CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125288Orig1s000

<u>STATISTICAL REVIEW(S)</u>

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Addendum

CLINICAL STUDIES

BLA/Serial Number:	125,288
Product Name:	Belatacept for Injection
Indication(s):	Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants
Applicant:	Bristol-Myers Squibb Company
Date(s):	Stamp date: December 15, 2010
	PDUFA date: June 16, 2011
	Review date: March 11, 2011
Review Priority:	Standard review of resubmission to Complete Response letter
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Keywords: clinical studies, BLA review, renal transplant, long term data

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1. INTRODUCTION

The BLA submission for belatacept was originally submitted on June 30, 2009. On May 1, 2010, BMS was issued a Complete Response letter. One of the clinical deficiencies stated in the letter was the lack of sufficient long term data to evaluate the long term effect of belatacept on the rate of post-transplant lymphoproliferative disorder (PTLD), renal effects, cardiovascular events, and graft and patient survival. To address this deficiency, it was requested that the 36 month data for the two Phase 3 studies be submitted for review. The 36 month study reports for Studies IM103008 and IM103027 were provided in a submission dated September 24, 2010. BMS was allowed to respond to the deficiencies in a rolling fashion. A submission received December 15, 2010 provided the final piece of information necessary to fully address all of the deficiencies stated in the Complete Response letter.

As a brief overview, the development program of belatacept consisted of 2 complementary Phase 3 trials in de novo renal transplantation populations. IM103008 enrolled recipients of organs from living donors and deceased standard criteria donors. IM103027 enrolled recipients of organs from deceased donors with extended criteria. These extended criteria were donor age $\geq$ 60 years; or donor age 50 to 59 and $\geq$ 2 of the following: cerebrovascular accident, hypertension, and serum creatinine > 1.5 mg/dL; or anticipated cold ischemia time $\geq$ 24 hours; or donor with cardiac death (non-heart beating donor). Both trials were 3 year multi-center, multi-national, randomized, active controlled trials. Patients were randomized to receive treatment with either belatacept MI (more intensive), belatacept LI (less intensive), or CsA. All patients received induction with basiliximab and maintenance therapy with mycophenolate mofetil, and corticosteroids. The trials were open label with respect to belatacept and CsA but the two belatacept regimens were blinded through 12 months.

Studies IM103008 and IM103027 were both designed as 36 month studies. The primary efficacy evaluation of these studies was conducted at 12 months. However, secondary objectives included the assessment of the effects of belatacept, relative to cyclosporine (CsA) at 36 months on patient and graft survival, measures of acute rejection, calculated glomerular filtration rate (GFR), post transplant diabetes mellitus, measures of hypertension including systolic and diastolic blood pressure, and measures of dyslipidemia including serum total, LDL, and HDL cholesterol and triglycerides. The 12 month efficacy data was thoroughly reviewed in a Statistical Review and Evaluation dated March 23, 2010. On the basis of a more favorable risk/benefit profile seen from the review of the 12 month efficacy data, the belatacept LI regimen is the dose being considered for approval by the Medical Division. Additionally, due to the increased risk of developing PTLD that was observed, the use of belatacept will be contraindicated in EBV negative or unknown status patients to minimize the risk for PTLD.

This review is an addendum to the full statistics review and will present the results of the 36 month data primarily in a descriptive fashion. For a complete discussion of study design and the primary assessment of efficacy, please refer to that review. The IM103008 and IM103027 36 month study reports and datasets provided in the electronic submission were reviewed. These

can be found in the electronic submission located at:
\\cbsap58\m\eCTD_Submissions\STN125288\0055

2.   STATISTICAL EVALUATION

2.1 Evaluation of Efficacy

2.1.1   Patient Disposition

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

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

Study		Belatacept MI	Belatacept LI	CsA
008	Randomized and transplanted (ITT)	219	226	221
	Randomized, transplanted and treated	219	226	215
	Number discontinuing treatment by 36 months	61 (27.9)	56 (24.8)	72 (33.5)
	Adverse event	16 (7.3)	16 (7.1)	32 (14.9)
	Lack of efficacy	29 (13.2)	26 (11.5)	18 (8.4)
027	Randomized and transplanted (ITT)	184	175	184
	Randomized, transplanted and treated	183	174	179
	Number discontinuing treatment by 36 months	74 (40.4)	60 (34.5)	79 (44.1)
	Adverse event	34 (18.6)	35 (20.1)	44 (24.6)
	Lack of efficacy	19 (10.4)	15 (8.6)	17 (9.5)

2.1.2   Efficacy Results

The Medical Division's basis for proof of efficacy of belatacept was the assessment of the composite endpoint of biopsy proven acute rejection (BPAR), graft loss, death, or loss to follow-up at 12 months. The results at 36 months are presented in the following table. At 36 months, the rates of BPAR, graft loss, death, or loss to follow-up were similar between the belatacept LI and CsA treatment groups in both trials.

Table 2
Biopsy Proven Acute Rejection, Graft Loss, Death, or Loss to Follow-up at 36 Months
IM103008 and IM103027

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

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

Patient and graft survival at 36 months is presented in Table 3. In IM103008, there were 8, 12, and 14 fewer belatacept MI, belatacept LI, and CsA patients surviving with a functioning graft at month 36 compared to month 12. In IM103027, there were 11, 12, and 13 fewer belatacept MI, belatacept LI, and CsA patients surviving with a functioning graft at month 36 compared to month 12.

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

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

***Reviewer's Comment**: This analysis, as compared to that presented by the Applicant, treats all patients with unknown status at 36 months as having a graft loss or died and not just those who met various other unfavorable events during the 36 months post-transplantation.*

Table 4 summarizes the incidence and severity of biopsy proven acute rejection at 36 months. The results are consistent with those seen at 12 months. In IM103008, there are numerically more biopsy proven acute rejections in the belatacept treated patients than in the CsA treated

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

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

| Study		Belatacept MI	Belatacept LI	CsA
008	**Acute Rejection**	59/219 (26.9)	50/226 (22.1)	31/221 (14.0)
	Mild IA	7	6	8
	Mild IB	6	10	9
	Moderate IIA	20	19	9
	Moderate IIB	23	14	5
	Severe III	3	1	0
027	**Acute Rejection**	41/184 (22.3)	42/175 (24.0)	42/184 (22.8)
	Mild IA	2	5	2
	Mild IB	6	3	6
	Moderate IIA	14	24	25
	Moderate IIB	18	10	9
	Severe III	1	0	0

In IM103008, a total of 8 belatacept MI (3 graft loss only, 2 graft loss and died, 3 died only), 11 belatacept LI (5 graft loss only, 6 died only), and 3 CsA (1 graft loss only, 1 graft loss and died, 1 died only) patients experienced graft loss or death by month 36 following the episode of BPAR. In IM103027, the totals were 7 belatacept MI (4 graft loss only, 3 died only), 10 belatacept LI (4 graft loss only, 3 graft loss and died, 3 died only), and 13 CsA (5 graft loss only, 3 graft loss and died, 5 died only) patients.

Mean calculated GFR at months 1, 3, 12, 24, and 36 is presented in Table 5 and depicted in Figures 1 and 2 for IM103008 and IM103027, respectively. The differences in renal function for the belatacept regimens compared to CsA that were apparent in the first month after transplant and maintained up to 24 months continue to be maintained up to 36 months. Slopes of the calculated GFR curves from Month 3 (the time when post-transplant GFR appeared to stabilize) to Month 36 were calculated and are summarized in Table 6. For the CsA groups, the slopes were -2.21 mL/min/1.73m^2/year (IM103008) and -1.97 mL/min/1.73m^2/year (IM103027) indicating a slight annual decline in renal function. For the belatacept regimens, the 95% confidence intervals about the slopes do not exclude 0 indicating that there may not be any improvement but only maintenance of calculated GFR over time.

Table 5
Mean (standard deviation) Calculated GFR
IM103008 and IM103027

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

Figure 1
Mean Calculated GFR through 36 Months
IM103008
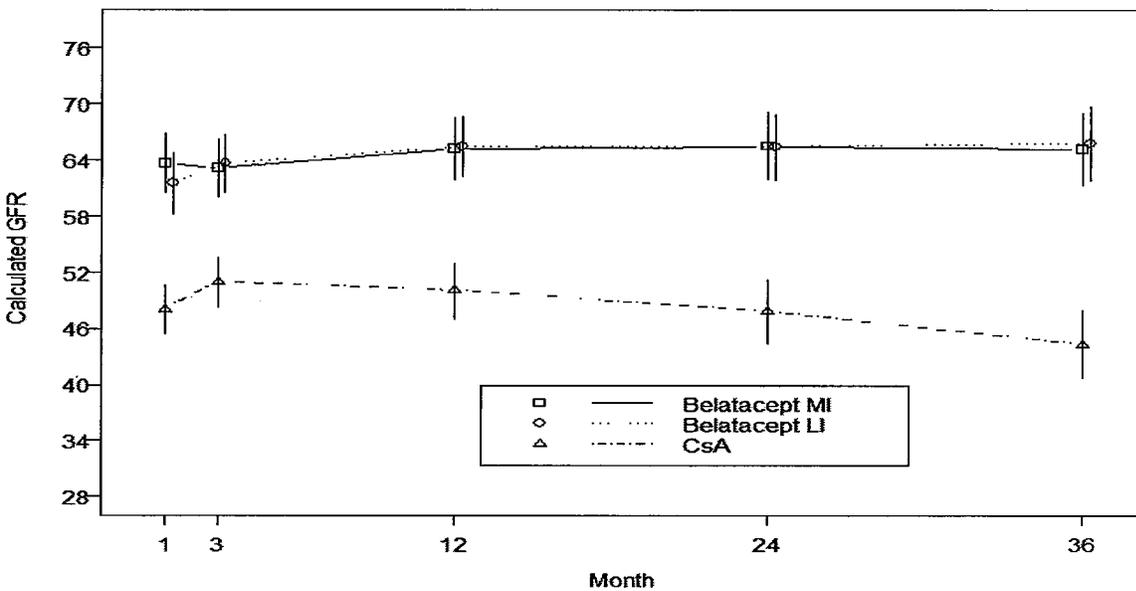
Error bars represent the 95% confidence interval about the mean

Figure 2
Mean Calculated GFR through 36 Months
IM103027
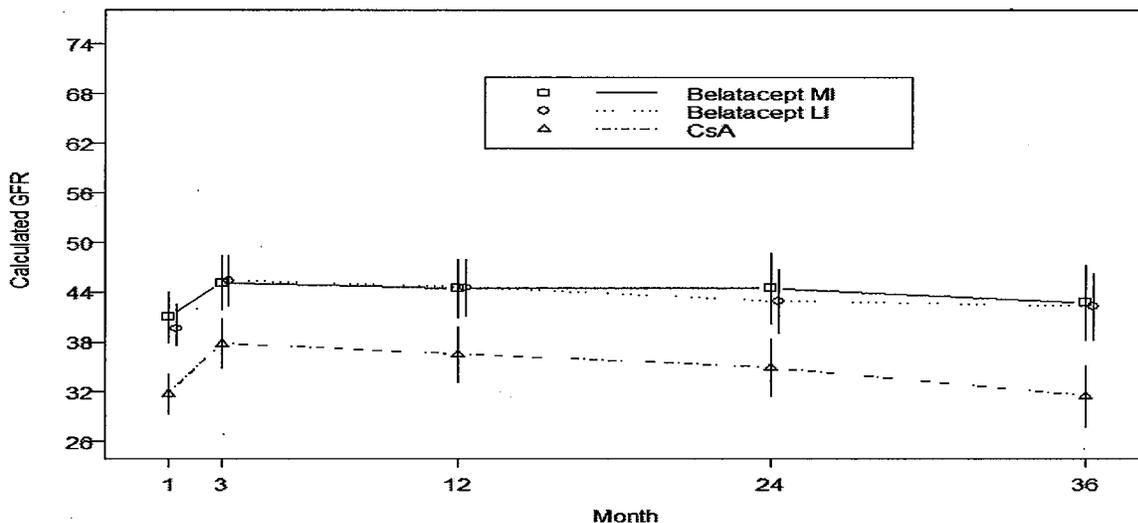
Error bars represent the 95% confidence interval about the mean

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

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

*mL/min/1.73 m²/year

In order to determine the impact of the difference in the number and severity of acute rejection events, analyses of calculated GFR at 12 months by rejection status were conducted. These analyses were repeated at 36 months. Table 7 presents the mean calculated GFR at 36 months for patients who experienced an acute rejection and for those who didn't by 36 months. As was seen at 12 months, in patients with acute rejection and in subjects without acute rejection, mean calculated GFR was higher in the belatacept groups than in the CsA group. Mean calculated GFR was lower for patients who experienced an acute rejection compared to those who did not experience an acute rejection. The differences in calculated GFR for those who did and did not experience an acute rejection were greatest for belatacept treated patients compared to CsA patients in IM103008 but more similar in IM103027. Interpretation of these analyses should be

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made with caution because of limitations in the data due to the following reasons: missing GFR at 36 months for some patients; not all patients remained on study therapy for the entire 36 months and those who didn't may have switched to a regimen containing a calcineurin inhibitor; and these subsets of patients are based on an outcome variable that is affected by treatment.

