpk.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0004\m5\datasets\poppk\analysis
IM103008	adar.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0000\m5\datasets\im103008\analysis\st
IM103008	adpi.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0000\m5\datasets\im103008\analysis\st
IM103027	adar.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0000\m5\datasets\im103027\analysis\st
IM103027	adpi.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0000\m5\datasets\im103027\analysis\st
IM103008	admng.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0000\m5\datasets\im103008\analysis\st
IM103008	addg.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0000\m5\datasets\im103008\analysis\st
PPK_ER	er_cavg.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0004\m5\datasets\poppk\analysis
CSS	ptld2.xp	\\Cbsap58\M\CTD_Submissions\STN125288\0010\m5\datasets\css\analysis\interim-lt
CSS	adae.xpt	\\Cbsap58\M\CTD_Submissions\STN125288\0000\m5\datasets\css\analysis\interim-lt

4.3.2 Software

SAS, R, and NONMEM were used for the reviewer's analyses.

4.3.3 Models and Results

4.3.3.1 Observed trough concentrations in pivotal studies

In pivotal studies, belatacept trough serum concentrations were measured at nominal Days 5, 56, 70 (MI only), 84, 112, 168, 252, 280, 308, 336 and 364. Similar to the sponsor's findings, ~80% of the patients receiving the LI and MI dosing regimens achieved trough concentration higher than the targeted C_{trough} at each of the measured time points. Trough concentrations of belatacept were similar in subjects on the LI or MI regimen on Day 5, higher on sampling days between Day 56 and Day 168 in subjects on

the MI regimen compared with those on the LI regimen and comparable after Day 168 (Figure 1 and Table 4).

Table 4. Belatacept exposure in RT patients during the first year of therapy

Normal Day Post-transplant	LI regimen		MI regimen	
	Sponsor's targeted Belatacept Cmin (mcg/mL)	Observed Belatacept Cmin (mcg/mL) Mean ± SD Median (range) N	Sponsor's targeted Belatacept Cmin (mcg/mL)	Observed Belatacept Cmin (mcg/mL) Mean ± SD Median (range) N
5	20	37.6±18.5 35.2 (1.4, 268) 356	20	38.8±17.3 36.7 (13.6,202) 359
56	5	11.3±17.3 9.4 (0.941, 299) 348	20	27.6±14.1 26.1 (0.0015, 203) 348
70	5	-	20	26.7±17.7 26.7 (0.0015, 276) 316
84	5	11.2±22.2 8.04 (0.0015, 279) 324	20	30.0±20.4 27.4 (7.33, 277) 331
112	5	8.6±4.8 7.54 (0.586, 27.9) 308	5	14.0±13.6 11.6 (1.63, 207) 301
168	2	4.6±2.7 4.035 (0.163, 18.8) 308	5	10.5±12.1 8.95 (0.0714, 197) 306
252	2	4.5±3.1 4.23 (0.0719, 32.9) 301	2	5.2±4.1 4.5 (0.0015, 52.4) 300
280	2	5.2±8.1 4.23 (0.0015, 119) 240	2	5.1±3.4 4.46 (0.0015, 35.2) 241
308	2	6.7±15.6 4.015 (0.387, 138) 262	2	6.4±14.0 4.23 (0.0247, 152) 257
336	2	5.1±5.6 4.46 (0.331, 75.9) 229	2	4.8±2.4 4.3 (0.00422, 13.9) 236
364	2	5.2±8.0 4.24 (0.0015, 112) 211	2	4.9±2.6 4.55 (0.0015, 14.2) 219

4.3.3.2 Exposure-Response relationship for acute rejection

Exposure-response analysis using data from IM103008 and IM103027 suggests that higher belatacept exposure seems to be related with lower incidence of acute rejection during Month 1 post transplant (Figure 5). However the incidence of acute rejection during Month 1 post transplant accounts for only ~1/3 of total acute rejection and there is no apparent exposure-response relationship for acute rejection after Month 1 post transplant.

Similar to the sponsor's findings, baseline body weight was found to be a risk predicting factor for acute rejection in patients with the belatacept treatment (Figure 6). This association is unlikely due to lower exposure in high body weight patients since patients with higher body weight tend to have higher exposure given the mg/kg dosing regimen. Similar (but seems weaker) association between acute rejection and body weight has also been observed with the CsA treatment. However, there is no relationship between body weight or exposure and graft loss/death. This lack of relationship does not support potential for long term consequences due to higher acute rejection in heavier patients.

Figure 5. Exploration of exposure effect on acute rejection (Month 1)

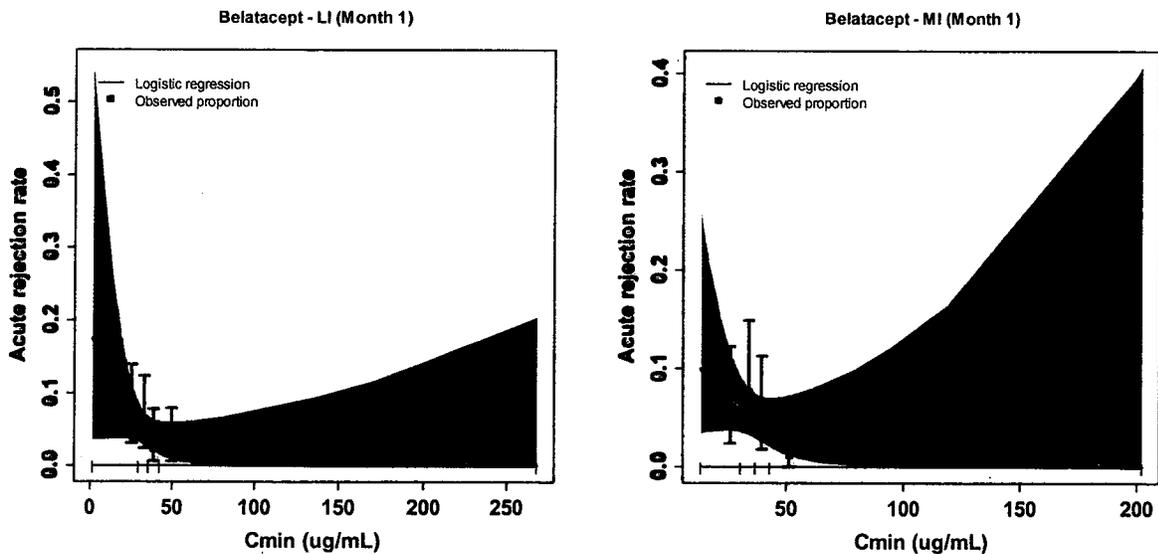


Figure 6. Body weight is associated with the acute rejection rate with belatacept treatment

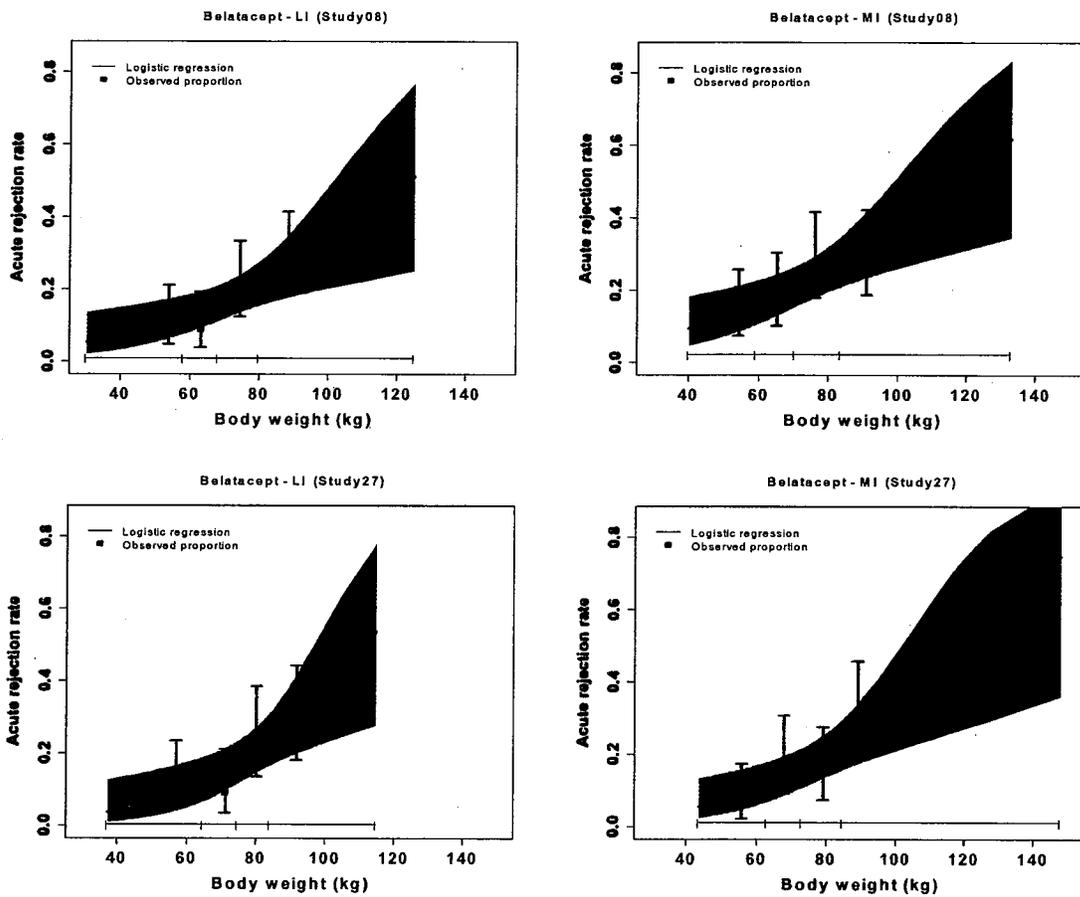
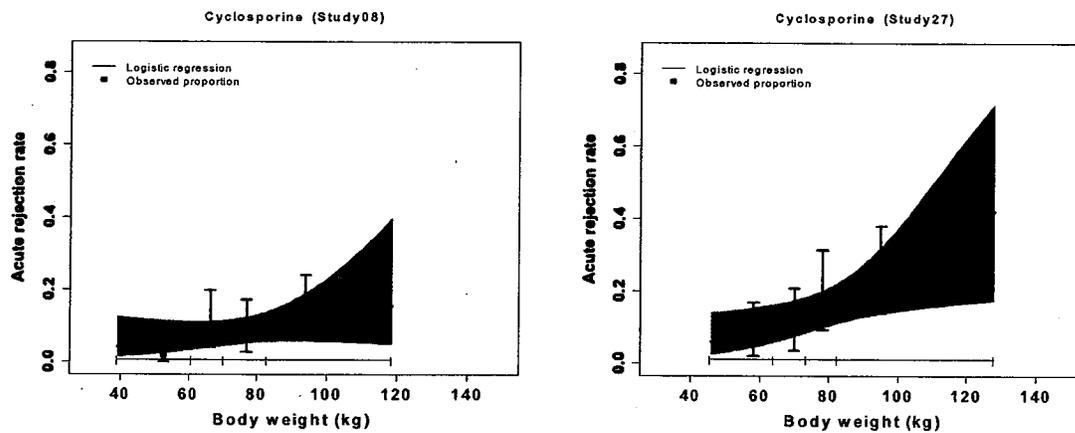


Figure 7. Body weight is associated with the acute rejection rate with cyclosporine treatment



4.3.3.3 Exposure-Response relationship for renal function

In pivotal trials IM103008 and IM103027, renal impairment was defined as a measured GFR (mGFR) <60 mL/min/1.73 m² or a decrease in measured GFR ≥ 10 mL/min/1.73 m² from Month 3 to Month 12 (mGFR10). In those studies, GFR were estimated at Month 3 and Month 12 by measurement of the clearance of a true glomerular filtration marker (non-radiolabeled iohalamate). 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 C_{trough} in Studies IM103008 and IM103027 (

Table 5).