Table 7
Calculated GFR at 36 Months by Biopsy Proven Acute Rejection Status at 36 Months
IM103008 and IM103027

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

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

Reviewer's Comment: In addition to the analysis above which only imputes missing GFR values for patients who had a graft loss or died within 36 months, the Applicant provided an analysis which applied a last observation carried forward (post rejection) approach for imputing missing data. The estimates of the mean calculated GFR were slightly lower than those presented in Table 7. However, the conclusions regarding the comparisons between treatment groups and rejection status were similar.

Due to the increased risk of developing PTLD that was observed for belatacept treated patients and the known fact that EBV negative patients are also at increased risk for developing PTLD, the Medical Division intends to approve the use of belatacept LI for only EBV positive patients and contraindicate the use of belatacept in EBV negative or unknown status patients to minimize the risk for PTLD. Tables 8 and 9 summarize the results for the endpoints of biopsy prove acute rejection, graft loss, death, or lost to follow-up at 36 months and patient and graft survival at 36 months for EBV positive patients only. The conclusions drawn for the EBV positive patients are similar to those drawn for the overall population.

Table 8
Biopsy Proven Acute Rejection, Graft Loss, Death at 36 Months
EBV Positive Subjects
IM103008 and IM103027

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

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

Table 9
Patient and Graft Survival at 36 months for EBV Positive Subjects
IM103008 and IM103027

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

2.2 Evaluation of Safety

Nearly all patients experienced 1 or more adverse event during the first 12 months of the Phase 3 trials and these numbers did not change through 36 months. In IM103008, serious adverse events up to month 36 were reported for 61% belatacept MI patients, 58% belatacept LI patients, and 68% CsA patients. In IM103027, serious adverse events up to 12 months were reported for 81% belatacept MI patients, 79% belatacept LI patients, and 79% CsA patients. No new safety concerns were identified between the original BLA database lock and the current submission.

Table 10
Overall Adverse Events through Month 36
IM103008 and IM103027

	IM103008			IM103027		
	Belatacept MI (n=219)	Belatacept LI (n=226)	CsA (n=221)	Belatacept MI (n=184)	Belatacept LI (n=175)	CsA (n=184)
Any AE	218 (99.5)	225 (99.6)	219 (99.1)	182 (98.9)	174 (99.4)	184 (100.0)
Serious AE	133 (60.7)	131 (58.0)	150 (67.9)	149 (81.0)	139 (79.4)	146 (79.3)

AE= adverse event

Table 11 summarizes the total number of deaths and/or graft losses observed up to 12, 24, and 36 months in the Phase 3 trials. Overall, the total number of deaths up to 36 months were 25 (6.2%) in the belatacept LI group, 31 (7.7%) in the belatacept MI group, and 32 (7.9%) in the CsA group. Overall, the total number of graft losses up to 36 months were 30 (7.5%) in the belatacept LI group, 28 (6.9%) in the belatacept MI group, and 33 (8.1%) in the CsA group.

Table 11
Graft Loss and/or Death
IM103008 and IM103027

	IM103008			IM103027		
	Belatacept MI (n=219)	Belatacept LI (n=226)	CsA (n=221)	Belatacept MI (n=184)	Belatacept LI (n=175)	CsA (n=184)
Death/Graft Loss						
Up to Month 12	10	8	14	23	20	25
Up to Month 24	13	12	20	29	28	30
Up to Month 36	17	18	24	36	31	36
Death						
Up to Month 12	6	4	7	8	5	8
Up to Month 24	7	8	13	13	11	12
Up to Month 36	9	10	15	22	15	17
Graft Loss						
Up to Month 12	4	5	8	17	16	20
Up to Month 24	7	5	8	18	20	22
Up to Month 36	10	9	10	18	21	23

Hypertension, dyslipidemias, and new onset diabetes after transplantation (NODAT) are class effects of calcineurin inhibitors (e.g. CsA). Therefore, the Applicant prospectively studied these endpoints to support the benefits of belatacept. Table 12 summarizes the mean systolic and diastolic blood pressure at Month 36 for both studies. As was seen at Month 12, the mean systolic and diastolic blood pressures were lower for patients in both belatacept groups relative to the CsA group. At 36 months, the differences in mean blood pressures between the belatacept groups and CsA are only significant in IM103008.

Reviewer's Comment: *Caution should be exercised when interpreting these analyses as these analyses are conducted as observed i.e. no imputation for missing data. By 36 months, blood*

pressure values are missing for approximately 20 to 35% of patients in IM103008 and 32 to 49% of patients in IM103027.

Table 12
Mean Blood Pressure at Month 36
IM103008 and IM103027

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

Mean (standard deviation)
Number in analysis
*comparison of mean value of belatacept regimen to CsA p-value<0.027

Mean total cholesterol and mean triglyceride levels at Month 36 were lower for patients in both belatacept groups relative to the CsA group in both studies (statistically significant for IM103008 only). Mean LDL cholesterol levels at 36 months were significantly lower for patients in both belatacept groups relative to the CsA group in IM103008 but similar across treatment groups in IM103027. Mean HDL levels at 36 months were similar across treatment groups in both studies.

Table 13
Serum Lipids at Month 36
IM103008 and IM103027

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

Mean (standard deviation)
Number in analysis
*comparison of mean value of belatacept regimen to CsA p-value<0.027

Reviewer's Comment: *Caution should be exercised when interpreting these analyses as these analyses are conducted as observed i.e. no imputation for missing data. By 36 months, serum*

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lipid values are missing for approximately 25 to 36% of patients in IM103008 and 40 to 46% of patients in IM103027.

NODAT was defined in the trials as the use of an antidiabetic agent for more than 30 days or at least two fasting plasma glucose values greater than or equal to 126 mg/dL in a subjects who was not diabetic at study entry. Across all treatment groups relatively few patients developed NODAT by Month 12. The greater numerical difference (fewer) in belatacept treated patients compared to CsA treated patients who developed NODAT that was seen by 12 months is not as apparent by 36 months.

Table 14
New Onset Diabetes Mellitus After Transplantation by 36 Months
IM103008 and IM103027

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

Denominator is number of subjects with out diabetes at transplant

Post transplant lymphoproliferative disorder (PTLD) was found to be observed at an increased frequency in the belatacept arms in the 3 core belatacept trials (IM103008, IM103027, and IM103100). PTLD is a composite term encompassing the following MedDRA preferred terms: lymphoproliferative disorder, hematological malignancy, lymphoma, CNS lymphoma, hepatosplenic t-cell lymphoma, EBV-associated lymphoproloferative disorder, and b-cell lymphoma. Up to 14-Dec-2009 (cut off for original review), there were 8 cases (1.7%) of PTLD in the belatacept MI group, 6 cases (1.3%) in the belatacept LI group, and 2 cases (0.4%) in the CsA group. Only 1 additional case of PTLD has been observed since then. This non-CNS case was observed in IM103027 in a subject receiving CsA and occurred approximately 4 years after transplant.

3. CONCLUSIONS AND RECOMMENDATIONS

The data through 36 months in both of the Phase 3 trials continue to support the conclusions drawn at 12 months regarding the efficacy of belatacept. At 36 months, there are comparable rates of the composite endpoint of biopsy proven acute rejection, graft loss, death, or lost to follow-up between the belatacept groups and CsA. There are also comparable rates of patient and graft survival between the belatacept groups and CsA at 36 months. Mean calculated GFR is higher in belatacept treated patients compared to CsA treated patients. The difference which was apparent at 1 month post transplant was maintained through 36 months.

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

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

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STATISTICAL SAFETY REVIEW AND EVALUATION

Medical Division: **Division of Special Pathogen and Transplant Products (DSPTP)**

Biometrics Division: **Division of Biometrics VII**

BLA NUMBER: 125288 (Document Submission: 12/20/2010)

NAME OF DRUG: NULOJIX™ (belatacept)

INDICATION(S): Prophylaxis of organ rejection in adult renal transplant patients

APPLICANT: Bristol-Myers Squibb

DOCUMENTS REVIEWED: Briefing package for meeting with Sponsor on 02/01/2011 (includes Study IM103076 Draft Protocol)

STATISTICAL REVIEWER: John Stephen Yap, PhD (DB7)

STATISTICAL TEAM LEADER: LaRee Tracy, MA, PhD (DB7)

BIOMETRICS DIVISION DIRECTOR: Aloka Chakravarty, PhD (DB7)

CLINICAL REVIEWER: Patrick Archdeacon, MD (DSPTP)

PROJECT MANAGER: June Germain, MS (DSPTP)

Background

The proposed indication for belatacept is for prophylaxis of organ rejection in adult renal transplant patients. The proposed dose is 10 mg/kg intravenously on the day of transplant (Day 1), Days 5, 14, 28, and Months 2 and 3 post-transplantation, and then 5 mg/kg monthly, starting at Month 4 post-transplantation.

The original Biologic Licensing Application (BLA) for belatacept was submitted by BMS to the FDA on June 30, 2009. The primary clinical studies used to support efficacy and safety claims were IM103100 (a 12-month phase 2 study) and IM103008/IM103027 (3-year phase 3 studies). In each of the primary clinical studies, *de novo* renal transplant patients were randomized to three treatment arms: a less intensive dose of belatacept, a more intensive dose of belatacept, and cyclosporine (CsA). BMS is seeking approval for only the less intensive dose. Each treatment arm included Basiliximab induction and maintenance with mycophenolate mofetil (MMF) and corticosteroids. The BLA was issued a complete response by the FDA on May 1, 2010 for clinical and product quality deficiencies (refer to CR letter dated 5/1/2010).

There was a safety concern associated with the use of belatacept. Specifically, there were relatively more post transplant lymphoproliferative disorder (PTLD) events found in the belatacept arms (both less and more intensive) than in the CsA control arm. BMS suggested that the increased risk of PTLD was restricted to patients who were Epstein-Barr virus (EBV) negative. However, a statistical safety review of the original BLA of data from other randomized clinical trials from previous New Drug Applications (NDAs) that contained CsA-based regimens similar to those in the BLA and data from the Organ Procurement and Transplant Network (OPTN)/United Network for Organ Sharing (UNOS) kidney transplant registry (see Statistical Safety Review by Dr. Anita Abraham of DB7) concluded that there is an increased risk of PTLD in belatacept-treated patients. This review noted that the increased risk was found in both EBV positive and negative subgroups. The proposed label for belatacept includes a contraindication in patients who are EBV seronegative or with unknown EBV serostatus.

In the BLA amendment, BMS proposes to conduct (b) (4) post-marketing studies (IM103074, IM103075, IM103076, (b) (4) to address outstanding concerns related to belatacept. This statistical safety review is in response to a consult from DSPTP requesting a statistical assessment on the study design for Study IM103076. A draft protocol for Study IM103076 was included in the briefing package for a face-to-face meeting submitted by BMS to the FDA on December 20, 2010.

Summary

(b) (4)

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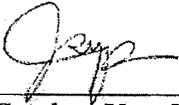
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02/10/2011
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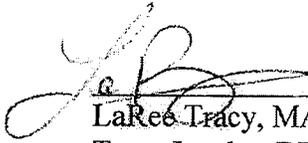
LaRee Tracy, MA, PhD
Team Leader, DB7

02/10/2011
Date

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125288 / N000
Product Name:	NULOJIX™ (belatacept) less intensive (LI) injection regimen
Indication(s):	Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.
Applicant:	Bristol Myers Squibb

Date(s):

Dated:	June 30, 2009
Received:	July 1, 2009
PDUFA:	May 1, 2010
Advisory Committee:	March 1, 2010

Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
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Keywords: kidney transplant, immunosuppression, registry data

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1. EXECUTIVE SUMMARY

This statistical safety review and evaluation was performed in response to a consult from the Division of Special Pathogen and Transplant Products (DSPTP) for Biologics License Application (BLA) 125-288/000 (received July 1, 2009). This BLA is for belatacept injections for the proposed indications of *prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving kidney transplants.* The applicant evaluated two belatacept regimens: less intensive (LI) and more intensive (MI); however, the applicant is seeking approval of only the LI regimen. Additionally, given findings described below, the applicant is proposing restricted use of the product in only adult kidney transplant patients who are confirmed Epstein-Barr virus positive at time of transplant.