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Table 5. Relationship between belatacept average C_{trough} (median; 10-90th percentile) and proportion of patients with a decrease in $mGFR \geq 10$ mL/min/1.73 m^2 from Month 3 to Month 12 ($mGFR_{10}$)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Month 1^a				
Median (10-90 th percentile) belatacept C_{trough} ($\mu\text{g/mL}$)	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 $mGFR_{10}$ (%; n/N)	22.4 (40/179)	24.0 (43/179)	25.1 (45/179)	18.0 (32/178)
Months 2 to 4				
Median (10-90 th percentile) belatacept C_{trough} ($\mu\text{g/mL}$)	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 $mGFR_{10}$ (%; n/N)	31.3 (57/182)	23.1 (42/182)	21.4 (39/182)	19.4 (35/180)
\geq Months 6				
Median (10-90 th percentile) belatacept C_{trough} ($\mu\text{g/mL}$)	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 $mGFR_{10}$ (%; n/N)	28.4 (46/162)	28.4 (46/162)	23.5 (38/162)	20.5 (33/161)
All Months				
Median (10-90 th percentile) belatacept C_{trough} ($\mu\text{g/mL}$)	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 $mGFR_{10}$ (%; n/N)	31.4 (61/194)	21.7 (42/194)	22.7 (44/194)	14.1 (27/192)

Data from de novo transplant patients who received the LI or MI regimens in pivotal trials IM103008 and IM103027 were combined for the quartile analysis.

^a taken on day 5 post-transplant

Additional analyses were conducted to evaluate the relationship between renal function (i.e., $mGFR_{10}$) and belatacept C_{trough} (i.e., average of C_{trough} from Month 3 to Month 12 in each patient) as a function of belatacept dosing regimen in each pivotal study. In Study IM103008, the percent of patients with $mGFR_{10}$ decreased with increasing belatacept C_{trough} in both the belatacept LI and MI treatment groups (Table 6). It should be noted that the percent of patients with $mGFR_{10}$ in the lower quartile of belatacept C_{trough} among the

patients who received the LI regimen (39%) was numerically greater than that in the CsA treatment group (28%, 60/221).

Table 6. Percent of patients with a decrease in mGFR ≥ 10 mL/min/1.73 m² from Month 3 to Month 12 (mGFR10) (n/N, %) as a function of average C_{trough} for the same periods (Study IM103008)

LI Regimen		MI Regimen	
Average C _{trough} Quartiles (Range)	Patients with mGFR10 (n/N, %)	Average C _{trough} Quartiles (Range)	Patients with mGFR10 (n/N, %)
Q1 (<3.24 µg/mL)	17/44 (39%)	Q1 (<6.75 µg/mL)	13/41 (32%)
Q2 (3.24-5.03 µg/mL)	9/43 (21%)	Q2 (6.75-9.34 µg/mL)	10/41 (24%)
Q3 (5.03-6.5 µg/mL)	9/43 (21%)	Q3 (9.34-12.3 µg/mL)	10/41 (24%)
Q4 (>6.5 µg/mL)	10/44 (23%)	Q4 (>12.3 µg/mL)	7/40 (18%)

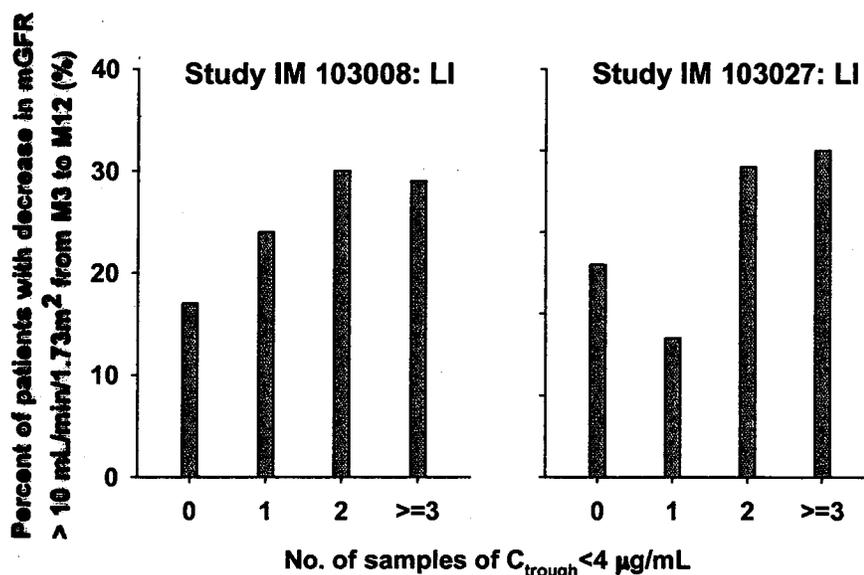
In Study IM103027, the relationship between the percent of patients with mGFR10 and belatacept C_{trough} does not appear to be as clear as in Study IM103008 (Table 7). The baseline kidney function among the patients who received kidneys from extended-criteria donors (Study IM103027) may be more variable than among the patients who received kidney from standard-criteria donors (Study IM103008). This may be a possible reason for the different observation between Studies IM103008 and IM103027.

Table 7. Percent of patients with a decrease in mGFR ≥ 10 mL/min/1.73 m² from Month 3 to Month 12 (mGFR10) (n/N, %) as a function of average C_{trough} for the same periods (Study IM103027)

LI Regimen		MI Regimen	
Average C _{trough} Quartiles (Range)	Patients with mGFR10 (n/N, %)	Average C _{trough} Quartiles (Range)	Patients with mGFR10 (n/N, %)
Q1 (<3.92 µg/mL)	10/30 (33%)	Q1 (<7.32 µg/mL)	7/30 (23%)
Q2 (3.92-6.03 µg/mL)	13/28 (46%)	Q2 (7.32-9.88 µg/mL)	9/29 (31%)
Q3 (6.03-8.14 µg/mL)	6/30 (20%)	Q3 (9.88-13.2 µg/mL)	3/30 (10%)
Q4 (>8.14 µg/mL)	8/29 (28%)	Q4 (>13.2 µg/mL)	5/29 (17%)

A retrospective analysis of data obtained from pivotal Studies IM103008 and IM103027 showed that the percent of patients with mGFR₁₀ increased as the number of belatacept C_{trough} samples per patient that were <4 µg/mL increased (Figure 8), partially substantiating that TDM with belatacept LI regimen may provide better clinical outcome, at least, in terms of improvement of GFR in kidney transplant patients. In this analysis, a threshold C_{trough} of 4 µg/mL was estimated as approximately 25 percentile C_{trough} in patients who received the LI belatacept regimen (Table 6 and Table 7).

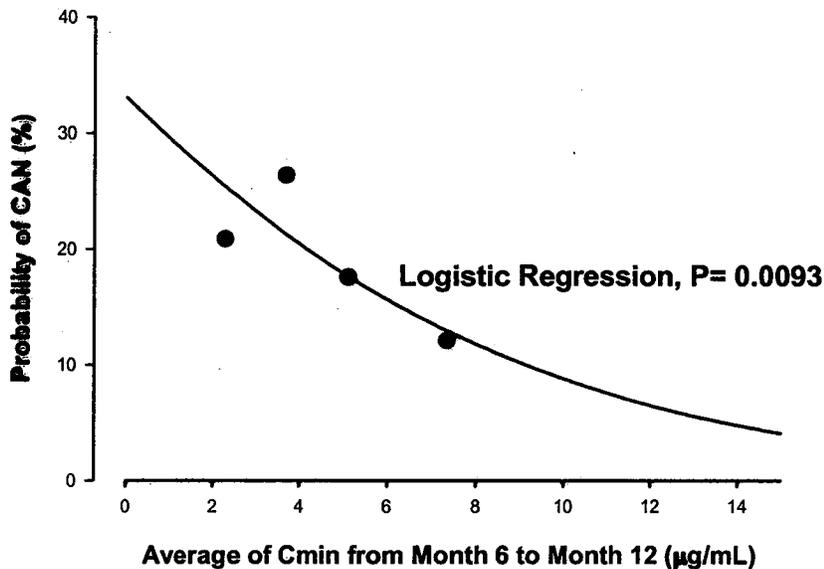
Figure 8. Percent of patients with decrease in mGFR >10 mL/min/1.73m² from Month 3 to Month 12 as a function of the number samples of belatacept C_{trough} <4 µg/ml



4 µg/mL was estimated as approximately 25 percentile C_{trough} in patients who received the LI belatacept regimen

The clinical pharmacology reviewer's exposure-response analysis showed that the incidence of CAN measured at Month 12 significantly decreased with an increase in belatacept average C_{trough} from Month 6 to Month 12 in Study IM103008 (Figure 9). However, no apparent relationship between the incidence of CAN and belatacept average C_{trough} was observed in Study 103027, where patients received kidneys from extended-criteria donors (data not presented). In Study 103027, the incidence of CAN measured at Month 12 may have been confounded with the baseline (i.e., pre-transplant) kidney pathological status. For these analyses, data from the LI and MI treatment groups were combined. Average C_{trough} from Month 6 to Month 12 were used because the belatacept doses during this period were same between the LI and MI regimens, in addition to the presumed relatively stable clinical status of the patient after Month 6 of renal transplantation.

Figure 9. Incidence of CAN at Month 12 as a function of average C_{trough} from Month 6 to Month 12 (Study IM103008)



Data from the LI and MI treatment groups were combined. Logistic regression was performed using average C_{trough} from Month 6 to Month 12 per patient as a continuous variable and the incidence of CAN as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the response rates in each of the 4 quartiles of C_{trough} (closed circles) are plotted to assess the goodness-of-fit.