The primary efficacy and safety supporting the belatacept BLA comes from three similarly designed randomized clinical trials in *de novo* kidney transplantation: a Phase 2 trial (IM103100) and two Phase 3 trials (IM103008 and IM103027). Among these three trials, there was an increased incidence of post-transplant lymphoproliferative disease (PTLD), a potentially life-threatening complication, in the belatacept treated patients compared to the control, cyclosporine (CsA) treated patients. In the Phase 2 and Phase 3 pivotal trials, 13 out of 949 patients (1.4%) receiving belatacept developed PTLD compared to 2 out of 478 patients (0.4%) receiving cyclosporine. The applicant concedes that the risk of PTLD appeared higher among in the belatacept regimens compared to the cyclosporine control. However, the applicant has suggested that the increased risk is restricted to patients who were Epstein-Barr virus negative (EBV negative) at baseline. Additionally, while the incidence of PTLD in EBV positive patients on belatacept was numerically greater than in EBV positive patients on CsA-based regimen in the Phase 2 and Phase 3 trials, the applicant concludes that it was similar to the incidence of PTLD in EBV positive patients derived using kidney transplant registry data.

To investigate these claims, a safety statistics analysis was conducted to obtain a more accurate point estimate of the expected rate of PTLD, by EBV status, among *de novo* kidney transplant recipients using data from previously submitted New Drug Applications (NDAs) and data from the Organ Procurement and Transplant Network (OPTN)/United Network for Organ Sharing (UNOS) kidney transplant registry.

1.1 Conclusions and Recommendations

In the studies submitted by the applicant, to date, there have been eight (1.7%), six (1.3%) and two (0.4%) reported cases of PTLD in the belatacept MI, LI, and CsA groups respectively among the three belatacept trials. Among EBV positive patients, there were two (0.5%), four (1.0%) and zero (0%) PTLD cases in the belatacept MI, LI and CsA groups respectively. The difference between the belatacept LI and CsA is 1%, exact 95% CI (0, 2.5). Among EBV negative patients, there were five (11.1%), two (3.9%), and one (1.8%) PTLD cases in the belatacept MI, LI and CsA groups respectively. The difference between the belatacept LI and CsA is 2.1%, exact 95% CI (-5.9, 11.9).

Note: At the time of the submission, complete follow-up data were available for all patients out to 24-months post-transplant and additional follow-up past 24-months in a subset of randomized patients. Of the PTLD cases reported above, 1 case in the belatacept LI (EBV positive serostatus) and 1 in the CsA (EBV status unknown) regimens were reported after 24-months post-transplant.

When considering information from three previously submitted randomized clinical trials (RCTs) that contained an CsA-based immunosuppressant regimen similar to the CsA regimen used in the belatacept trials, there were zero cases of PTLD reported (0%) among a total of 534 EBV positive kidney transplant recipients who received a CsA-based regimen. Among 158 EBV negative kidney transplant recipients, there was 1 (0.6%) case of reported PTLD.

The analysis of OPTN/UNOS registry data found the 2-year incidence of PTLD in EBV positive patients on a calcineurin-inhibitor (CNI)-based regimen of either cyclosporine or tacrolimus, to be 0.051 per 100 person-years (PY) and 0.483 per 100 PY in EBV negative patients. This incidence rate can be compared to the estimated 24-month incidence rates of PTLD of 0.346 per 100 PY in EBV positive and 4.4 per 100 PY in EBV negative patients taking belatacept (LI and MI pooled). The 24-month incidence rates among EBV positive and negative patients in the belatacept LI alone regimen were 0.41 per 100 and 2.43 per 100 PY respectively.

Number needed to harm (NNTH) estimates were derived to further elucidate the increased risk of PTLD of belatacept compared to CsA. Given an incidence rate of 0.0035 per PY in the pooled belatacept MI and LI regimens and of 0.0 per PY in the CsA regimen from studies 008, 027 and 100, the estimated NNTH is 145 (95% CI: -532, 64). This suggests that for every 145 EBV positive patients treated with a belatacept-based regimen instead of a CsA-based regimen for two years, one would expect at least one additional case of PTLD. The range for this NNTH suggests that as few as 64 belatacept patients to as many as 532 CsA patients need to be treated for two years to expect at least one case of PTLD. To improve the precision of this estimate, the pooled belatacept LI and MI incidence rate is compared to estimates using data from CsA-based regimens from previous RCTs. The estimated NNTH is 161 (95% CI: 69, 698) patients. When comparing the estimated incidence rate of PTLD from the belatacept trials to the incidence rate of PTLD based on registry data, the estimated NNTH is 170 (95% CI: 116, 319).

When considering all the evidence that has been analyzed from the CsA control regimens in the belatacept trials, other similarly-designed randomized clinical trials that included a CsA-based immunosuppressant regimen, and kidney transplant registry data, it is apparent that there is an increased risk of PTLD in belatacept treated patients and that this increase was found in both EBV negative and positive subgroups. The analyses conducted found that while the incidence of PTLD was lower among EBV positive patients compared to EBV negative patients, still among EBV positive patients alone, the incidence in the belatacept regimens was higher compared to the incidence in the control regimen.

1.2 Brief Overview of Clinical Studies

Three sources of data were considered in this review. The applicant submitted two Phase 3 studies and one Phase 2 study. Secondly, data from other randomized clinical trials from previous applications that contained CsA-based regimens similar to those in the studies provided by the applicant were considered. Thirdly, registry data from OPTN/UNOS of kidney transplant recipients who received similar maintenance regimens as those used in the belatacept trials were analyzed.

Belatacept Randomized Clinical Trials

All three clinical trials submitted by the applicant included a less intensive (LI) regimen and more intensive (MI) regimen of belatacept and a CsA control regimen. The belatacept LI regimen in the Phase 2 trial differed from the belatacept LI regimen studied in the Phase 3 trial in that patients received less study drug.

Study IM103100 was a Phase 2, 1-year, open-label, randomized, active-controlled, multiple-dose study of the efficacy, safety, and pharmacokinetic (PK) of two partially-blinded belatacept regimens vs. CsA as part of a quadruple therapy with MMF, corticosteroids, and basiliximab in patients undergoing first or subsequent renal transplants.

Study IM103008 was a Phase 3, randomized, active-controlled, parallel-group study of the efficacy of two partially-blinded belatacept regimens vs CsA as part of a quadruple therapy with mycophenolate mofetil (MMF), corticosteroids, and basiliximab in patients receiving a renal transplant from a living donor or a deceased donor with anticipated cold ischemia time (CIT) less than 24 hours.

Study IM103027 was a Phase 3, randomized, active-controlled, parallel-group study of the efficacy of two partially-blinded belatacept regimens vs CsA as part of a quadruple therapy with mycophenolate mofetil (MMF), corticosteroids, and basiliximab in patients who are recipients of a renal transplant from an 'extended criteria' donor (e.g., recipients of potentially suboptimal allografts due to donor characteristics such as age and comorbidities, CIT, or other factors).

Other Randomized Clinical Trials in *de novo* Kidney Transplantation

Randomized clinical trials performed in *de novo* kidney transplantation previously submitted to FDA were reviewed to identify cases of PTLD by treatment group and EBV status. Trials that were performed only in *de novo* kidney transplant recipients, collected at least 12-month post-transplant follow-up data, included a treatment regimen consisting of a CNI, MMF, and IL-2a induction therapy, and corticosteroids, collected pre-transplant EBV serostatus, and included detailed adverse event data (coded in MedDRA preferred) were considered. Three trials were identified that fit these criteria: Study 158, A2309 and Symphony.

Kidney Transplant Registries

Analysis by FDA and independently by the Scientific Registry of Transplant Recipients (SRTR) was conducted using the registry data provided by the OPTN/UNOS. The SRTR is a non-profit private group which holds the OPTN contract awarded by the Health Resources and Services Administration (HRSA) for the statistical analyses of OPTN/UNOS data. In addition to this data source, analyses provided by the applicant using data from the Centers for Medicare and Medicaid Services (CMS) and in a published article based on data from the Collaborative Transplant Study (CTS) were cited for comparison.

1.3 Statistical Issues and Findings

Limitations
As the occurrence of PTLD is rare, it was not possible to detect statistically significant differences between treatment regimens using only the data from the belatacept trials provided. Due to this limitation we explored data from other sources, including previously submitted RCTs and transplant registry data. However, the use of prior RCTs has certain limitations including the following:

- The inclusion of data from previously submitted RCTs provided additional data to more accurately estimate the incidence of PTLD on a CsA-based immunosuppressant regimen; however these trials only included follow-up data out to 12-months post transplant, as opposed to the 2-year follow-up data available from the belatacept trials. This prevented a direct comparison of the 2-year incidence of PTLD.

- PTLD was not systematically measured in the same way across the prior RCTs in that there were slight differences in which MedDRA codes were used to designate a case of PTLD. Additionally, there is no validated MedDRA or ICD-9 code specific for PTLD.

- Person-year data were unavailable in one of three prior RCTs preventing a pooled calculation of incidence rate. Incidence rates are preferable to incidence calculations in that they standardize the amount of time patients are exposed, making estimates from one analysis to another more comparable. Also, incidence rates account for varying length of follow-up time, which is useful when there are disproportionate rates of premature treatment discontinuation or drop-out.

- Pooling data across multiple studies has several limitations associated with varying study designs, study populations, treatment regimens and endpoint assessment. While it is possible to limit the differences between studies being compared by including only studies with similar inclusion/exclusion criteria, endpoints and study designs, it is unusual to that any two studies are identical in all design and outcome measures.

The analyses of registry data have several limitations that should be considered. These include the following:

- While OPTN/UNOS data are regarded as the 'gold-standard' source of information for U.S. transplant patients, the data from any registry may under-estimate the true rates of reported events.

- While reporting to OPTN/UNOS is a requirement for participating transplant programs, the quality of reporting can vary across centers.

- The patient population followed by OPTN/UNOS is not identical to that studied in the belatacept kidney trials. Over 50% of the participating transplant centers in the belatacept Phase 3 clinical trials were from outside the United States.

- Technology and diagnostic registry reporting methods by OPTN/UNOS have changed in recent years such that reporting rates of PTLD and the evaluation of EBV serostatus may have changed over time.

- The CTS analysis included only patients whose transplant centers confirmed that complete malignancy information had been reported. Therefore, the CTS registry has the potential for over-reporting as well as under-reporting of information. Additionally, as most CTS members are located in Europe, the patient population differs from the intended population. Additionally, the time frame of the CTS analyses spans from 1995-2007, which differs from that the time frame evaluated using other registry data. This time frame might lead to biased findings given that collection of EBV serology was not universally performed until the early 2000s.

- A recent SRTR analysis of CMS data using the same ICD-9 codes, found that the most commonly reported ICD-9 code (among the searched list) was 202.80 and that the number of events reported using this code from 2001 to 2008 increased in an unusual fashion: the events reported in 2001-2008 were 67, 130, 145, 184, 241, 295, 289 and 322 respectively (each of these numbers represents events reported that calendar year, not cumulatively to that point). The reason for the geometric progression of events reported using this code is unclear but is not thought to correlate with a true increase in the incidence of PTLD during the study time. The most likely explanation would appear to relate to coding errors and differences in reporting practices across medical centers. While FDA obtained the CMS datasets through USRDS to evaluate the applicant's claim, the FDA ultimately determined that the approach did not add value to its understanding of PTLD in EBV positive patients and therefore elected not to present any estimates based on CMS data.

- The applicant did not provide the data and statistical code used in their analyses of OPTN/UNOS or CMS data. As such, FDA was unable to validate or replicate the applicant's findings.

Given the limitations outlined above, it is inappropriate to fully rely on results from any single analysis or comparison of registry data to draw final conclusions. Instead, results across all data analyses should be considered in order from those considered least potentially biased (i.e. comparing rates of PTLD between treatment groups within the belatacept randomized clinical trials) to the more potentially biased (i.e. comparing incidence from belatacept to outside sources such as other randomized trials and registries).

Statistical Findings
An increase in the incidence of PTLD in the belatacept regimens was found across the three core belatacept trials. This finding was supported by comparing the incidence of PLTD in the belatacept regimens to the incidence in CsA-based regimens of previously submitted RCTs and when comparing to incidence estimates from registry data. Specifically:

- In two Phase 3 trials submitted by the applicant, there were more cases of PTLD found in the belatacept groups (in both regimens) compared to the CsA control regimen. In the Phase 2 trial, there were more cases of PTLD in the belatacept MI regimen compared to the CsA-control regimen.

- The pooled belatacept LI regimens from the three studies included in this review had 4 more cases of PTLD (6/472; 1.3%) than the pooled control (CsA) regimens (2/478; 0.4%). Among the subset of EBV positive patients, there are 4 cases of PTLD in the pooled LI regimen compared to 0 cases in the pooled CsA regimen. *Note: One case in the LI regimen occurred after the 24-month follow-up period. Follow-up data were provided only up to 24-months for all randomized patients.*

- Findings of no cases of PTLD, among EBV positive patients receiving a CsA-based regimen, from previously submitted RCTs (in *de novo* kidney transplantation) is consistent with the finding of no cases among all patients randomized to a CsA-based regimen in the three belatacept trials.

- Further, when comparing the rate of PTLD in EBV positive patients randomized to a belatacept regimen to the estimated rates based on registry data, we find more than a 3-fold increase in the rate of PTLD in EBV positive patients randomized to belatacept compared to EBV positive patients receiving a CNI-based immunosuppressant regimen.