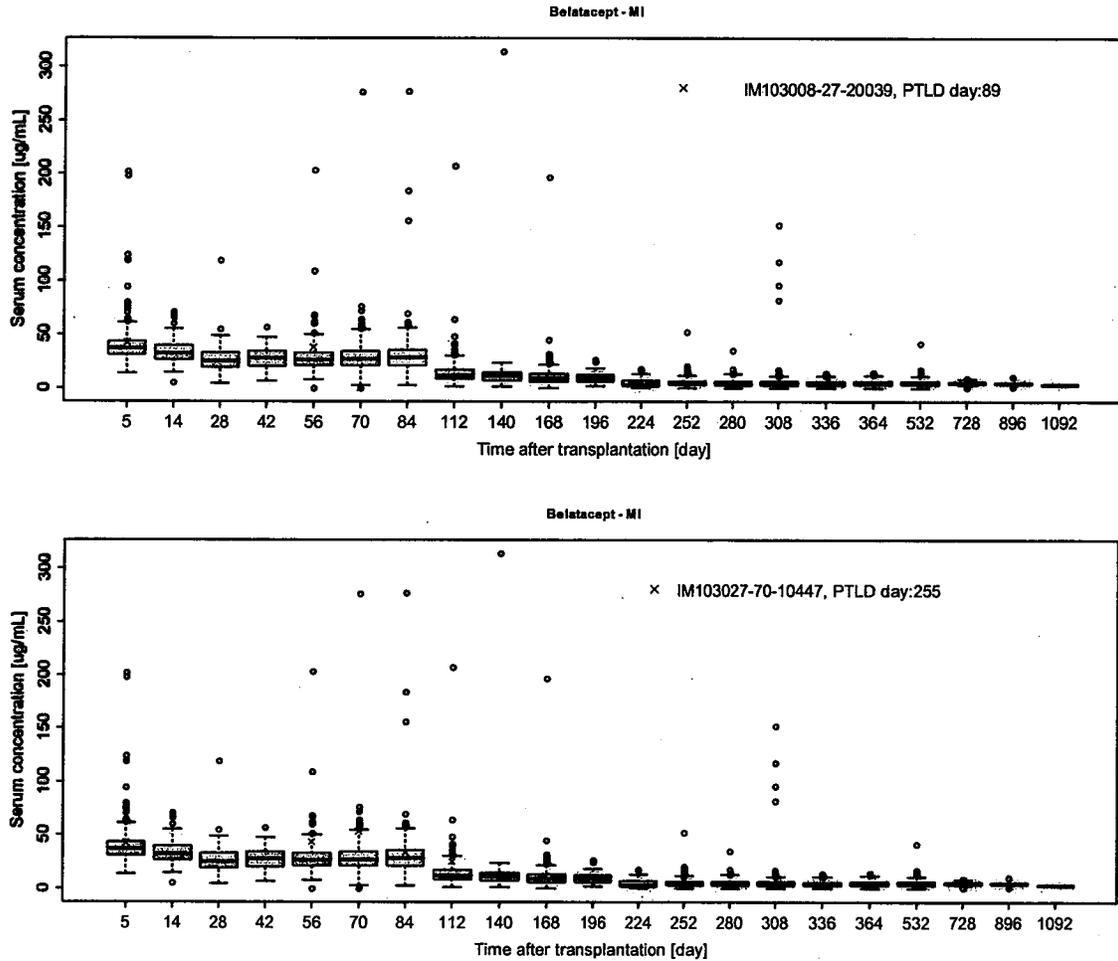
4.3.3.4 Exposure-Response relationship for PTLD

There are 13 belatacept PTLD (8 MI and 5 LI) incidences in the 3 core studies (3 in IM103100, 5 in IM103008, and 5 in IM103027). Up to Month 12, the incidence of PTLD was similar in the belatacept LI and MI groups (4 [0.8%] subjects in each group). Given the low incidence of PTLD and the complicate dosing strategy, the direct analysis for exposure-response relationship is not very meaningful. Here, we applied graphical analysis individually comparing belatacept exposure in patients with PTLD to exposure of the entire studied population. As shown in Figure 10 and Figure 16, there is no evident difference in exposure between subjects with and without PTLD. Hence, we consider the incidence of PTLD does not seem to be related with belatacept exposure at the studied doses.

Similar to the sponsor's findings, the known risk factors for PTLD, such as recipient EBV-negative status at the time of transplantation, CMV infection, and the use of T cell depleting therapy, were confirmed in belatacept-treated subjects (Figure 11). Also higher body weight seems to associate to higher average exposure and higher incidence of PTLD. But given the current study design and the small number of events, there is no power of detect the exposure-response relationship for PTLD. The sponsor proposed to only market belatacept in patients whose status is EBV-positive. Our analysis suggests

that checking the CMV infection negative status in EBV-positive patients can further reduce the PTLD incidence rate from 0.62% to 0.29% (Figure 12).

Figure 10. Comparison belatacept serum trough concentration for subjects with and without PTLD



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Figure 11. Recipient EBV status, the use of T cell depleting agent (TCDA), and CMV infection are associated with the incidence of PTLD with Belatacept Treatment

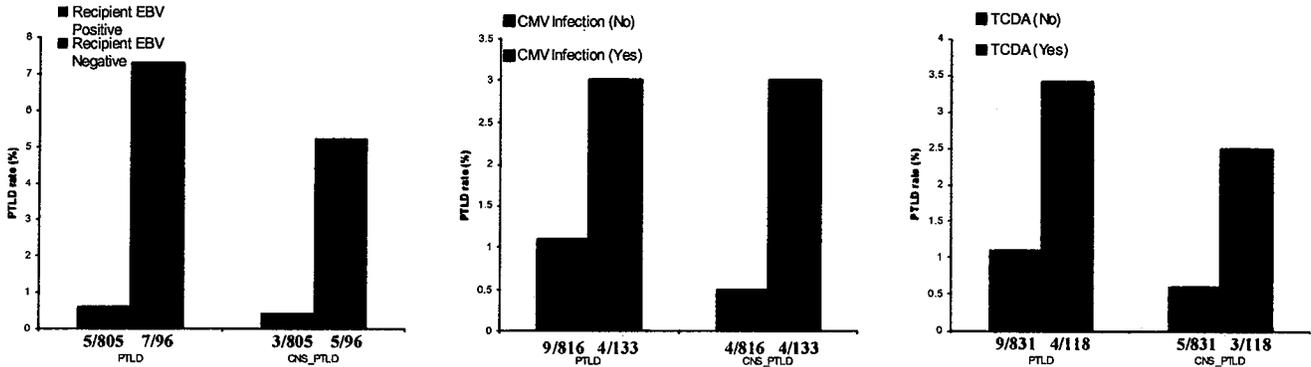
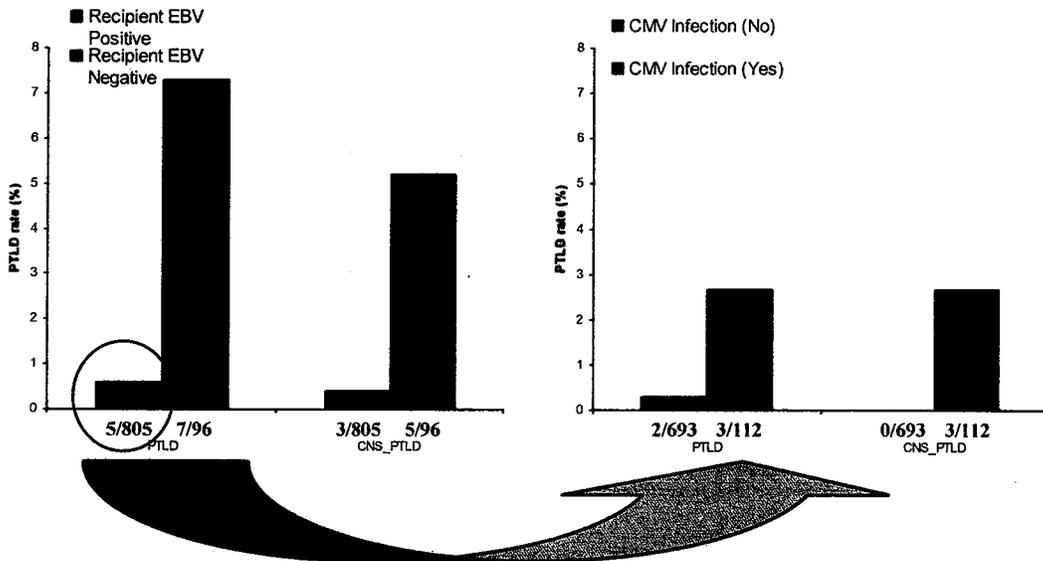


Figure 12. The PTLD incidence rate further reduce to 0.29% in patients who are CMV infection negative (from 0.62% in patients who are already EBV status positive)

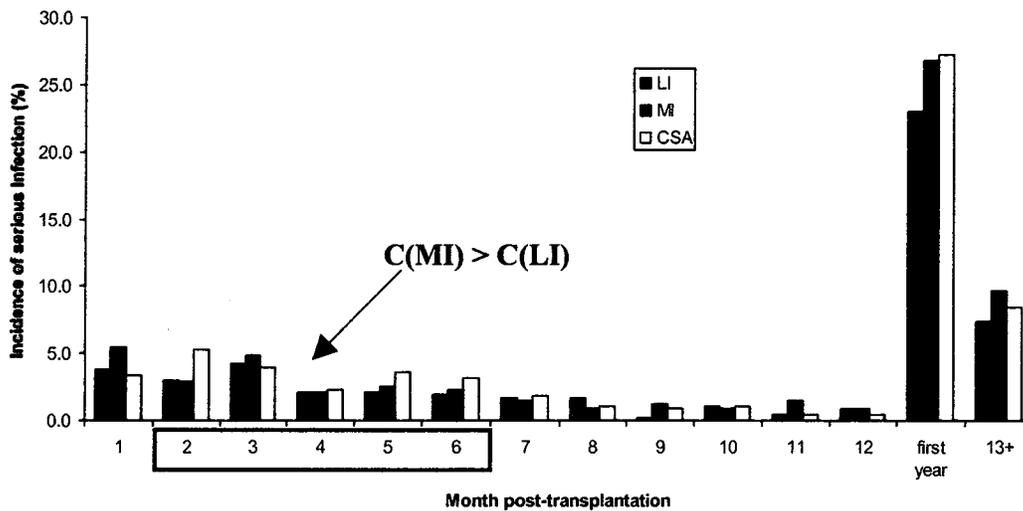


4.3.3.5 Exposure-Response relationship for serious infection

Data from the 3 core studies (IM103100, IM103008 and IM103027) were used to explore the exposure-response relationship for serious infection. As shown in Figure 13, up to Month 12, first serious infection (same as serious infection) happened more frequently in the first 6 months. As mentioned in 4.3.3.1, from Month 2 to Month 6 exposure in subjects on the MI regimen is generally higher than those on the LI regimen. However, the incidence rate of first serious infection does not seem to be different between the MI regimen and the LI regimen in that period. The exposure-response analysis (logistic

regression and quartile plot) using the first serious infection data up to Month 1 also confirm there is no apparent relationship between belatacept exposure and incidence of serious infection.