The increased risk of PTLD in patients randomized to belatacept is greatest among EBV negative patients. As such, the applicant has proposed to limit use of this product to kidney transplant recipients who are confirmed EBV positive. Results in the EBV positive subgroup are of primary importance.

2. INTRODUCTION

2.1 Overview

NULOJIX™ (belatacept) is a recombinant soluble fusion protein consisting of the extracellular domain of human CTLA-4 and a fragment of a modified Fc domain of human IgG1. Belatacept has been developed as a new therapeutic agent for immunosuppression in kidney transplant recipients; it was studied as a replacement for cyclosporine (CsA) in an immunosuppressive regimen that also included an interleukin (IL)-2 antagonist, mycophenolate mofetil (MMF) and corticosteroids.

Calcineurin inhibitors (CNIs), starting with the advent of cyclosporine have been largely responsible for the high rates of one-year patient and graft survival presently observed among kidney transplant patients. While one-year survival rates have improved, CNIs are associated with some poor long-term outcomes, such as decreased renal function due to cumulative immunologic and non-immunologic injuries to the allograft. The applicant has suggested that patients treated with an immunosuppressive regimen including belatacept, in lieu of cyclosporine, may avoid the consequences of CNI-related adverse effects. The applicant evaluated two belatacept regimens: less intensive (LI) and more intensive (MI); however, the applicant is seeking approval of only the LI regimen. Additionally, given findings described below, the applicant is proposing restricted use of the product in only patients who are confirmed Epstein-Barr virus (EBV) positive at time of kidney transplant.

This review is in response to a safety consult from DSPTP to Division of Biometrics VII on August 12, 2009. This consult requested a safety statistical assessment and evaluation of findings of a higher incidence of PTLD in the belatacept regimens compared to the CsA control regimen across the three belatacept randomized clinical trials. PTLD is a life-threatening complication that can occur following solid organ transplantation and encompasses a heterogeneous group of lymphoproliferative disorders ranging from reactive, polyclonal hyperplasias to aggressive non-Hodgkin's lymphomas. The highest incidence of PTLD occurs during the first year after transplant and is associated with EBV serostatus (Gottschalk et al., 2005).

Among one Phase 2 trial (IM103100) and two Phase 3 trials (IM103008 and IM103027) submitted by the applicant to support claims of efficacy and safety of belatacept, the incidence of PTLD was higher among belatacept treated patients compared to CsA treated patients. The applicant suggested that this increased incidence of PTLD in belatacept treated patients was due to the use of the product in the EBV negative population (a population known to have an increased risk for development of PTLD). The applicant provided results from analyses of various kidney transplant registries suggesting that the estimated incidence of PTLD, among EBV positive patients from registries is similar to the incidence among EBV positive belatacept-treated patients. The applicant therefore proposes to restrict use of belatacept in only patients who are confirmed EBV positive at time of transplant.

To further assesses these findings, DSPTP requested that the incidence of PTLD be evaluated in (1) data from the three belatacept randomized trials, (2) data from prior randomized clinical trials in *de novo* kidney transplantation that included a treatment group receiving a CNI, MMF and IL-2 antagonist and corticosteroids and (3) data from the OPTN/UNOS kidney transplant registry. Registry and prior RCT data were used to obtain a more accurate estimate of the incidence of PTLD, by EBV status, among patients receiving a CNI-based immunosuppressant regimen.

2.2 Data Sources

Three sources of data were used for analyses of the incidence of PTLD in kidney transplant patients.

<u>Belatacept Randomized Clinical Trials</u>
To determine the incidence rate of PTLD in belatacept treated patients, the Phase 2 and Phase 3 studies submitted by the applicant were analyzed.

The following sources were used in analyses of BLA data:

IM103008:
\\cbsap58\M\eCTD_Submissions\STN125288\0000\m5\datasets\im103008\analysis

IM103027:
\\cbsap58\M\eCTD_Submissions\STN125288\0000\m5\datasets\im103027\analysis

IM103100:
\\cbsap58\M\eCTD_Submissions\STN125288\0000\m5\datasets\im103100\analysis

Epidemiology study (IM103028), entitled, "Population-based observation study of post-transplant comorbidity in renal transplant recipients in the United States: An analysis of the USRDS database" and six subsequent addendums submitted by applicant which contained references to analyses of OPTN/UNOS and CMS registry data:

\\cbsap58\M\eCTD_Submissions\STN125288\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\renal-transplant\5354-other-stud-rep\im103028 (original report and addendum #1)

\\cbsap58\M\eCTD_Submissions\STN125288\0017\m5\53-clin-stud-rep\535-rep-effic-safety-stud\renal-transplant\5354-other-stud-rep\im103028 (addendum #2)

\\cbsap58\M\eCTD_Submissions\STN125288\0018\m5\53-clin-stud-rep\535-rep-effic-safety-stud\renal-transplant\5354-other-stud-rep\im103028 (addendum #3)

\\cbsap58\M\eCTD_Submissions\STN125288\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\renal-transplant\5354-other-stud-rep\im103028 (addendum #4)

\\cbsap58\M\eCTD_Submissions\STN125288\0032\m5\53-clin-stud-rep\535-rep-effic-safety-stud\renal-transplant\5354-other-stud-rep\im103028 (addendum #5)

\\cbsap58\M\eCTD_Submissions\STN125288\0034\m5\53-clin-stud-rep\535-rep-effic-safety-stud\renal-transplant\5354-other-stud-rep\im103028 (addendum #6)

Two additional sources of data were analyzed to estimate the background rate of PTLD with regards to EBV status amongst patients receiving a CNI-based regimen. One source of data was gathered from CsA-based regimens studied in previously submitted randomized clinical trials. The other source of data used was the OPTN/UNOS registry.

Data from Prior Randomized Clinical Trials   .
Three randomized clinical trials, from three separate NDAs, that collected information on patients for at least 12-months post-transplant (including baseline EBV status) and that included a control group receiving an immunosuppressant regimen including CsA, MMF, corticosteroids and IL-2 antagonist induction were considered. Locations of these data are as follows:

Study 02-0-158
NDA 50-811: Prograf XL
Original submission: \\FDSWA150\NONECTD\N50811\N_000\2005-12-19
\\Fdswa150\nonectd\N50811\N_000\2006-02-16\crt

Study A2309
NDA 21-560: Zortress (everolimus)
Re-submission: \\Cdsesub1\evsprod\NDA021560\0010

Symphony Trial
The datasets are at \\FDSWA150\NONECTD\N50759\N_000\2007-12-12\crt\datasets\ml16979
The study report (with the protocol in the appendices) is at
\\FDSWA150\NONECTD\N50759\N_000\2007-10-15\clinstat\mmfcombotac

Kidney Transplant Registry
Registry data come from analysis files (dated 2008) provided by the USRDS upon written request. The USRDS is a national data system that collects, analyzes, and distributes information regarding end-stage renal disease in the United States. The USRDS obtains data from the CMS, UNOS, and the end-stage disease networks. Data requests can be made directly to USRDS for which the USRDS provides standardized data files and user guides. Transplant specific information is collected directly from transplant center and reported to OPTN/UNOS. Data was requested regarding all kidney transplants in the United States and multiple analysis files were received that were used to acquire the variables of interest. The data provided by the USRDS came in three separate analysis file systems:
  1) Core Standard Analysis Files: Includes files that provide basic demographic, claims and death data for patients, facility information, medical evidence, waitlist information, etc.

2) <u>Hospitalization Files:</u> Includes files on all inpatient hospital visits of patients in the USRDS database, including ICD-9 codes

3) <u>Transplant Standard Analysis Files:</u> Includes all transplant details collected by OPTN/UNOS since 1988, separated by Kidney transplant only and Kidney and Pancreas transplant patients. Data from follow-up forms included.

The variables used and their sources are detailed in Table 12 of the Appendix.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This review focuses on specific safety analyses requested in the consult from DSPTP. For a complete statistical evaluation of the efficacy results for the belatacept BLA, please refer to the review authored by Dr. Cheryl Dixon, Division of Biometrics IV, Office of Biostatistics.

3.2 Evaluation of Safety

Study Design and Endpoints

Belatacept Randomized Clinical Trials: IM103100, IM103008, IM103027

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 applicant is seeking approval for the belatacept LI regimen studied in the Phase 3 trials for kidney transplantation.

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

The LI regimen in the Phase 2 study (IM103100) was different from the regimen in Phase 3 in that there was no dose given on Day 5. The applicant added the Day 5 infusion of belatacept to the LI regimen for Phase 3 in an attempt to "ensure that target drug concentrations were achieved in the early period after transplantation and to reduce the rates of subclinical rejection." The Phase 2 LI regimen consisted of belatacept (10 mg/kg) administration on Days 1, 15, 29, 57, and 85; patients were then reallocated to a 5 mg/kg maintenance dose every 4 weeks or every 8 weeks. Therefore, patients in the Phase 2 study LI regimen received less overall belatacept exposure relative to those in the Phase 3 study LI regimen.

The MI regimen in the two Phase 3 trials consisted of belatacept (10 mg/kg) 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 dose of 5 mg/kg every 4 weeks (± 5 days). The MI regimen in the Phase 2 study (IM103100) was essentially identical except that patients were reallocated during the maintenance period to a 5 mg/kg dose every 4 weeks or every 8 weeks. Consequently, approximately half of the patients received less frequent dosing after Month 6 (every 8 weeks) in the Phase 2 study relative to those in the Phase 3 study (every 4 weeks).

Three randomized clinical trials were submitted to support claims of efficacy and safety of belatacept. The studies are described below.

Study IM103100
Study IM103100 was a Phase 2, 1-year, open-label, randomized, active-controlled, multiple-dose study of the efficacy, safety, and pharmacokinetic (PK) of 2 partially-blinded belatacept regimens vs. CsA as part of a quadruple therapy with MMF, corticosteroids, and basiliximab in patients undergoing first or subsequent renal transplants using a non-inferiority design. Patients were randomized in a 1:1:1 ratio to treatment with either belatacept regimen (MI or LI) or CsA. On Days 85 (LI regimen) and 169 (MI regimen), belatacept-treated patients were reallocated to 1 of the 2 maintenance treatment schedules based upon the frequency of dosing. These schedules provided a 5 mg/kg dose of belatacept every 4 or 8 weeks, respectively, through Day 365. Patients randomized to CsA received doses twice daily that were designed to achieve a specified range of target serum concentrations consistent with current medical practice.

The primary objective of this study was to assess the efficacy (prophylaxis of acute rejection) at 6 months of belatacept vs. CsA, when used in combination with MMF, corticosteroids, and basiliximab.

Study IM103008
Study IM103008 was a Phase 3, randomized, active-controlled, parallel-group study of the efficacy of two partially-blinded belatacept regimens vs. CsA as part of a quadruple therapy with mycophenolate mofetil (MMF), corticosteroids, and basiliximab in patients receiving a renal transplant from a living donor or a deceased donor with anticipated CIT < 24 hours. Patients were randomized 1:1:1 to treatment with either belatacept (more intensive [MI] or less intensive [LI] regimen) or CsA. Blinding between the LI and MI groups was preserved with the use of placebo infusions in the LI treatment group at Weeks 6 and 10.

Each belatacept-based regimen was compared with the CsA-based regimen on the following 3 co-primary efficacy outcome measures:
- composite endpoint of subject and graft survival by 12 months, using a non-inferiority design with a margin of 10%
- composite endpoint of 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, using a superiority test
- incidence of acute rejection (AR) by 12 months, using a non-inferiority design with a margin of 20%

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Study IM103027
Study IM103027 was a Phase 3, randomized, active-controlled, parallel-group study of the efficacy of two partially-blinded belatacept regimens vs. CsA as part of a quadruple therapy with MMF, corticosteroids, and basiliximab in patients who are recipients of a renal transplant from an 'extended criteria' donor (e.g., recipient of potentially suboptimal allografts due to donor characteristics such as age and comorbidities, CIT, or other factors). Patients were randomized 1:1:1 to treatment with either belatacept (more intensive [MI] or less intensive [LI] regimen) or CsA. Blinding between the LI and MI groups was preserved with the use of placebo infusions in the LI treatment group on Weeks 6 and 10.

The primary objective was to evaluate the effects of belatacept, relative to CsA, on:
- Composite endpoint of subject and graft survival by 12 months
- Composite endpoint of measured glomerular filtration rate [GFR] < 60 mL/min/1.73 m2 at Month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73 m2 from Month 3 to Month 12

The PTLD endpoint was measured in the three belatacept studies using the following pre-specified MedDRA preferred terms (PTs):
- Lymphoproliferative disorder
- Hematological malignancy
- Lymphoma
- CNS lymphoma
- Hepatosplenic T-cell lymphoma
- Post transplant lymphoproliferative disorder
- B-cell lymphoma

Cases were subsequently confirmed via review of case report forms or patient narratives when available.

EBV serostatus was identified based on baseline or pre-randomization serology report. Missing or unknown reports were deemed EBV unknown.

Prior Randomized Clinical Trials: Study 158, A2309 and Symphony

NOTE: Data abstraction and analyses of prior randomized clinical trials was performed by Dr. LaRee Tracy, Division of Biometrics VII. To present the totality of evidence, results from these analyses are presented in this review.

Previously submitted randomized clinical trials performed in *de novo* kidney transplantation were reviewed to identify cases of PTLD by treatment group and EBV status. RCTs that were performed only in *de novo* kidney transplant recipients, collected at least 12-month post-transplant follow-up data, included a treatment regimen consisting of a CNI, MMF, and IL-2a

induction therapy, and corticosteroids, collected pre-transplant EBV serostatus, and included detailed adverse event data (coded in MedDRA preferred) were considered.

The endpoint assessed in review of these studies was documented PTLD based on a thorough search of adverse event listing for the following MedDRA PTs:
- Lymphoproliferative disorder
- Hematological malignancy
- Lymphoma
- CNS lymphoma
- Hepatosplenic T-cell lymphoma
- EBV-associated lymphoproliferative disorder
- B-cell lymphoma

Cases were subsequently confirmed via review of case report forms or patient narratives when available.

EBV serostatus was identified based on baseline or pre-randomization serology report. Missing or unknown reports were deemed EBV unknown.

Three RCTs included in the analysis are summarized below.

Study 02-0-158 (study 158): A Phase 3, randomized, open-label, multi-center, active-controlled, 12 month study in *de novo* kidney transplant recipients.

Randomized Treatment Regimens:
Prograf/MMF (n=212); Prograf XL/MMF (n=214); Neoral/MMF (n=212)
MMF given as 1.0 g twice daily, all groups received corticosteroids and basiliximab induction

Study A2309: A Phase 3, randomized, open-label, multi-center, multi-national, 24-month study in *de novo* kidney transplant recipients.

Randomized Treatment Regimens:
Everolimus starting dose 1.5 mg/day (target trough 3-8 ng/mL) (n=277)
Everolimus starting dose 3.0 mg/day (target trough 6-12 ng/mL) (n=279)
Neoral, 1.44 g/day Myfortic (n=277)
All groups received basiliximab induction and corticosteroids
NOTE: Only 12-month data available at time of the review.

Symphony Trial: A Phase 3/4, randomized, open-label, multi-center, multi-national, active-controlled, 12-month study in *de novo* kidney transplant recipients.

Randomized Treatment Regimens:
Cyclosporine standard dose, MMF, corticosteroids (n=390)
Cyclosporine low-dose, daclizumab, MMF, corticosteroids (n=399)

Tacrolimus low-dose, daclizumab, MMF, corticosteroids (n=401)
Sirolimus low-dose, daclizumab, MMF, corticosteroids (n=399)

The two cyclosporine regimens were considered in this review.

Kidney Transplant Registries

OPTN/UNOS
The OPTN/UNOS registry is composed of data generated by every kidney transplant program located in the United States; reporting to OPTN/UNOS is mandatory and monitored. The registry includes data regarding every organ donation and transplant event in the U.S. since October 1, 1987. A required transplant recipient follow-up form is generated six months post-transplant and on the treatment anniversary for every living organ recipient. Included on this form is a section for post transplant malignancy with a specific query regarding "De Novo Lymphoproliferative disease and Lymphoma" which was used as our outcome variable for PTLD. Additionally, EBV serostatus data is collected prior to transplant.

Using data provided by the OPTN/UNOS, the incidence of PTLD with regards to EBV serostatus was evaluated. To perform this analysis, all patients 18 years of age and older who had a transplant between 2000 and 2006 and who had at least 1 year of follow-up data after transplant, with no history of prior malignancy and were received an IL-2 induction agent were considered. PTLD cases were identified using the "de novo lymphoproliferative disease" variable recorded on the transplant follow-up form at 6-months, 1, 2 and 3 years. EBV serostatus was recorded using the EBV IgG variable in the database at baseline (prior to transplant). PTLD incidence rates, per person-years, were calculated at 1, 2 and 3 years.

Results of FDA analyses of OPTN/UNOS were compared to those generated from analyses performed by the applicant and the SRTR. A table outlining the similarities and differences in the analyses performed by these three groups are outlined in Table 13 of the Appendix.

CTS
The CTS is a registry based out of the University of Heidelberg in Germany; its member centers are predominantly located in Europe. Unlike OPTN/UNOS, reporting to CTS by transplant center is voluntary. The CTS recently published an article regarding the epidemiology of non-Hodgkin's lymphoma in its registry population. While neither the applicant nor FDA obtained primary data from CTS to perform independent analyses, Dr. Gerhard Opelz – the director of CTS and the primary author of the publication – provided his result for incidence at PTLD among EBV+ kidney recipients at 2 years follow-up.

CMS Claims Data
The applicant provided estimates of PTLD incidence based on an analysis of CMS inpatient and outpatient claims data where cases were identified via specific ICD-9 codes (i.e. 200.x, 202.x and 204.x) which have not been validated to correspond to PTLD. This analysis was limited to only kidney transplant recipients who had Medicare as primary payer at the time of

transplantation and therefore represents only a subset of the overall kidney transplant population. Additionally, this analysis identified cases of PTLD only using ICD-9 codes without supporting clinical information to confirm the presence or absence of PTLD.

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Patient Disposition, Demographic and Baseline Characteristics

Please refer to the statistical review authored by Dr. Cheryl Dixon for details on patient disposition, demographic and baseline characteristics.

Statistical Methodologies

Belatacept Randomized Clinical Trials: IM103100, IM103008, IM103027

To calculate the incidence of PTLD, data were censored at 24-months post-transplant to account for the fact that not all patients had follow-up data after 24 months at the time of the BLA submission. Person-years were calculated by multiplying the number of patients by the amount of time they were exposed until they experienced the event of PTLD or until the end of the follow-up time, whichever was earlier. To calculate the 2-year incidence rate, the number of cases of PTLD were divided by the number of person-years of exposure. This value was then multiplied by 100 to give the 2-year incidence rate of PTLD per 100 person-years.

Prior Randomized Clinical Trials: Study 158, A2309 and Symphony

NOTE: Data abstraction and analyses of prior randomized clinical trials was performed by Dr. LaRee Tracy, Division of Biometric VII. To present the totality of evidence, results from these analyses are presented in this review.

Incidence of PTLD was calculated as the proportion of PTLD cases over the total number of randomized patients per treatment group and by EBV serostatus. Given the lack of detailed follow-up data in the Symphony trial, incidence per person-years could not be estimated.

OPTN/UNOS Registry

Incidence of PTLD was calculated at 1-year, 2-years and 3-years. The number of person-years contributed by a patient was calculated as the time to PTLD or the time to the cut-off point, based on which came first. Incidence of PTLD per 100 person-years was then calculated at the

number of patients experiencing a PTLD event divided by the number of person-years contributed by the kidney-recipients in the cohort multiplied by 100.

Calculation of Number of Patients Needed to Harm

To further elucidate the increased risk of PTLD in EBV positive patients taking belatacept, NNTH estimates were calculated for belatacept regimens from the pooled belatacept trials, the pooled cyclosporine groups from previously submitted RCTs, and the registry estimates calculated by FDA, the SRTR, and the applicant.

The NNTH is a simple point estimate of the number of EBV positive kidney transplant recipients that need to be treated with a belatacept-based regimen rather than a cyclosporine-based regimen in order to observe one additional case of PTLD. It is calculated by taking the inverse of the difference in incidence of PTLD among the belatacept-treated patients and the incidence of PTLD among the cyclosporine-treated patients. The difference in incidence rates used to calculate the NNTH is defined as the annualized absolute risk increase (AARI) and assumes constant risk. The formula for the AARI when using 2-year data is as follows:

$$AARI = \frac{events_{belatacept}}{\left(person-years_{belatacept}\middle/2\right)} - \frac{events_{cyclosporine}}{\left(person-years_{cyclosporine}\middle/2\right)}$$

Results and Conclusions

Evaluation of PTLD Incidence in Belatacept Trials

Table 1 details the occurrences of PTLD in all three belatacept trials. The data presented in this review focus on all cases of PTLD that occurred on or before the 24-month cutoff. This is done so that fair comparisons can be made to the 2-year data used in the registry analysis. However, it should be noted that two additional cases of PTLD occurred in the belatacept trials after this 24-month cutoff, one case occurred in and EBV positive patient on the LI regimen, and the other occurred in a EBV unknown patient on the CsA regimen. As shown in the table, across all three trials, the preponderance of PTLD cases is in the belatacept arms. In the Phase 2 trial, PTLD cases were reported on in the belatacept MI regimen; however, in both Phase 3 trials, cases were reported in both belatacept regimens and the incidences were higher compared to the CsA control.

Table 1: 24-Month Incidence of PTLD Among All Randomized Patients in the Belatacept Trials

Trial	Belatacept MI	Belatacept LI	CsA
100 (Phase 2)	3/74 (4.1)	0/71 (0)	0/73 (0)
008 (Phase 3, SCD)	3/219 (1.4)	2/226 (0.9)	1/221 (0.4)
027 (Phase 3, ECD)	2/184 (1.1)	3/175 (1.7)	0/184 (0)
Total	8/477 (1.6)	5/472 (1.0)	1/478 (0.2)

Table 2 summarizes the incidence of PTLD in the pooled belatacept trials and includes the distribution by EBV serostatus at 24-months. This table also presents the risk difference of PTLD in each belatacept arm as compared to the CsA control arm. As shown in the table, when considering EBV positive patients, there are 3 cases of PTLD in the belatacept LI regimen compared to 0 cases of PTLD in CsA regimen, risk difference 0.7%, 95% CI (-0.2, 2.2). When including the additional case of PTLD that occurred in the LI regimen after 24-months, this risk difference is statistically significant at $\alpha = 0.05$.

Table 2: All PTLD Cases in Pooled Belatacept Trials 008, 027 and 100 at 24-months

	Belatacept MI N = 477	Belatacept LI N = 472	CsA N = 478	Risk Difference 95% CI (pooled LI/MI–CsA)	Risk Difference 95% CI (MI–CsA)	Risk Difference 95% CI (LI–CsA)
PTLD in all patients	8 (1.7)	5 (1.0)	1 (0.4)	0.012 (0.001, 0.022)*	0.015 (0.003, 0.031)*	0.010 (-0.002, 0.023)
EBV positive	N = 404 2 (0.5)	N = 401 3 (1.0)	N = 399 0 (0)	0.010 (0, 0.020)*	0.005 (-0.005, 0.019)	0.007 (-0.002, 0.022)
EBV negative	N = 45 5 (11.1)	N = 51 2 (3.9)	N = 57 1 (1.8)	0.055 (-0.036, 0.134)	0.094 (0, 0.228)*	0.022 (-0.062, 0.122)
EBV unknown	N = 28 1 (3.6)	N = 20 0 (0)	N = 22 0 (0)	0.021 (-0.133, 0.109)	0.038 (-0.125, 0.184)	0

All confidence intervals reported are exact confidence intervals due to the small number of events
*p<0.05 (Fisher's Exact test)

Evaluation of PTLD Incidence in the CsA-based Regimens from Prior RCTs Reviewed by FDA

Three randomized clinical trials that collected at least 12-months post-transplant information on patients and that included a control regimen consisting of CsA, MMF, corticosteroids, and IL-2 antagonist induction treatment group were identified. In study 158, there was one case of PTLD in the CsA-based treatment group, which occurred in a patient who was EBV negative at baseline. In the Symphony trial and study A2309, there were zero cases of PTLD among all patients randomized to a CsA-based immunosuppressive regimen. These results are presented by study and EBV status in Tables 3, 4, and 5.

Table 3: PTLD by Recipient EBV Status (Study 158)

	Prograf XL/MMF N=214	Prograf/MMF N=212	Neoral/MMF N=212
EBV negative	0/40 (0)	0/42 (0)	1/35 (2.9)##
EBV positive	0/157 (0)	1/141 (0.7)#	0/158 (0)
EBV unknown	0/17 (0)	0/29 (0)	0/19 (0)

#PT 10233002; lymphoproliferative disorder (start day=23); no CRF available in submission
##PT 10232006; B-cell lymphoma and lymphoproliferative disorder (both reported on day 220); CRF available in submission

Table 4: PTLD by Recipient EBV Status (Study A2309)

	Everolimus 1.5 mg N=277	Everolimus 3.0 mg N=279	Neoral/Myfortic N=277
EBV negative	0/40 (0)	0/38 (0)	0/46 (0)
EBV positive	1/182 (0.5)*	1/185 (0.5)**	0/172 (0)
EBV unknown	0/55 (0)	0/56 (0)	0/59 (0)

*CRAD001A2309_0514_00016, B-cell lymphoma, day 251
**CRAD001A2309_0181_00007, Epstein-Barr virus associated lymphoproliferative disorder, day 375

Table 5: PTLD by Recipient EBV Status (Symphony Trial)

	CsA/MMF/CS no induction N=384	CsA/MMF/CS/Daclizumab N=407	Tac/MMF/CS/Daclizumab N=403
EBV negative	0/63 (0)	0/80 (0)	0/77 (0)
EBV positive	0/211 (0)	0/204 (0)	0/208 (0)
EBV unknown	0/110 (0)	0/123 (0)	1/118 (0.8)*

* There were no cases of PTLD reported in the datasets for tacrolimus-based group; however, in the study report there is a comment regarding a case of CNS lymphoma (EBV status not reported nor is patient ID).