Figure 13. Comparison of incidence of first serious infection among treatments by months post transplant



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in <u>\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\</u>
run3.mod	PPK analysis (final model)	\Belatacept_BLA125288_JL\PPK Analyses\Final Model
ER.mod	PPK ER analysis and bootstrap for AR	\Belatacept_BLA125288_JL\ER Analyses\Final Model_NM
pk_test.sas	check the observed trough concentrations for LI and MI regimen in pivotal studies	\Belatacept_BLA125288_JL\ER Analyses
adpk_ar.sas	explore the E-R relationship for AR	\Belatacept_BLA125288_JL\ER Analyses
cminAr.r	do logistic regression and plot the E-R correlation for AR	\Belatacept_BLA125288_JL\ER Analyses
adweight_ar_008.sas	explore the weight effect on AR in Study 008	\Belatacept_BLA125288_JL\ER Analyses
weightAR08.r	do logistic regression and plot the weight-Ar correlation in	\Belatacept_BLA125288_JL\ER Analyses

	Study 008	
adweight_ar_027.sas	explore the weight effect on AR in Study 027	\Belatacept_BLA125288_JL\ER Analyses
weightAR27.r	do logistic regression and plot the weight-Ar correlation in Study 027	\Belatacept_BLA125288_JL\ER Analyses
adPK_mGFR10_008.sas	explore the E-R relationship for mGFR10 in Study 008	\Belatacept_BLA125288_JL\ER Analyses
adpk_CAN.sas	explore the E-R relationship for CAN	\Belatacept_BLA125288_JL\ER Analyses
adpk_PTLd.sas	explore the E-R relationship for PTLd	\Belatacept_BLA125288_JL\ER Analyses
cminPTLdplot.r	plot trough concentration for patients with/without PTLd	\Belatacept_BLA125288_JL\ER Analyses
ptld_freq.sas	explore the risk factors of PTLd	\Belatacept_BLA125288_JL\ER Analyses
ptldcns_freq.sas	explore the risk factors of CNS PTLd	\Belatacept_BLA125288_JL\ER Analyses
adPK_AE.sas	explore the E-R relationship for serious infection	\Belatacept_BLA125288_JL\ER Analyses

6 APPENDIX

6.1 Population PK Analyses of Belatacept

The PPK analyses for belatacept were performed with data from 5 clinical studies, 2 Phase 1 studies in healthy subjects (IM103001 and IM103024), and 1 Phase 2 (IM103100) and 2 pivotal studies in RT subjects (IM103008 and IM103027). A total of 984 subjects and 13014 PK samples were included in the PPK analysis dataset.

6.1.1 Methods

The population PK model of belatacept is comprised of the following components:

1. a structural pharmacokinetic model (linear 2 compartments)
2. an interindividual variability (IIV) model (lognormal distributed random effect on CL, VC, and VP with a full block correlation matrix of all the random effects)
3. a residual error model (combined additive and proportional model)
4. covariate models: The effects of all pre-specified covariates on structural model parameters were evaluated during the model development (Table 8).

Table 8. Covariate - PK parameter relationships evaluated in the full model

Covariate	Clearance (CL)	Central Volume (VC)	Inter-compartmental Clearance (Q)	Peripheral Volume (VP)	Time-varying
Age	√	√			no
Gender	√	√			no
Race	√				no
Body weight	√	√	√	√	yes
Albumin	√				no
GFR	√				yes
Diabetes	√				no
Subject type	√	√		√	no
Dose (5 mg/kg vs. 10 mg/kg)	√				yes

Source: the sponsor's report, Population Pharmacokinetics and Exposure-Response Report, page 53.

The relationship between the typical value of a parameter (P_{TV}) and a continuous valued covariate (R) was tested using the relationship:

$$P_{TV} = P_{TV,ref} \left(\frac{R}{R_{ref}} \right)^{P_1}$$

where $P_{TV,ref}$ and P_1 are fixed effect parameters, and R_{ref} is the reference value of the covariate.

Time-varying continuous valued covariates were assessed by evaluating the effect of both the baseline value of the covariate, as well as the effect of the change from baseline:

$$P_{TV}(t) = P_{TV,ref} \left(\frac{R_b}{R_{ref}} \right)^{P_1} \left(\frac{R(t)}{R_b} \right)^{P_2}$$

where $P_{TV,ref}$, P_1 , and P_2 are the fixed effect parameters, and R_b is the baseline value of the time-varying covariate for each individual, and $R(t)$ is the time-varying covariate.

The relationship between the typical value of a parameter and a categorical covariate (R) was tested using the following relationship:

$$P_{TV} = P_{TV,ref} \prod_{m=1}^{M-1} (\exp(P_m I_m))$$

where $P_{TV,ref}$, and P_i ($i=1, \dots, M-1$) are fixed effect parameters, I_m are indicator variables where $I_m=1$ for the m^{th} category and 0 otherwise.

Time-varying categorical covariates were assessed by the following relationship:

$$P_{TV}(t) = P_{TV,ref} \prod_{m=1}^{M-1} (\exp(P_m I_m(t)))$$

where $P_{TV,ref}$, and P_i ($i=1, \dots, M-1$) are fixed effect parameters, $I_m(t)$ are indicator variables where $I_m(t)=1$ for the m^{th} category and 0 otherwise.

6.1.2 Results

Baseline body weight, time-varying body weight, age and patient type were found to be the covariates affecting PK parameters (Table 9). Key belatacept PK parameters (CL and VC) increase with increasing baseline body weight, supporting a weight-based dose of belatacept. As the increase in belatacept CL is less than proportional to the increase in body weight, belatacept exposure tends to increase with body weight for RT patients given body weight normalized doses of belatacept. However, the increase in exposure is not expected to be clinically important. Belatacept CL decreases with age, but the magnitude of the age effect on belatacept PK is unlikely to be clinically meaningful.

Table 9. Parameter estimates for the Final PPK model

Name [Units]	Estimate ^a	Standard Error (RSE%) ^b	95% Confidence Interval ^c
Fixed Effects			
$CL_{IV,ref}$ [L/h]	0.0366	0.000308 (0.84)	0.0360 - 0.0372
$VC_{IV,ref}$ [L]	3.59	0.0326 (0.91)	3.52 - 3.66
$Q_{IV,ref}$ [L/h]	0.0568	0.00168 (2.96)	0.0537 - 0.0599
$VP_{IV,ref}$ [L]	5.11	0.151 (2.95)	4.82 - 5.40
CL ~ BBWT (ref = 75 kg)	0.736	0.0348 (4.73)	0.668 - 0.804
VC ~ BBWT (ref = 75 kg)	0.708	0.0408 (5.76)	0.632 - 0.784
VP ~ BBWT (ref = 75 kg)	0.854	0.058 (6.79)	0.741 - 0.967
Q ~ BBWT (ref = 75 kg)	0.464	0.107 (23.1)	0.250 - 0.678
Q ~ BWT	2.07	0.311 (15.0)	1.44 - 2.70
CL ~ AGE (ref = 50 yr)	-0.185	0.0192 (10.4)	-0.222 - -0.148
VP ~ PTYPE (ref = Healthy)	0.335	0.0311 (9.28)	0.274 - 0.396
Random Effects			
ZCL [-]	0.0456 (0.214)	0.00258 (5.66)	0.0404 - 0.0508
ZVC [-]	0.0313 (0.177)	0.0035 (11.2)	0.0246 - 0.0380
ZVP [-]	0.0830 (0.288)	0.00782 (9.42)	0.0674 - 0.0986
ZCL:ZVC	0.0258 (0.683)	0.00254 (9.84)	0.0207 - 0.0309
ZCL:ZVP	0.0167 (0.271)	0.00341 (20.4)	0.00998 - 0.0234
ZVC:ZVP	0.0277 (0.543)	0.0036 (13.0)	0.0207 - 0.0347
Residual Error			
θ_{PROP} [-]	0.246	0.00463 (1.88)	0.237 - 0.255
θ_{DD} [$\mu\text{g/mL}$]	0.143	0.0256 (17.9)	0.0936 - 0.192

Source: /global/pkms/data/IM/103/C02/prd/sz/pk/nm/Final_Model

^a Random Effects parameter estimates are shown as variance (standard deviation) for diagonal elements (ZP) and covariance (correlation) for off-diagonal elements (ZP₁:ZP₂)

^b RSE% is the relative standard error (standard error as a percentage of estimate)

^c Confidence intervals of Random Effects parameters are for variance or covariance, all confidence intervals are from 500 bootstrap runs

Source: the sponsor's report, *Population Pharmacokinetics and Exposure-Response Report*, page 83.

Reviewer's comments: Sponsor's population PK analysis acceptable. The percent of Eta shrinkage is small (<20%) compared to the population model estimated IIV, implying there is sufficient PK information from individual subjects to provide reliable individual parameter estimates for majority of the patients. The PK of belatacept is time-invariant. Body weight based dosing of belatacept is appropriate given the dependence of belatacept clearance on body weight.

Figure 14. Comparison belatacept serum trough concentration for subjects with and without PTLD (continued)