Among a total of 534 EBV positive kidney transplant recipients, across studies 158, A2309 and Symphony, who received a CsA-based regimen, zero cases of PTLD were reported. Therefore, the estimated overall incidence of PTLD among EBV positive patients from these three trials previously submitted to FDA by other applicants was: 0% (0/534), 95% exact CI (0, 0.0069). Further details of this analysis are provided in Table 8.

Table 6: PTLD Incidence from Previous Randomized Clinical Trials in the Pooled CsA-based Groups*

EBV Serostatus	N	PTLD (%) [95% CI]
EBV positive	534	0 (0) [0, 0.688]
EBV negative	161	1 (0.621) [0.016, 3.412]
EBV unknown	201	0 (0) [0, 1.819]

*Regimen including CsA, MMF, CS, and IL-2 (daclizumab or basilixumab)

Estimation of PTLD Incidence among Kidney Transplant Recipients Using Registry Data

Using data provided by the OPTN/UNOS the incidence of PTLD with regards to EBV serostatus was evaluated at 1-year and 2-years for first-time kidney recipients receiving IL-2 induction and on a CNI-based regimen. Table 7 presents the incidence rates as calculated by the FDA of these data.

Table 7: Analysis of OPTN/UNOS Registry Data, First -Time Kidney Recipients on IL-2 Induction and CNI-based Regimen, N=77,203

	1-year		2-year	
	#cases/ total PYs	Incidence per 100 PYs (exact 95% CI)	#cases/ total PYs	Incidence per 100 PYs (exact 95% CI)
EBV positive	11/13245	0.08 (0.04, 0.15)	12/23640	0.05 (0.03, 0.09)
EBV negative	12/2162	0.556 (0.29,0.97)	17/3937	0.43 (0.25, 0.69)
EBV unknown	11/9328	0.12 (0.06, 0.21)	15/17102	0.09 (0.05, 0.14)

The applicant also performed an analysis of CMS claims data using ICD-9 codes to identify PTLD cases among patients on a CNI-based regimen and with no TCD induction. As the rate of particular codes was shown to vary from year to year based on an independent consultation done by the SRTR (results not presented here) and the applicant did not provide the data or statistical code used in their analysis, the applicant's CMS analysis was not replicated nor considered valid by FDA. Results from the applicant's analyses of the OPTN/UNOS registry data and the CMS claims data are presented in Table 8 for completeness.

Table 8: Applicant's Analysis of OPTN/UNOS Registry and CMS Claims Data

	OPTN/UNOS Incidence per 100 PYs (95% CI)	CMS Claims Incidence per 100 PYs (95% CI)
EBV positive	0.09 (0.06, 0.12)	0.24 (0.18, 0.33)
EBV negative	0.54 (0.39, 0.73)	0.95 (0.67, 1.36)

Additionally, in an article published in the *Transplantation* journal in October 2009 based on an analysis of CTS data conducted by Gerhard Opelz, et al. estimated the incidence of post-transplant non-Hodgkin lymphoma in kidney recipients by EBV serostatus. This analysis, based on data reported to the CTS from 1995 to 2007, found that there was an increased risk of post-transplant non-Hodgkin's lymphoma in EBV negative recipients. The relevant results from this article are present in Figure 1 below. Based on this figure among EBV positive recipients, the cumulative incidence of PTLD at 2-years post-transplant is approximately 250 per 100,000 patients, which corresponds to an incidence rate of 0.125 per 100,000 person-years at 2-years. This estimate was verified by the primary author, Dr. Opelz (personal communication).

Figure 1: Cumulative incidence of non-Hodgkin's lymphoma in kidney transplant patients by EBV serostatus (Opelz et al., 2009)*
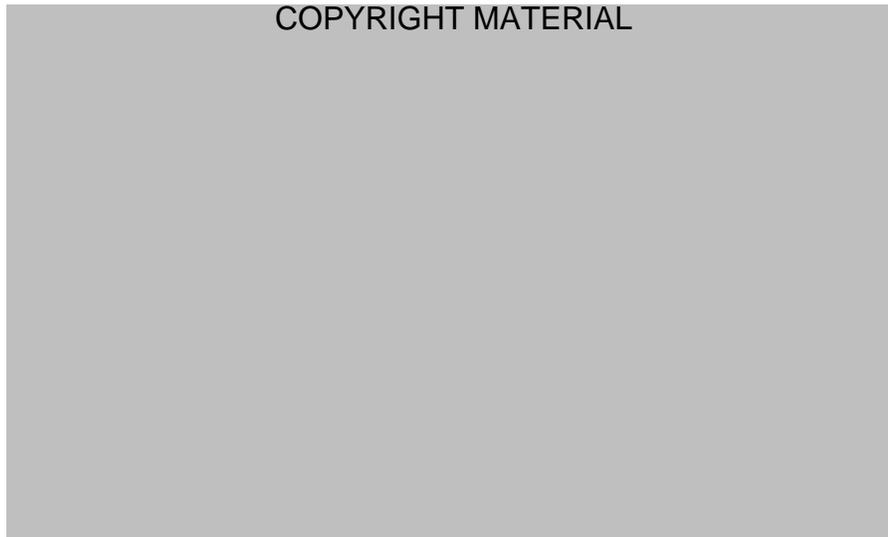
* Graph adapted from Opelz G, Daniel V, Naujakot C, Dohler B. (2009) "Epidemiology of Pretransplant EBV and CMV Serostatus in Relation to Posttransplant Non-Hodgkin Lymphoma." *Transplantation* 88(8);962-967

Table 9 presents the 2-year PTLD incidence rates, among EBV positive patients, from the pooled belatacept trials and the results from the analysis of the registry data as performed by the applicant, the FDA and the SRTR. Additionally the 2-yr incidence among EBV positive patients from the CTS analysis published by Opelz et al. is also provided. The belatacept MI and LI arms from the belatacept trials are pooled to provide a conservative estimate for which to compare against the registry estimates. The pooling of belatacept arms is more appropriate since the pooled belatacept incidence (0.35 per 100 PY) is lower than the belatacept LI incidence (0.41 per

100 PY) and given that the registry data estimates are based on data from patients receiving varying (by doses received) CNI-based regimens. As shown in the table below, the estimates from the registries are similar to each other and range from 0.05 to 0.12. We also note that when comparing the PTLD incidence rate in the pooled belatacept arms to the largest estimate of the OPTN/UNOS registry data, there is still a greater than three-fold higher rate of PTLD in the belatacept arms compared to what is found in the registry data.

Table 9: 2-year PTLD incidence rates per 100 Person-Years among EBV positive Belatacept Patients in Trials 008, 027 and 100 compared to EBV+ Patients Maintained on CNI-based Regimens Followed in the OPTN/UNOS and CTS Registries

	Belatacept (pooled LI and MI) N = 949	BMS UNOS* N = 85,651	FDA UNOS* N = 77,203	SRTR UNOS* N = 83,929	Opelz CTS^ N=16,426
2-YR Incidence	0.35	0.09	0.05	0.05	0.12
Exact 95% CI	(0.11, 0.81)	(0.06, 0.12)#	(0.03, 0.09)	(0.02, 0.09)	Unable to estimate

* OPTN/UNOS analyses consider all recipients with cyclosporine or tacrolimus maintenance regimens Incidence per 100,000 person-years
#Approximate 95% confidence interval
Unable to estimate confidence interval for Opelz estimate given the level of data available.
^Opelz et al., Transplanation, 2009

For further detailed comparisons between the three OPTN/UNOS registry analyses and the pooled belatacept trials, see Table 14 of the Appendix.

Estimation of Number Needed to Harm

Table 10 lists the calculated point estimates and 95% confidence intervals for the NNTH estimates from the pooled belatacept trials. The NNTH estimates are based on each comparison of the respective belatacept group vs. CsA. Confidence intervals were derived assuming a Poisson distribution (Sahai and Kurshid, 1996). At 24-months post-transplant, there were 5/805 and 0/399 PTLD cases in the pooled belatacept (MI and LI) and CsA control respectively resulting in an estimated NNTH of 161 (i.e. [1/(5/805-0/399)]) among EBV positive kidney transplant recipients with exact 95% confidence interval of (-341, 68). This is interpreted as ranging from as few as 68 belatacept patients need to be treated for one case of PTLD to as many as 341 CsA patients to expect an additional case of PTLD at two years of follow up.

When considering the belatacept LI arm alone in Table 12, we see that the number needed to harm estimate is 122.0. The 95% CI for this estimate is -726 to 56, meaning as few as 57 patients that receive belatacept LI instead of CsA to as few as 726 that receive CsA instead of belatacept LI will result in an additional case of PTLD.

Table 10: Estimated Number Needed to Harm in EBV positive patients (vs. CsA) based on Incidence of PTLD: Trials 008, 027 and 100

EBV positive	Belatacept (pooled LI and MI)	Belatacept LI	Belatacept MI	CsA
Incidence/PY	0.0035	0.0041	0.0028	0.0000
ARRI (vs CsA)	0.0069	0.0082	0.0056	NA
2-YR NNTH	144.7	122.0	178.8	NA
95% CI NNTH	(-532, 64)	(-726, 56)	(-432, 74)	NA

PY= person-year; AARI: annualized absolute risk increase; NNTH: 1/AARI
CsA is the reference group, therefore values for ARRI, and 2-yr NNTH for CsA are not applicable.
Confidence intervals were derived assuming a Poisson distribution (Sahai and Kurshid, 1996)

Due to the way NNTH estimates are calculated (i.e. as the inverse of the ARRI or inverse of risk difference), when the possibility of no difference between regimens cannot be ruled out, the confidence interval includes infinity. This is illustrated below in Figure 2.

Figure 2: Interpretation of Number Needed to Harm CI's That Include Infinity

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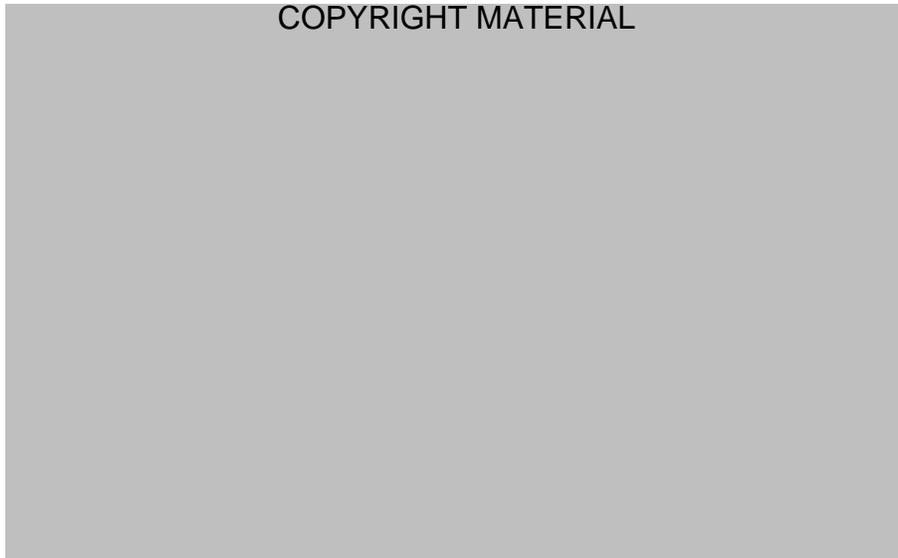
Graph adapted from method used in Altman, D "Confidence intervals for the number needed to treat." *BMJ* 1998;317:1309-1312 (7 November). Graphing method used to help interpret confidence intervals for number needed to harm/benefit when CI contains infinity.

Table 11 lists the calculated point estimates of the NNTH when comparing the PTLD incidence rate of 0.0035 per PY of the pooled belatacept LI and MI arms from belatacept trials 008, 027 and 100 to the PTLD incidence rate in the CsA-based regimens from previous randomized controlled trials and the to the PTLD incidence rate in CNI-based regimens from the registry data (as analyzed by the FDA and the SRTR). As shown, the estimates suggest that the NNTH ranges from as few as 69 (based on comparison against prior RCTs) to as many as 354 (from OPTN/UNOS estimates). As can be observed in this table, the point estimates of NNTH are

consistent across the different data sources. Additionally, the 95% CI narrows when additional data from the pooled RCTs or from the registry data are included in calculating the estimates.

Table 11: Estimated Number Needed to Harm in EBV positive Patients based on Incidence of PTLD

EBV positive	Comparison of **Belatacept** MI&LI Pooled Incidence* vs. Est. Incidence from Prior RCTs or OPTN/UNOS		
	Pooled RCT CsA Regimen**	FDA OPTN/UNOS CNI regimen	SRTR OPTN/UNOS CNI regimen
2-Year Incidence per PY	0	0.0005	0.0005
2-YR NNTH	161	170	169
95% CI NNTH	(69, 698)	(116, 319)	(111, 354)

*Pooled incidence of 0.0035 per PY in the belatacept LI and MI regimens from studies 100, 008, 027
**Pooled data from CsA-regimens from belatacept studies 008, 027 and 100 and from three prior RCTS (studies A2309, 158 and Symphony)

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The nature of this consult did not focus on special/subgroup populations outside of EBV serostatus, therefore, no analyses were performed to look at special/subgroup populations. Please refer to the efficacy review for BLA 125288 by Dr. Cheryl Dixon for other subgroup analyses.

4.1 Gender, Race and Age

N/A

4.2 Other Special/Subgroup Populations

N/A

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

PTLD is a rare occurrence, therefore, it is hard to determine the true rate of PTLD in the intended *de novo* kidney transplant population. Among EBV positive patients, there were zero cases of PTLD in CsA-regimens among the three belatacept trials compared to 2 and 4 cases in the belatacept MI and LI regimens respectively. Given these findings, additional analyses of previous randomized clinical trials and of registry data were conducted to arrive at a more accurate point estimate of the incidence of PTLD in a CsA- or CNI (CsA or tacrolimus)-based regimen for comparison against findings from the belatacept trials.

When considering previous RCTs, the pooling of data from similar CsA control regimens is useful to more accurately estimate of the incidence of PTLD among patients receiving a CsA-based regimen. However, there are some inherent inconsistencies when comparing studies from different sources. For example, there are slight differences in which MedDRA codes were used to label cases of PTLD and the patient populations and lengths of follow-up differed.

While OPTN/UNOS data are regarded as the 'gold-standard' source of information for U.S. transplant patients, the data from this registry may under-estimate the true rates of reported events, as all cases of PTLD may not be reported consistently. Additionally, while reporting to OPTN/UNOS is a requirement for participating transplant programs, the quality of reporting can vary from center to center and from program to program. Also, the patient population followed by OPTN/UNOS is not identical to that studied in the belatacept kidney trials. For instance, approximately 50% of the study patients were from outside the United States and less than 14% were of Black race. Given these limitations, findings from comparisons across these data sources should be interpreted with caution.

5.2 Conclusions and Recommendations

In the studies submitted by the applicant, to date, there have been eight (1.7%), six (1.3%) and two (0.4%) reported cases of PTLD in the belatacept MI, LI, and CsA groups respectively among the three belatacept trials. Among EBV positive patients, there were two (0.5%), four (1.0%) and zero (0%) PTLD cases in the belatacept MI, LI and CsA groups respectively. The difference between the belatacept LI and CsA is 1%, exact 95% CI (0, 2.5). Among EBV negative patients, there were five (11.1%), two (3.9%), and one (1.8%) PTLD cases in the belatacept MI, LI and CsA groups respectively. The difference between the belatacept LI and CsA is 2.1%, exact 95% CI (-5.9, 11.9). *Note: At the time of the submission, complete follow-up data were available for all patients out to 24-months post-transplant and additional follow-up past 24-months in a subset of randomized patients. Of the PTLD cases reported above, 1 case in the belatacept LI (EBV positive serostatus) and 1 in the CsA (EBV status unknown) regimens were reported after 24-months post-transplant.*

When considering information from three previously submitted randomized clinical trials (RCTs) that contained an CsA-based immunosuppressant regimen similar to the CsA regimen used in the belatacept trials, there were zero cases of PTLD reported (0%) among a total of 534 EBV positive kidney transplant recipients who received a CsA-based regimen. Among 158 EBV negative kidney transplant recipients, there was 1 (0.6%) case of reported PTLD.

The analysis of OPTN/UNOS registry data found the 2-year incidence of PTLD in EBV positive patients on a calcineurin-inhibitor (CNI)-based regimen of either cyclosporine or tacrolimus, to be 0.051 per 100 PY and 0.483 per 100 PY in EBV negative patients. This incidence rate can be compared to the estimated 24-month incidence rates of PTLD of 0.346 per 100 PY in EBV positive and 4.4 per 100 PY in EBV negative patients taking belatacept (LI and MI pooled). The 24-month incidence rates among EBV positive and negative patients in the belatacept LI alone regimen were 0.41 per 100 and 2.43 per 100 PY respectively.

NNTH estimates were derived to further elucidate the increased risk of PTLD of belatacept compared to CsA. Given an incidence per PY of 0.0035 of the pooled data from the belatacept MI and LI regimens and of 0.0 in the CsA regimen from studies 008, 027 and 100, the NNTH is estimated as 145 (95% CI: -532, 64) patients. This suggests that for every 145 EBV positive patients treated with a belatacept-based regimen instead of a CsA-based regimen for two years, one would expect at least one additional case of PTLD. The range for this NNTH suggests that as few as 63 belatacept patients to as many as 532 CsA patients need to be treated for two years to expect at least one case of PTLD. To improve the precision of this estimate, the incidence is compared to the data from control arms from previous RCTs; we find the estimate of the NNTH to be 161 (95% CI: 69, 698) patients. When comparing the data from the belatacept trials to the incidence of PTLD found using the registry data, the NNTH estimate is 170 (95% CI: 116, 319).

When considering all the evidence that has been analyzed from the CsA control regimens in the belatacept trials, other similarly-designed randomized clinical trials that included a CsA-based immunosuppressant regimen, and kidney transplant registry data, it is apparent that there is an increased risk of PTLD in belatacept treated patients and that this increase was found in both EBV negative and positive subgroups. The analyses conducted found that while the incidence of PTLD was lower among EBV positive patients compared to EBV negative patients, the incidence in the belatacept regimens was higher compared to the control regimens among EBV positive patients.

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APPENDIX

Table 12: Source data for FDA analysis of OPTN/UNOS database

Source Data	Database Name	Variable of Interest	Reason	Variable Name
Transplant Files	txunos_ki	Organ Type	Restrict to kidney-only tx	don_org
		Date of Transplant	Calculate age at transplant and restrict dates	tdate
		Date of Birth	Calculate age at transplant	
		EBV variables	Determine EBV status	ebv, epstigg, epstigm, ebv_clinical, epstdna
		History of Malignancy	Determine if recipient had history of malignancy prior to tx	malign
		Multiple Organ Recipient	Restrict to single kidney recipients only	pitx
	txfuunos_ki	PTLD	Determine if subject had PTLD	denovlym
		Follow-up visit	Attain time-points	folcd
	txirunos	Induction and Maintenance Drugs	Restrict to appropriate regimens (Thymoglobulin, Atgam, Zenapax and Simulect)	rx_cd
		Induction and Maintenance	Determine whether drug was used for induction or maintenance	rx_ind, rx_maint
Core Files	tx	Order of Transplant	Only want patients receiving first transplant	inccount

Table 13: Comparison of Methods used in Analysis of the OPTN/UNOS Transplant Registry Data

	FDA OPTN/UNOS	BMS OPTN/UNOS	SRTR OPTN/UNOS
Inclusion/Exclusion			
Age	>=18	>=18	18-80
Time frame	2000-2006	2000-2006	3/01-7/07
Required at least 1-yr of follow-up	Yes	Not specified	Yes
Required Medicare as primary payer	No	No*	No
Excluded pts with prior documented history of malignancy	Yes	Yes	No
Included only 1st time recipients	Yes	Yes	No
Induction Regimen	IL-2 (Zenapax, Simulect)	No TCD Induction	IL-2 (Zenapax, Simulect)
PTLD Case Identification			
Transplant recipient follow-up form	Yes	Yes	Yes
Malignancy form	No	Yes	No

*Methods section of BMS states that only Medicare patients were included, however BMS has stated in their reply dated January 13, 2010, that this analysis was not restricted to Medicare patients as claims data was not used

Table 14: Comparison of PTLD Rates based on EBV status

| | Belatacept (pooled MI and LI) N = 949 | | BMS UNOS# N = 85,651 | | FDA UNOS** N = 77,203 | | SRTR UNOS** N = 83,929 | |
			No TCD Induction		IL-2 Induction n = 24,775*		IL-2 Induction n = 18,409*	
	# cases/total PYs	Incidence per 100 PYs (exact 95% CI)	# cases/total PYs	Incidence per 100 PYs (95% CI)	# cases/total PYs	Incidence per 100 PYs (exact 95% CI)	# cases/total PYs	Incidence per 100 PYs
EBV Positive								
1-yr	Not Available	Not Available	Not Available	Not Available	11/13245	0.083 (0.041, 0.149)	10/10396	0.096
1.5 yr	Not Available	Not Available	34/33792.9	0.10 (0.07, 0.14)	Not Available	Not Available	Not Available	Not Available
2-yr	5/1446.9	0.346 (0.112, 0.807)	Not Available	0.09 (0.06, 0.12)	12/23640	0.051 (0.026, 0.089)	10/20157	0.050
3-yr	Not Available	Not Available	55/57805.9	0.10 (0.07, 0.12)	15/31733	0.047 (0.026, 0.078)	18/28485	0.063
EBV Negative								
1-yr	Not Available	Not Available	Not Available	Not Available	12/2162	0.555 (0.287,0.970)	11/1519.5	0.724
1.5 yr	Not Available	Not Available	72/7187.6	1.00 (0.80, 1.26)	Not Available	Not Available	Not Available	Not Available
2-yr	7/160.0	4.374 (1.759, 9.015)	Not Available	0.54 (0.39, 0.73)	17/3937	0.432 (0.252,.691)	18/2938.5	0.613
3-yr	Not Available	Not Available	84/12338.3	0.66 (0.55, 0.84)	19/5308	0.358 (0.216, .559)	21/4109.5	0.511
EBV Unknown								
1-yr	Not Available	Not Available	Not Available	Not Available	11/9328.5	0.118 (0.059, 0.211)	7/6486.5	0.108
1.5 yr	Not Available	Not Available	59/30487.5	0.19 (0.15, 0.25)	Not Available	Not Available	Not Available	Not Available
2-yr	1/86.1	1.161 (0.000, 6.4715)	Not Available	Not Available	15/17102.5	0.088 (0.049, .145)	7/12542.5	0.056
3-yr	Not Available	Not Available	80/52908.6	0.15 (0.12, 0.19)	21/23224.5	0.090 (0.056,0.138)	10/17725.5	0.056

#Results obtained from Appendix B of the BMS IM103028 Addendum 3 report and BMS "Additional Responses to FDA Comments: January 25, 2010"
*The "n" listed under the indicated induction regimen refers to the number of patients in the subset.
** OPTN/UNOS analyses consider all recipients with Cyclosporine or Tacrolimus maintenance regimen

SIGNATURES

Primary Statistical Reviewer:
Date: March 25, 2010

Anita Abraham, MS, DrPH
Mathematical Statistician, Division of Biometrics VII

Statistical Team Leader:

LaRee Tracy, MS, PhD
Team Leader (Act), Division of Biometrics VII

Statistical Staff Director:
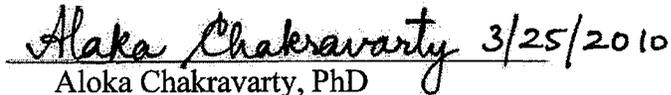
Aloka Chakravarty, PhD   3/25/2010
Director (Act), Division of Biometrics VII

cc:
HFD-590/June Germain, Project Manager
HFD-590/Patrick Archdeacon, Medical Officer
HFD-590/Joette Meyer, Medical Team Leader
HFD-700/Anita Abraham, Primary Statistical Reviewer
HFD-700/LaRee Tracy, Statistical Team Leader
HFD-700/Karen Higgins, Statistical Team Leader
HFD-700/Aloka Chakravarty, Statistical Staff Director

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125,288
Product Name:	Belatacept for Injection
Indication(s):	Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants
Applicant:	Bristol-Myers Squibb Company
Date(s):	Stamp date: July 1, 2009
	PDUFA date: May 1, 2010
	Review date: March 23, 2010
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Cheryl Dixon, Ph.D.
Concurring Reviewers:	Karen Higgins, Sc.D., Team Leader
	Daphne Lin, Deputy Division Director
Medical Division:	Division of Special Pathogen and Transplant Products
Clinical Team:	Patrick Archdeacon, M.D., Medical Officer
	Joette Meyer, Pharm.D., Team Leader
Project Manager:	June Germain

Keywords: clinical studies, NDA review, renal transplant, choice of endpoints, non-inferiority

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In two Phase 3 trials (one of living or standard criteria deceased donors and one of extended criteria donors), the belatacept more intensive (MI) and belatacept less intensive (LI) regimens were both shown to be non-inferior to cyclosporine (CsA), based on a non-inferiority margin of 20%, with respect to the incidence of biopsy proven acute rejection, graft loss, death, or lost to follow-up at 12 months. The margin of 20% was justified from a data driven standpoint. If a smaller margin is deemed more appropriate from a clinical standpoint, then the belatacept LI regimen would be non-inferior to CsA in both Phase 3 trials based on a 15% margin. This endpoint provides the proof of efficacy for belatacept to support the indication of prophylaxis of organ rejection in adult patients receiving a kidney transplant. Even though belatacept was shown to be non-inferior to CsA with respect to this endpoint, it is important to note that there were numerically more acute rejections seen in the belatacept groups than the CsA group in both trials. Additional evidence of benefit of belatacept is shown based on acceptable and similar rates of patient and graft survival at 12 months, higher glomerular filtration rate (GFR) through 24 months, improved blood pressure at 12 months, improved non-HDL cholesterol and triglycerides at 12 months, and lower incidence of new onset diabetes after transplantation (NODAT) at 12 months. However, the rate of post transplant lymphoproliferative disorder (PTLD), a serious adverse event, was higher in the belatacept groups (more cases of PTLD occurred in the belatacept MI group) compared to the CsA group and was mainly driven by the event of CNS PTLD. Given the increased risk of PTLD seen for belatacept treated patients as well as the known increased risk for EBV-negative patients in general, use of belatacept is being considered only for EBV-positive patients. Although it appears that the risk of PTLD and CNS PTLD in EBV-positive patients remains higher in the belatacept groups compared to the CsA group, a more favorable risk benefit profile is seen with this subgroup.