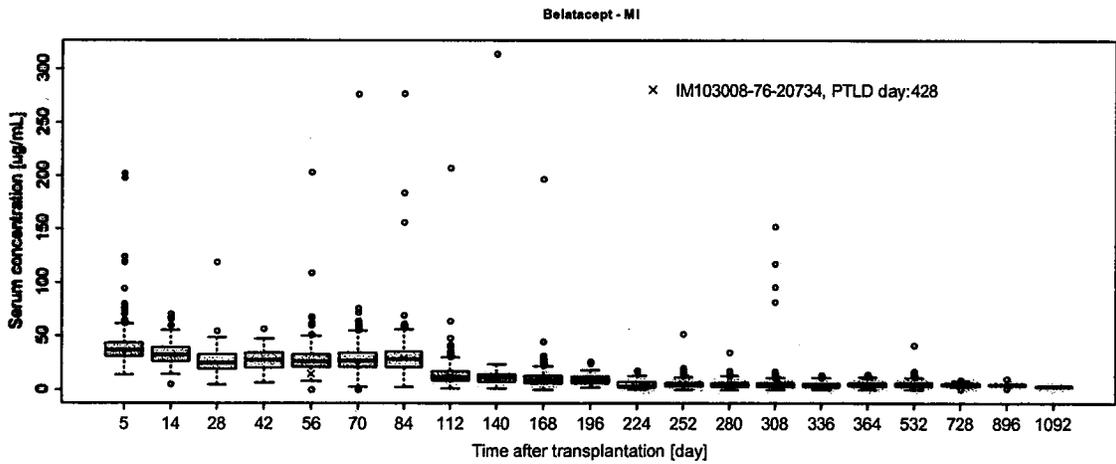
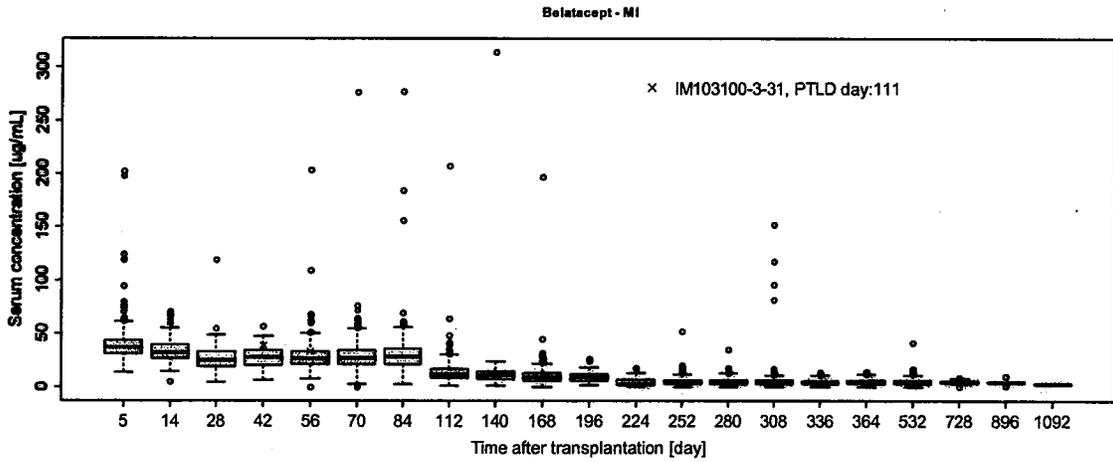
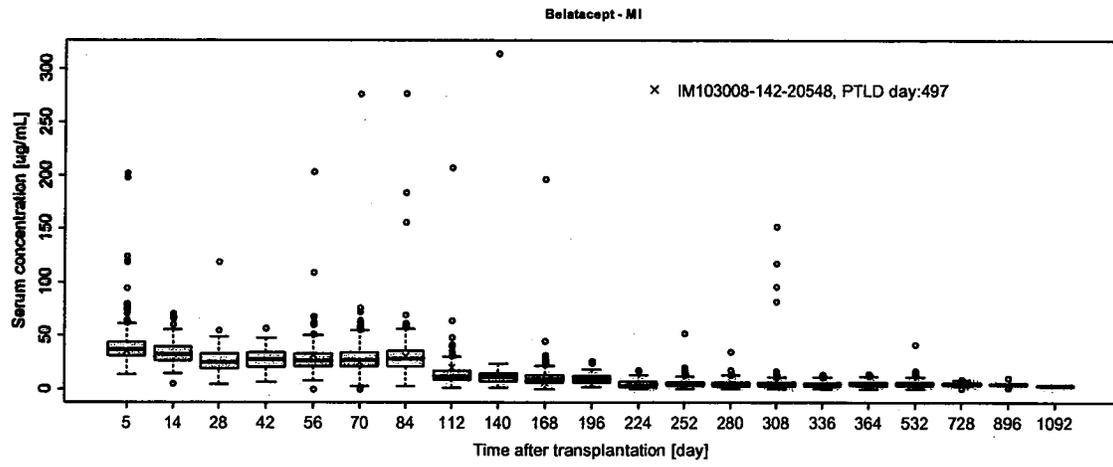


Figure 15. Comparison belatacept serum trough concentration for subjects with and without PTLD (continued)

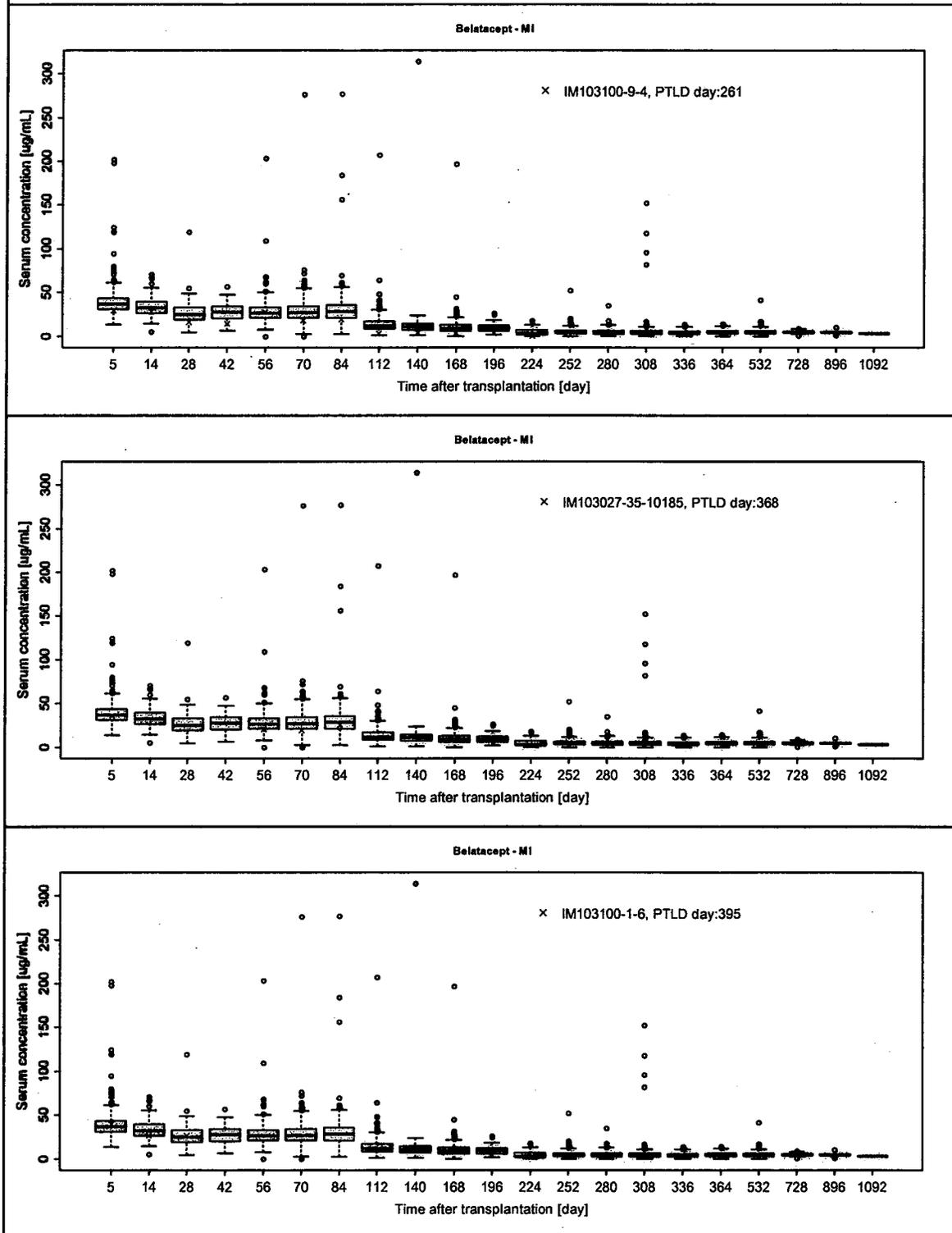
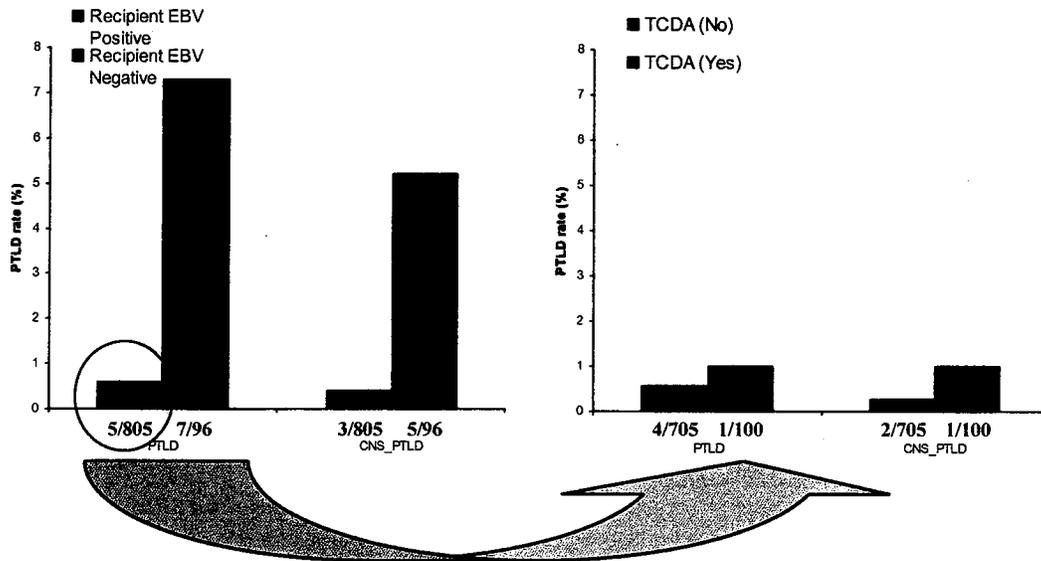


Figure 16. The PTLD incidence rate further reduce to 0.58% in patients who are TCDA No (from 0.62% in patients who are already EBV status positive)



4.2. Pharmacogenomics

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ORIGINAL

CLINICAL PHARMACOLOGY GENOMICS GROUP REVIEW

NDA/BLA Number	BLA 125288
Applicant Name	Bristol-Myers Squibb Company
Submission Date	30-June. 2009
Generic Name	Belatacept
Proposed Indication	Submission for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants
Genomics Reviewers	Shashi Amur, Ph.D. and Li Zhang, Ph.D.
Team Leader	Issam Zineh, PharmD, MPH

1. BACKGROUND

Belatacept (BMS-224818) is a second generation CTLA4Ig fusion protein that differs from abatacept by 2 amino acids and this difference confers a higher avidity for CD80 and CD86 (B7-1 and B7-2, respectively). Belatacept binds to the B7 complex on the surface of antigen-presenting cells (APCs), an interaction required for T-cell activation in the context of antigen presentation and provides immunosuppression needed for preventing allograft rejection.

Clinical efficacy and safety of belatacept in renal transplant recipients was evaluated in two pivotal Phase 3 studies, IM103008 and IM103027. In addition, a supportive Phase 2 study, IM103100, was conducted for efficacy (see Appendix 1). All the three studies in *de novo* renal transplant recipients were partially-blinded, randomized, active-controlled, multiple-dose, and multicenter studies (Although the Phase 2 and 3 studies were open label studies with respect to the allocation of subjects to a belatacept-based regimen or a CsA-based regimen, the studies remained fully blinded with respect to the belatacept dose regimen assignment). All subjects received basiliximab induction and maintenance therapy with mycophenolate mofetil (MMF) and corticosteroids. Subjects in each study were randomized in a 1:1:1 ratio to treatment with belatacept MI (more intensive regimen), belatacept LI (less intensive regimen), or cyclosporine A (CsA).

In the 3 core studies, 1427 subjects were randomized and received a renal transplant (intent-to-treat [ITT] population) whose descriptions follow: 477 to belatacept MI, 472 to belatacept LI, and 476 to CsA. The MI regimen consisted of belatacept (10 mg/kg) administration on Day 1 (the day of transplantation, prior to implantation); Day 5, 14, 28, 42, and 56; then every 4 weeks through 6 months after transplantation. Starting at Month 7 after transplantation, belatacept was administered at the maintenance dose of 5 mg/kg every 4 weeks (\pm 5 days). The LI regimen consisted of belatacept (10 mg/kg) administration on Day 1; Day 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 (\pm 5 days). Subjects received belatacept

for a median of 2 years in IM103008 and IM103027, and 5.7 years in IM103100. Cyclosporine was given twice daily for trough serum 150-300 ng/mL during Month 1 and 100-250 ng/mL thereafter.

Post-Transplant Lymphoproliferative Disorder (PTLD):

The primary risk observed with belatacept was PTLT, 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 PTLT. The incidence of PTLT was found to be higher in belatacept-treated patients (14/949; 1.48%) than in cyclosporine-treated patients (2/476; 0.4%) in the Phase 2 and 3 studies. Nine of 14 cases of PTLT in belatacept-treated patients presented in the CNS and half of these CNS cases were fatal. At the recommended clinical dose, the frequency of PTLT was 1.27% (6/472); 3 of these cases presented in the CNS, 1 of which was fatal. With the MI regimen, the frequency of PTLT was 1.7% (8/477). **The purpose of this review is to assess risk factors for belatacept-associated PTLT.**

2. BLA CONTENT RELATED TO PTLT

Adverse events

The frequencies of AEs and treatment-related AEs were similar across treatment groups at Month 12 and up to database lock. Common AEs usually occurred within the first year of transplant, and often within the first 3 months after transplant. Within the first 12 months after transplantation, the most commonly reported AEs (i.e., incidence $\geq 10\%$) among belatacept-treated subjects were anemia, constipation, and urinary tract infection. The number of deaths was lower in the belatacept LI group than in the belatacept MI and CsA groups. Similarly, the frequency of SAEs was lower in the belatacept LI group than in the belatacept MI and CsA groups. The proportion of subjects with AEs leading to treatment discontinuation was lower in both belatacept groups than in the CsA group at 12 months and up to database lock.

Malignant Neoplasms

Up to Month 12, the frequency of all malignant neoplasms was lower in the belatacept LI compared with the belatacept MI and CsA groups (Table 2.1.5.1A). Up to database lock, the cumulative frequency of all malignant neoplasms was similar in the belatacept LI group and CsA groups, and lower in the belatacept LI group compared with the belatacept MI group. There was an imbalance of PTLT incidence in both belatacept arms relative to CsA (Table 2.1.5.1A).

Table 2.1.5.1A: All Malignant Neoplasms (Pooled Core Studies)

	Number of Subjects (%)					
	Day 0-12 Months			Day 0-Database Lock		
	MI N=477	LI N=472	CsA N=476	MI N=477	LI N=472	CsA N=476
All malignant neoplasm ^a	17 (3.6)	10 (2.1)	16 (3.4)	43 (9.0)	26 (5.5)	31 (6.5)
Malignant neoplasms excluding non- melanoma skin cancers	12 (2.5)	9 (1.9)	11 (2.3)	32 (6.7)	23 (4.9)	23 (4.8)
PTLD	4 (0.8)	4 (0.8)	1 (0.2)	8 (1.7)	5 (1.1)	2 (0.4)
Non-melanoma skin cancer	5 (1.0)	1 (0.2)	5 (1.1)	15 (3.1)	6 (1.3)	11 (2.3)

^a Subjects counted once in the All malignant neoplasm row could be counted in more than 1 row appearing below it.

Source: ISS Appendices 8.4.3, 8.4.4, 8.4.11, 8.4.15, 8.4.45, 8.4.49

Please note that a new PTLD case was observed after nearly 4 years after transplant in belatacept LI recipient (EBV positive, CMV positive) and is not included in the table.

Post Transplant Lymphoproliferative Disorder

PTLD is assessed in this section as a composite term encompassing the following MedDRA PTs: lymphoproliferative disorder, hematological malignancy, lymphoma, CNS lymphoma, hepatosplenic T-cell lymphoma, EBV-associated lymphoproliferative disorder and B-cell lymphoma (ISS Appendix 15.4).

Overall, a total of 16 cases of PTLD were reported in the 3 core studies (8 [1.7%], 6 [1.3%], and 2 [0.4%] in the belatacept MI, LI, and CsA groups, respectively). Nine of the 16 PTLD cases presented with CNS involvement (6 belatacept MI, 3 belatacept LI; none in the CsA group). At the time of database lock, however, 13 cases of PTLD were observed in belatacept-treated patients (8 in the belatacept MI, and 5 in the LI groups). Thus, the sponsor has used 13 cases of PTLD in their analyses.

3. KEY QUESTIONS AND SUMMARY OF GENOMICS FINDINGS

3.1 Is EBV status sufficient to predict PTLD? What other factors (clinical and biomarkers) predict PTLD?

Sponsor Analysis:

EBV-negative recipient status was the most significant risk factor for PTLD. Other risk factors included use of T cell depleting therapy and CMV disease. The incidence of PTLD in the belatacept database was also compared with a large epidemiologic database maintained by the USRDS, compiled from linked UNOS and Medicare data. Comparison of belatacept clinical study and USRDS data showed an increased risk of PTLD for EBV-negative belatacept-treated subjects. Among EBV positive recipients, the incidence rate was consistent with that observed for patients in the USRDS database. In the 3 core

studies, CNS presentation occurred more frequently in the belatacept MI group compared with the belatacept LI group. Six deaths were reported in the 13 belatacept-treated subjects with PTLD (4 MI, 2 LI). Four of these fatal cases (3 MI and 1 LI) had CNS involvement. Both of the subjects with renal PTLD in CsA-treated subjects were fatal.

Across the 3 core studies up to Month 12, 4 cases of PTLD in IM103008, 3 cases in IM103027 and 2 cases in IM103100 were reported. The frequency of PTLD was higher in the belatacept LI group (4 [0.8%] subjects) compared with the CsA group (1 [0.2%] subject), and similar in the belatacept LI and MI groups (4 [0.8%] subjects in each group) (Table 2.1.5.2A). Four additional cases of PTLD were reported after Month 12 in the belatacept MI group, 2 additional cases in the LI and 1 in the CsA groups, respectively. Accordingly, up to database lock, a total of 15 cases of PTLD were reported in all 3 core studies (Table 2.1.5.2A). The cumulative frequency of PTLD (8 [1.7%], 5 [1.1%], and 2 [0.4%], in the belatacept MI, LI, and CsA groups, respectively), was higher in both belatacept arms compared with the CsA group, though slightly lower in the belatacept LI compared with the MI group. Up to database lock, the overall frequency of PTLD in combined belatacept MI and LI groups was 1.4% (13/949) compared with 0.4% (2/476) for the CsA group.

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Table 2.1.5.2A: Number of Subjects with Post Transplant Lymphoproliferative Disorder Up to Month 12 and Up To Database Lock in Core Studies

	Number of Subjects (%)								
	IM103008			IM103027			IM103100		
	MI N=219	LI N=226	CsA N=221	MI N=184	LI N=175	CsA N=184	MI N=74	LI N=71	CsA N=71
PTLD (including CNS)									
Day 0-12 Months	1 (0.5)	2 (0.9)	1 (0.5) ^a	1 (0.5)	2 (1.1)	0	2 (2.7)	0	0
Day 0-database lock	3 (1.4)	2 (0.9)	1 (0.5)	2 (1.1)	3 (1.7) ^a	0	3 (4.1)	0	1 (1.4)
CNS PTLD									
Day 0-12 Months	0	0	0	1 (0.5)	1 (0.5)	0	1 (1.4)	0	0
Day 0-database lock	2 (0.9)	0	0	2 (1.1)	2 (1.1)	0	2 (2.7)	0	0

^a One event in the CsA group in IM103008 and one event in the LI group in IM103027 was reported more than 56 days after the last dosing date

Source: CSR Addn Table S.6.10 [-008, -027]³⁻⁵; CSR Table S.6.3 [-100]⁶ and LTE CSR Appendix 12.5 [-100]⁷

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All observed belatacept PTLD events up to database lock occurred during the first 18 months post transplant. Over 50% of subjects had more than 2 years of exposure to belatacept. These data suggest a declining hazard over time, consistent with that reported in the literature.

PTLD Subject Characteristics:

Among belatacept-treated subjects with PTLD, the mean age was 41 to 53 years; the majority of subjects with PTLD were males. Among the 15 subjects with PTLD, 8 subjects had EBV-negative and 5 subjects had EBV-positive serologies at baseline and in 2 subjects, EBV status was unknown. The predominant histological PTLD phenotype was of B cell origin, with the exception of one subject in the belatacept LI group that had a predominant T cell PTLD.

Among the 8 belatacept cases with CNS PTLD, 5 occurred in EBV-negative subjects and 3 occurred in EBV-positive subjects (Table 2.1.5.2D). A total of 4 subjects with CNS PTLD died: 2 subjects with EBV-positive serologies (1 belatacept MI and 1 belatacept LI) and 2 subjects with EBV-negative serologies (both in the belatacept MI group) (ISS Appendix 8.1.1). A new PTLD case was observed after nearly 4 years after transplant in belatacept LI recipient (EBV positive, CMV positive) and is not included in the table.

Table 2.1.5.2D: PTLD by Recipient EBV Status and Site of Presentation from Randomization Through Database Lock in Core Studies

PTLD Site/EBV serology status	Number of Subjects With PTLD		
	MI N = 8	LI N = 5	CsA N = 2
Renal	2	3	2
EBV-negative	1	1	1
EBV-positive	0	2	0
EBV-unknown	1	0	1
Fatal	1	0	2
CNS	6	2	0
EBV-negative	4	1	0
EBV-positive	2	1	0
Fatal	3	1	0

Source: ISS Appendix 8.1.1

Risk Factors for Developing PTLD

There are several known risk factors for PTLD, including recipient EBV-negative recipient status at the time of transplantation, CMV disease, and use of T cell depleting therapy. A comprehensive evaluation of risk factors for the development of PTLD among belatacept subjects was performed by the sponsor. The risk factor analysis was performed only on belatacept-treated subjects since the number of PTLD cases with CsA was small (2 subjects).

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Univariate analysis: The effects of gender, belatacept dose (MI vs LI), biopsy proven acute rejection (BPAR) and steroid treatment for AR on disease risk were also examined. The univariate analysis showed that recipient EBV-negative status was the most significant risk factor for PTLD (Table 2.1.5.2E).

Reviewer comments:

Based on the sponsor's analysis, the EBV status does appear to be the most significant risk factor for PTLD. However, use of T-cell depleting agents (HR 2.97), male gender (HR 2.94) and CMV disease (HR 2.14) also appear to be significant factors.

Multivariate analysis: The most significant risk factor for belatacept PTLD and for CNS PTLD was EBV-negative recipient status (Table 2.1.5.2F). Other independent risk factors were T cell depleting agents and CMV disease. The sponsor analysis showed that gender and age were not significantly associated with development of either PTLD or CNS PTLD in multivariable analyses.

Table 2.1.5.2E: Univariate Risk Factor Assessment for Post-transplant Lymphoproliferative Disorder in Belatacept-treated Subjects

Risk Factors	Number of PTLD/Number At risk	Hazard Ratio (95% CI)
Age group		
Age ≥ 60 at transplant	4/222	1.28 (0.40, 4.05)
Age < 60 at transplant	9/727	--
Gender		
Female	2/302	0.34 (0.08, 1.51)
Male	11/647	--
Recipient EBV Status^a		
Negative	7/96	12.80 (4.19, 39.12)
Positive	5/805	--
Biopsy Proven Acute Rejection		
Yes	5/230	2.07 (0.68, 6.33)
No	8/719	--
Steroid treatment for Acute Rejection^b		
Yes	2/153	0.37 (0.07, 2.00)
No	4/113	--
T Cell Depleting Agents		
Yes	4/118	2.97 (0.93, 9.47)
No	9/831	--
CMV Disease		
Yes	4/133	2.14 (0.68, 6.72)
No	9/816	--
Belatacept Dose Regimen		
LI	5/472	0.33 (0.07, 1.45)
MI	8/477	--

^a One subject had unknown EBV serology^b Analysis excluded IMJ03100 study population since steroid treatment for AR was not differentiated from maintenance steroids. Subjects must have had a suspected rejection episode to be included in the analysis. Subjects who received T cell depleting agents for acute rejection were not included in this analysis.

Source: ISS Appendices 8.1.5, 8.1.6, 8.1.8, 8.1.9, 8.1.12, 8.1.19, and 8.1.20

Table 2.1.5.2F: Multivariate Risk Factor Assessment for Post-transplant Lymphoproliferative Disorder Based on Pooled ITT Belatacept-Treated Subjects

Risk Factors	All Belatacept PTLD		Belatacept CNS PTLD	
	Hazard Ratio	(95% CI)	Hazard Ratio	(95% CI)
Age ≥ 60	1.99	(0.59, 6.73)	2.05	(0.47, 8.94)
Gender (female vs. male)	0.16	(0.02, 1.29)	All cases in males	
Recipient EBV-Negative Status	15.32	(4.65, 50.49)	19.72	(4.44, 87.61)
T Cell Depleting Agents	5.02	(1.41, 17.77)	5.87	(1.32, 26.12)
CMV Disease	3.84	(1.11, 13.26)	7.14	(1.69, 30.22)
Belatacept Dose Regimen (LI vs MI)	0.88	(0.27, 2.89)	0.37	(0.07, 1.86)

Source: ISS Appendix 8.1.12 and 8.1.13

Number of risk factors: The strongest risk factor identified for PTLD was EBV-negative recipient status. The impact of the presence of multiple risk factors was further explored in subjects stratified by EBV status. EBV-negative recipients with no other risk factors had a relative hazard of developing PTLD and CNS PTLD of 6.22 (95% CI = 1.56, 24.91) and 8.34 (95% CI = 1.39, 49.95), respectively, in comparison to EBV-positive recipients. EBV-negative subjects with one additional risk factor (either T cell depleting therapy or CMV disease) had a relative hazard of developing PTLD and CNS PTLD of 25.6 (95% CI = 7.21, 91.23) and 39.02 (95% CI = 7.85, 94.11), respectively, compared with EBV-positive subjects (ISS Appendices 8.1.11, 8.1.12, 8.1.13, and 8.1.20). This further suggests that the risk for PTLD is increased in the presence of several risk factors.

Table 2.1.5.2G: Proportion of Subjects who Developed PTLD by the Number of Risk Factors

Number of Risk Factors ^a	Number of Subjects with Risk Factor		
	MI N = 477	LI N = 472	CsA N = 476
0	1/321 (0.3)	2/326 (0.6)	1/312 (0.3)
1	2/129 (1.6)	3/129 (2.3)	1/142 (0.7)
2	5/27 (18.5)	0/16	0/22
3	0	0/1	0

^a Risk factors include use of lymphocyte depleting agents, CMV disease and EBV-negative recipient
Source: ISS Appendix 8.1.1 and 8.1.16

Reviewer Comments:

PTLDs are relatively uncommon life threatening complication of both solid organ and allogeneic bone marrow transplantation and occur in 1-10% of transplant patients [1]. Several risk factors/predisposing factors such as EBV status, CMV status, use of immunosuppression especially T-cell depletive therapies and genetic predisposition of recipients have been reported to be associated with PTLD [2]. The latter include polymorphisms in IL-10, TGF-beta, deletions/gains in genes such as BCL2 and PAX5 and human leukocyte antigen (HLA) haplotypes [1, 3- 5]. In addition, microsatellite instability and alterations of c-MYC, BCL-6, p53, DNA hypermethylation and aberrant hypermutation of protooncogenes have been reported to be associated with PTLD [6]. Recently, EBV load (true positive viral load) has been suggested to be a possible clinically useful biomarker for assessing PTLD risk in seropositive patients [7]. In addition, detection of transcripts specific for type III latency has been reported to differentiate between latent and productive EBV infection in transplant recipients with high virus load [8].

In the current submission, EBV status, CMV disease and lymphocyte-depleting agents have been tested as possible risk factors for PTLD. From the Sponsor's analysis, three risk factors (EBV negative serology, CMV disease, and use of T-cell depleting therapy) appear to be correlated with higher risk in the MI regimen and only EBV status in the LI regimen.

Reviewers' independent analyses:

PTLD-associated risk factor analysis:

We employed receiver operating characteristic (ROC) curve analysis to evaluate the risk factors associated with PTLT associated in belatacept-treated patients. Data from studies IM103100, IM103008 and IM103027 were used to generate ROC plots. Table 1 below summarizes the results of the ROC analyses.

EBV serostatus was the most significant single risk factor, followed by CMV serostatus. A combination of these two risk factors was more informative than either variable alone. Consideration of EBV and CMV serostatus was more informative than consideration of EBV serostatus + CMV infection or NRISK (the sponsor's risk score that does not take into account CMV serostatus), suggesting that the joint consideration of EBV and CMV serology could be a convenient approach to gauging patients' PTLT risk prior to initiation of belatacept therapy.

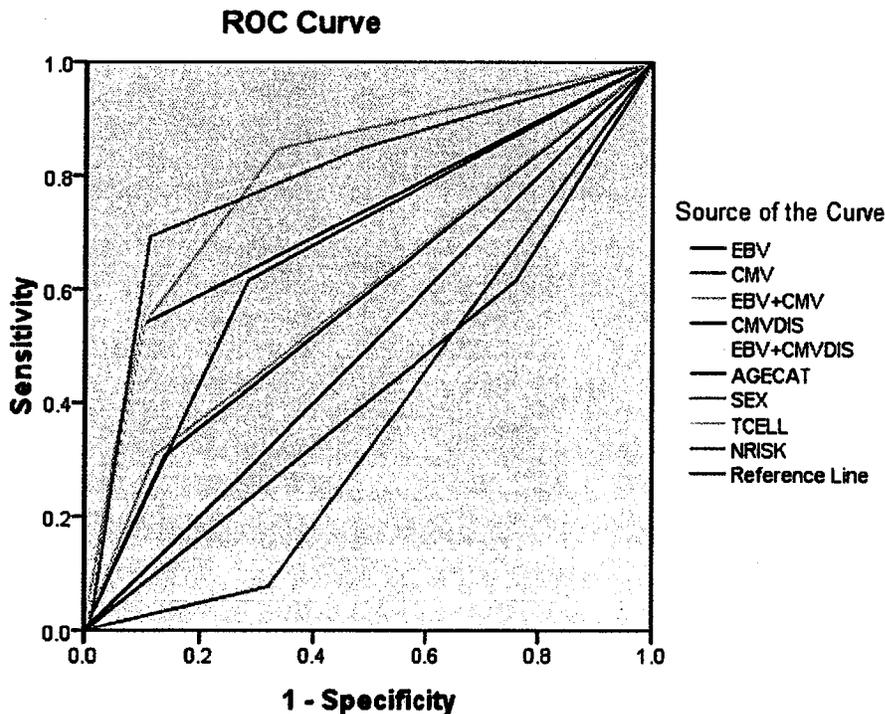


Figure 1: Correlates of PTLT risk in belatacept-treated patients

EBV: Epstein-Barr virus serostatus; CMV: Cytomegalovirus serostatus; CMVDIS: CMV infection prior to PTLT diagnosis; AGE CAT: Age category (below or above 60 years); SEX: Female/Male; TCELL: Lymphocyte depletion prior to PTLT through treatment with T-cell depleting agents; NRISK: A combination of risk factors; AGE CAT, EBV, TCELL and CMV DIS.

Table 1: ROC results for PTLT risk factors in belatacept-treated patients

Test Result Variable(s)	ROC	Std. Error	P-value
-------------------------	-----	------------	---------

EBV	.719	.085	.007
CMV	.666	.079	.039
EBV+CMV	.806	.065	<.0001
CMVDIS	.584	.087	.296
EBV+CMVDIS	.794	.070	<.0001
AGECAT	.428	.084	.370
SEX	.378	.065	.132
TCELL	.593	.087	.247
NRISK	.799	.071	<.0001

Analysis was limited to belatacept-treated patients that had complete data for the above parameters. N= 13 patients treated with belatacept developed PTLD (data for all variables available); N= 884 patients did not develop PTLD.

Risk factors for PTLD in EBV positive, belatacept-treated patients:

The sponsor has decided to restrict the use of belatacept to EBV positive transplant patients and contraindicate the use of belatacept in EBV negative patients. However, 6/13 PTLD cases were found in EBV positive, belatacept-treated patients. The EBV status is not available for one PTLD case. This observation suggested that additional risk factors may be responsible for the occurrence of PTLD in belatacept-treated transplant patients. To that end, we carried out chi-square analyses to examine the impact of CMV serostatus on PTLD risk when limiting the analysis to EBV positive, belatacept-treated patients (Table 2). The PTLD case for which the EBV status was not available, was excluded from our analyses. **Among EBV positive patients, those with CMV negative serology were more likely to develop PTLD than those who are CMV positive (1.91% vs 0.34%), representing an approximately 6-fold higher risk (OR 5.75 [1.05-31.66]; univariate association of CMV serostatus to PTLD p=0.023).** Of note, among EBV negative patients, those with CMV negative serology were only marginally more likely to develop PTLD than those who were CMV positive (8.16% vs 6.38%), representing a non-significant 30% higher risk (OR 1.3 [0.23-7.87]).

Table 2: PTLD rates among EBV seropositive belatacept-treated patients based on CMV serostatus

<i>PTLD by CMV serostatus in EBVseropositive belatacept-treated population</i>				
		PTLD		Total
		No	Yes	
CMV	+	590	2 (0.34%)	592
	-	205	4 (1.91%)	209
Total		795	6 (0.75%)	801

Consistent with what is previously known about CMV disease (vis-à-vis serology) as a PTLD risk factor, our analyses also demonstrated PTLD risk in EBV positive patients to be higher among those with CMV disease vs. no disease (2.68% vs 0.43%), representing

6-fold higher risk (OR 6.33 [1.26- 31.77]). This association was not significant among EBV negative patients (6.67% vs 7.41%).

Among EBV positive patients on the LI regimen, those with CMV negative serology were more likely to develop PTLD than those who were CMV positive (3.16% vs 0.33%), [Table 3] representing an approximately 10-fold higher risk (OR=9.75, 0.89 - 242.03); univariate association of CMV serostatus to PTLD p=0.047.

Table 3: PTLD rates among EBV seropositive belatacept-treated patients on the recommended regimen (LI) based on CMV serostatus

<i>PTLD by CMV serostatus in EBVsero positive belatacept-treated population on the recommended regimen (LI)</i>				
		PTLD		Total
		No	Yes	
CMV	+	299	1 (0.33%)	300
	-	92	3 (3.16%)	95
Total		391	4 (1.01%)	395

Conclusions on PTLD risk factors in belatacept-treated patients:

We found EBV serostatus (EBV negative recipients) to be the most significant risk factor PTLD in belatacept-treated patients, consistent with the sponsor’s analysis. In addition, we identified CMV serostatus (CMV negative recipients) as a risk factor for PTLD. In combination with EBV, CMV was identified as an important risk factor for PTLD in belatacept-treated patients on the basis of ROC analyses and on the imbalance of PTLD in EBV positive, CMV negative individuals. The results suggest that a combination of EBV and CMV serostatus is a better predictor of PTLD than EBV serostatus alone in belatacept-treated patients. Of note, neither CMV serostatus nor CMV disease appear to be robust risk factors for PTLD in EBV negative, belatacept-treated patients.

PTLD with CNS involvement (CNS-PTLD)-associated risk factor analysis:

We performed similar analyses as described above, but with a focus on CNS-PTLD. Consistent with the analysis for all PTLD events, EBV serostatus was the strongest risk factor CNS-PTLD (Table 4). Joint consideration of EBV and CMV serostatus only marginally improved predictions when looking at the “all-comer” belatacept population.

Table 4: ROC results for CNS-PTLD risk factors in belatacept-treated patients

Test Result Variable(s)	Area	Std. Error	P-value
EBV	.727	.101	.019
CMV	.635	.097	.162
EBV+CMV	.777	.089	.004
CMVDIS	.653	.104	.114

EBV+CMVDIS	.850	.064	<.0001
AGECAT	.398	.101	.290
SEX	.340	.066	.098
TCELL	.606	.105	.274
NRISK	.886	.038	<.0001

Analysis was limited to belatacept-treated patients that had complete data for the above parameters. N= 9 patients treated with belatacept developed CNS-PTLD (data for all variables available); N= 888 patients did not develop PTLD.

Risk factors for CNS-PTLD in EBV positive, belatacept-treated patients:

Consideration of CMV serostatus provided additional information regarding CNS-PTLD risk in EBV positive patients. Specifically, among EBV positive patients, CMV seronegative patients are more likely to develop CNS-PTLD than those who are CMV positive (0.96% vs 0.34%) [Table 5], representing an approximately 3-fold higher risk (OR 2.79 [0.286-28.47]) in CMV negative population. Though not statistically significant likely owing to small numbers of events, the directional association between CMV serostatus and CNS-PTLD risk in EBV positive patients is similar to that of overall PTLD risk in this population as described above.

Table 5: Belatacept CNS-PTLD rates among EBV positive patients based on CMV serostatus

<i>CNS-PTLD by CMV serostatus in EBV positive belatacept-treated population</i>				
		PTLDCNS		Total
		No	Yes	
CMV	Positive	590	2 (0.34%)	592
	Negative	207	2 (0.96%)	209
Total		797	4 (0.50%)	801

CMV disease itself was significantly associated with CNS-PTLD risk among EBV positive patients. Among EBV positive patients, only those with CMV disease developed CNS-PTLD (2.68% vs 0.15%. $p < 0.001$). However, because CMV disease is a late post-transplant sequella, the clinical utility of CMV disease as a prognosticator for PTLD risk is limited.

Conclusions on CNS-PTLD risk factors in belatacept-treated patients:

The association between CMV serostatus and CNS-PTLD was directionally consistent with the results for the overall PTLD analysis. Since CNS cases represented a subset of total PTLD burden, the results did not reach statistical significance.

Does the literature support the possibility of CMV serostatus being a risk factor for PTLD?

Two studies from Germany did not find a correlation between CMV status, while four studies from US do support a role for CMV status to PTLD. Schubert et al., (9) reported that age, EBV infection after transplantation and use of T-cell depleting agents were risk factors for PTLD in pediatric heart transplant patients, whereas CMV mismatch and CMV infection were not risk factors. In a large retrospective study from Germany also, Opelz et al., (10) reported that EBV status, age, CMV disease were important risk factors in kidney and heart transplant patients, but not CMV serostatus. In a study reported from Mayo clinic, EBV status, CMV status and T-cell depleting agents were reported to be associated with PTLD and CNS-PTL in liver, heart, lung and kidney-pancreas transplants (11). In another study with pediatric heart transplant patients, EBV status, and CMV status were found to be associated with PTLD (12). Marginal significance of CMV status was reported in heart and heart-lung transplant patients, while age of recipients and donors below 18 years and number of rejections were found to be significantly associated with PTLD (13). Stronger support for the involvement of CMV serostatus comes from a study of 59,560 kidney recipients from the OPTN/UNOS database. EBV serostatus, CMV serostatus and induction with thymoglobulin were identified to be statistically significant risk factors for PTLD (14).

The risk factors for PTLD may be different depending on the organ transplanted, age of the patients, co-medications, number of acute rejection episodes, etc. The risk factors for PTLD may be different in the context of the drug/biologic also. Based on the data in the BLA submission for belatacept, and some support from the literature, EBV and CMV status appear to be important risk factors for PTLD in kidney transplant patients.

Is the involvement of CMV status in development of PTLD biologically plausible?

EBV and CMV are members of the human herpes virus (HHV) family. EBV belongs to the gamma subfamily that has oncogenic potential whereas CMV belongs to the beta family that is problematic specifically in immunocompromised populations. However, *in vitro* evidence that CMV may promote neoplastic transformation is available (15-17). Also, CMV has been reported to be associated with a tumor suppressor gene, p53, and may play a permissive role in PTLD development (13).

While EBV serostatus is a well established risk factor for PTLD, the exact clinical significance of CMV serology as a risk factor for PTLD remains to be determined. It is possible that CMV seropositive donors may cause CMV infection/disease in CMV seronegative recipients. Moreover, CMV seronegative individuals could have latent CMV infection. This latent infection (viral genome maintained as an extrachromosomal plasmid in a small number of hematopoietic progenitor cells) may be reactivated when patients are immunocompromised. CMV may also have indirect effect(s) on PTLD. For example, CMV infection in CMV negative transplant patients could increase EBV replication, B-cell infection and shedding of virus in the oropharynx and contribute to PTLD development. Human CMV infection has also been shown to induce transcription and secretion of TGF- β 1 (Walker 1995).

Based on these reports, it appears that the involvement of CMV status in PTLD development is biologically plausible.

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4. COMMENTS

1. Our results confirm the sponsor's analysis results that EBV is the most significant risk factor for development of PTLD in belatacept-treated patients. We newly identified that CMV serostatus was also a significant risk factor for PTLD.
2. Our analyses indicate that among EBV positive patients (the population to which belatacept is likely to be restricted if approved), a significant imbalance of PTLD was observed in the CMV negative patients (6-fold higher risk vs. CMV positive [OR 5.75 [1.05-31.66]]), suggesting that CMV negative serostatus should be considered as an additional risk factor when considering belatacept as a treatment option.
3. Epidemiological and mechanistic support for association of CMV status to PTLD risk is available in the literature.
4. We recommend the label language in section 6 below be added to the belatacept product label.
5. We recommend that any PMCs or PMRs related to PTLD risk with belatacept elucidate the differential risk of PTLD based on CMV status in EBV positive transplant recipients.

5. RECOMMENDATIONS

The Office of Clinical Pharmacology genomics reviewer has reviewed the belatacept BLA. It is recommended that the label language in section 6 below be incorporated in the belatacept product label and that any PMCs/ PMRs related to PTLD risk of belatacept investigate the effect of CMV status on PTLD risk..

6. LABEL RECOMMENDATION

Section 5.1





7. Appendix: Brief Summary of Relevant Belatacept Clinical Trials

Phase 3 Studies

IM103008 (N = 666) is a 3-year study in subjects who received a kidney from a living donor or a standard criteria deceased donor. Approximately 2 years (median follow-up of 24.8 months) of data have been collected in this study in which the primary endpoint was at 12 months.

IM103027 (N = 543) is a 3-year study in subjects who received a kidney from a donor with extended criteria. These criteria were based in part on those issued by the United Network of Organ Sharing (UNOS); they also included other features widely used to identify potentially compromised organs, such as those from donors with cardiac death (DCD) or with prolonged cold ischemia time (CIT). Approximately 2 years (median follow-up of 26.5 months) of data have been collected in this study in which the primary endpoint was at 12 months.

Phase 2 Study

IM103100 (N = 218) was a 12-month study, with a long-term extension, in subjects undergoing renal transplant. This study enrolled recipients of living and deceased renal allografts. A total of 128 subjects completed the 12-month study and continued

on their respective therapy and dose schedule in the optional long-term extension. Up to 7 years of data (median follow-up 3.2 years) have been collected in the 12-month study and long-term extension period combined.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

multiple dose:	X	6 + 1		@ 10 mg/kg and 5 mg/kg; 1 study used belatacept MI (rather than LI) regimen with different set of background therapy
Dose proportionality -				
fasting / non-fasting single dose:	X	1		Infused over 1 h instead of 30 min; Manufacturing (b) (4)
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	1		Effect on MPA/MPAG conc.
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	X	1		IDO, ATP
Phase 3:	X	2		immunogenicity
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		
Population Analyses -	X			
Data rich:		(3)		Two Phase 1; one Phase 2
Data sparse:		(2)		Two Phase 3
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		(b) (4)
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		1		
Total Number of Studies		16 + 5		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug	X			1 (effect on MPA/MPAG

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

	interaction information?				concentrations relative to CsA)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	For IV administration
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			The sponsor provided a justification for the lack of a need for PK-based TDM of belatacept.
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Orphan Drug
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Orphan Drug
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			Sponsor's E-R analysis did not find association with AR, CMV, PTLD, and preservation of renal fxn.
General					

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Gerlie Gieser
Gerlie Gieser, PhD

Reviewing Clinical Pharmacologist

8/12/09

Date

Philip Colangelo, PharmD, PhD
Team Leader/Supervisor

PM Colangelo

8/12/09
Date