1.2 Brief Overview of Clinical Studies

The development program of belatacept consisted of 2 complementary Phase 3 trials in de novo renal transplantation populations. IM103008 enrolled recipients of organs from living donors and deceased standard criteria donors. IM103027 enrolled recipients of organs from deceased donors with extended criteria. These extended criteria were donor age $\geq$ 60 years; or donor age 50 to 59 and $\geq$ 2 of the following: cerebrovascular accident, hypertension, and serum creatinine > 1.5 mg/dL; or anticipated cold ischemia time $\geq$ 24 hours; or donor with cardiac death (non-heart beating donor). Both trials were 3 year multi-center, multi-national, randomized, active controlled trials. Patients were randomized to receive treatment with either belatacept MI, belatacept LI, or CsA. All patients received induction with basiliximab and maintenance therapy with mycophenolate mofetil, and corticosteroids. The trials were open label with respect to belatacept and CsA but the two belatacept regimens were blinded through 12 months.

Even though the duration of the trials was 36 months, 12 months was the primary time point for the evaluation of efficacy. Co-primary endpoints specified in the protocols were the composite endpoint of patient and graft survival by 12 months, the composite renal impairment endpoint defined as measured GFR < 60 mL/min/1.73 m^2 at Month 12 or a decrease in measured GFR $\geq$ 10 mL/min/1.73 m^2 from Month 3 to Month 12, and the incidence of acute rejection by 12 months (IM103008 only, considered a secondary endpoint in IM103027). Additional endpoints assessed included measured and calculated GFR, and established cardiovascular risk factors including hypertension, dyslipidemia, and NODAT.

1.3 Statistical Issues and Findings

The co-primary endpoints stated above were agreed to in principle during protocol design. However, further clinical consideration has called into question the ability of these endpoints to prove the efficacy of belatacept. First, the assessment of patient and graft survival was to be made based on showing that belatacept was non-inferior to CsA. Due to relatively high rates of patient and graft survival seen at 12 months and the choice of control regimen, an estimate of the size of the effect of CsA on patient and graft survival is not easily estimated and therefore a non-inferiority margin can not be defined for this endpoint. Second, interpretation of differences with respect to renal function (GFR in general and the definition of the composite renal function endpoint) are confounded due to differential effects of the treatments on renal hemodynamics. CsA has a known toxicity profile that causes a decrease in GFR whereas belatacept does not have this hemodynamic effect. Thus, comparison of a treatment with a known toxicity to a treatment without this known toxicity does not necessarily prove the efficacy of the treatment without the known toxicity. Additionally, one component of the composite renal impairment endpoint was measured GFR < 60 mL/min/1.73 m^2 at Month 12 and recipients of extended criteria donors rarely achieve a GFR > 60 mL/min. Therefore, given the limitations of the composite renal impairment endpoint in the setting of incomparable renal hemodynamics across treatment groups and in the setting of a trial of extended criteria donors, it is difficult to understand the significance or relevance of this endpoint as an endpoint to prove efficacy of belatacept. Acute rejection has been the traditional endpoint used by the Medical Division for assessing the efficacy of other products for the indication of prophylaxis of rejection in kidney transplant recipients. However, the definition of acute rejection used by the Medical Division is slightly different from that used by the Applicant. The Applicant defined acute rejection as central biopsy proven rejection that was either clinically suspected by protocol defined reasons or clinically suspected by other reasons and treated. The traditional assessment of acute rejection, however, has been based on any biopsy proven acute rejection, regardless of the reason for performing the biopsy. Additionally, patients who experience graft loss, death, or are lost to follow-up are not considered as having a positive outcome (i.e. no rejection). The Medical Division's assessment of acute rejection has been referred to as the efficacy failure endpoint which is the composite of biopsy proven acute rejection, graft loss, death, or lost to follow-up. As discussed in Section 5.1, a non-inferiority margin of 20% was able to be justified from a data driven standpoint for an assessment of acute rejection to allow for the demonstration of efficacy of belatacept. Therefore, given the limitation in the ability to justify a non-inferiority margin for patient and graft survival at 12 months and the limitations regarding the use of the composite renal impairment endpoint, the Medical Division is using acute rejection as traditionally assessed

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(i.e., efficacy failure defined as biopsy proven acute rejection, graft loss, death, or lost to follow-up) as the primary proof of efficacy of belatacept for both of the Phase 3 trials.

Both belatacept groups were non-inferior to CsA for the endpoint of biopsy proven acute rejection, graft loss, death, or lost to follow-up in both trials, based on a 20% non-inferiority margin. The rates of biopsy proven acute rejection, graft loss, death, or lost to follow-up were 27.4%, 21.7%, and 16.7% in the belatacept MI, belatacept LI, and CsA groups respectively in IM103008; 33.7%, 29.1%, and 28.3%, respectively in IM103027. The upper bounds of the 97.3% confidence intervals about the difference (belatacept- CsA) were for IM103008: 19.8% for the belatacept MI comparison and 13.7% for the belatacept LI comparison and for IM103027: 16.6% for the belatacept MI comparison and 11.9% for the belatacept LI comparison.

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

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

Hypertension, dyslipidemias, and NODAT are all class effects of calcineurin inhibitors, including CsA. Endpoints related to these risk factors were prospectively studied. Mean systolic and diastolic blood pressure were significantly lower at Month 12 for patients in both belatacept groups compared to the CsA group in both Phase 3 trials. Mean non-HDL cholesterol and triglyceride levels at Month 12 were significantly lower in both belatacept groups compared to the CsA group in both Phase 3 trials. Across all treatment groups in the Phase 3 trials, relatively few patients developed NODAT by Month 12. A trend towards fewer cases of NODAT for belatacept treated patients was apparent in the trials combined (4.8% belatacept MI, 4.6% belatacept LI, and 9.6% CsA).

An imbalance in the rates of PTLD was detected between the belatacept and CsA groups (1.7% belatacept MI, 1.3% belatacept LI, and 0.4% CsA). Most of these cases presented with CNS involvement. The imbalance was greatest among EBV-negative patients but was also detected among EBV-positive patients.

2. INTRODUCTION

2.1 Overview

This is a BLA submission for belatacept. Belatacept is a new class of therapeutic agents in transplantation immunosuppression. It is an intravenously administered biologic that targets key co-stimulatory signals required for full T-cell activation. The indication being sought by the applicant is prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. The proposed dosing regimen is the belatacept LI (less intensive) regimen which consists of 10 mg/kg administration on Day 1, 5, 14, and 28 and then every 4 weeks through 3 months after transplantation. Starting Month 4 after transplantation, the maintenance dose is 5 mg/kg every 4 weeks.

The development program for belatacept consisted of one Phase 2 and two Phase 3 trials. Primary support for the efficacy of belatacept is based on the two Phase 3 trials: IM103008 and IM103027. Both of the Phase 3 trials were 3 year multi-center, multi-national, randomized, active controlled trials in de novo kidney transplant patients. IM103008 enrolled recipients of organs from living donors or standard criteria deceased donors. IM103027 enrolled recipients of organs from extended criteria donors. Extended criteria donor kidneys included donor age ≥ 60 years; donor age 50 to 59 and ≥ 2 of the following: cerebrovascular accident, hypertension, and serum creatinine > 1.5 mg/dL; anticipated cold ischemia time ≥ 24 hours; or donor with cardiac death (non-heart beating donor). The belatacept regimens studied in the Phase 2 trial, IM103100, were slightly different from those used in the Phase 3 trials. Therefore, the efficacy results of IM103100 will not be discussed in this review.

2.2 Data Sources

The data analyzed in this review comes from the Phase 3 trials submitted as the pivotal evidence to support the efficacy of belatacept for the prophylaxis of organ rejection. The IM103008 and IM103027 12 month study reports and datasets provided in the electronic submission were reviewed. These can be found in the electronic submission located at:
\\cbsap58\m\eCTD_Submissions\STN125288\0000. Additional analysis datasets were provided in the electronic submission located at \\cbsap58\m\eCTD_Submissions\STN125288\0006. Datasets for the 120-day safety update were provided in the electronic submission at \\cbsap58\m\eCTD_Submissions\STN125288\0013.

Most of the 12 month efficacy analyses are based on the analysis datasets for the BLA database lock, referred to as the interim-lt datasets in the electronic submission. Analyses of calculated GFR through 24 months are based on the analysis datasets for the 120-day safety update, referred to as the su-120-day datasets in the electronic submission.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 IM103008
3.1.1.1 Study Design

IM103008 was a Phase 3, randomized, active controlled, parallel group trial of two belatacept regimens vs. cyclosporine (CsA) in patients receiving a renal transplant from a living donor or a deceased donor with anticipated cold ischemia time < 24 hours. All patients received induction with basiliximab and maintenance therapy with mycophenolate mofetil (MMF) and corticosteroids. The study was conducted at 104 sites worldwide including 34 in the United States, 10 in India, 7 in France, 6 each in Argentina, Brazil, Canada, and Mexico, 4 each in Australia and Germany, 3 each in Italy, South Africa, and Spain, 2 each in Belgium, Switzerland, and Poland, and 1 each in Austria, Czech Republic, Hungary, Israel, Sweden and Turkey. Patients were randomized in a 1:1:1 ratio to receive treatment with either belatacept more intensive (MI), belatacept less intensive (LI), or CsA. The trial was open label with respect to belatacept and CsA but the two belatacept regimens were blinded through 12 months.

The duration of the study is 36 months with a subsequent 8-week follow-up period for safety evaluations. Milestone visits are conducted at 3 months, 12 months, 24 months, and 36 months post-randomization for all patients even those who discontinue study medication during their participation in the trial. Protocol defined allograft biopsies were required at baseline and Month 12. Otherwise, biopsies were only required for suspected acute rejection. Biopsies were read by local pathologists to guide treatment and also by a blinded central pathologist. For purposes of study analysis, the assessment of the central pathologist was primary. Measured glomerular filtration rate (GFR) samples were required at Months 3, 12, and 24. Serum creatinine (to provide calculated GFR) was to be collected at all study visits from Day 2 to Month 36.

The primary objectives of the trial are to evaluate the effects of belatacept on patient and graft survival, renal function, and acute rejection at 12 months as compared to CsA. There were 3 co-primary endpoints specified in the protocol: the composite endpoint of patient and graft survival by 12 months, the composite renal impairment endpoint defined as measured GFR < 60 mL/min/1.73 m^2 at Month 12 or a decrease in measured GFR $\geq$ 10 mL/min/1.73 m^2 from Month 3 to Month 12, and the incidence of acute rejection by 12 months. Key secondary objectives were to evaluate the effects of belatacept, relative to CsA, on: measured GFR at Month 12 and biopsy-proven chronic allograft nephropathy (CAN) at 12 months. Other secondary objectives were to assess the effects of belatacept, relative to CsA, on: the composite endpoint of death, graft loss, and acute rejection by month 12, 24, and 36; patient and graft survival by 24 and 36 months; measured GFR at 3 and 24 months, and change from 3 months to 12 months and 24 months; calculated GFR at 6, 12, 24, and 36 months; measures of acute rejection by 6, 12, 24, and 36 months including incidence and severity of acute rejection; post-transplant diabetes mellitus by 12, 24, and 36 months; measures of hypertension at 12, 24, and 36 months including systolic and diastolic blood pressure; and measures of dyslipidemia at 12, 24, and 36 months including serum total, LDL, and HDL cholesterol and triglycerides.

Reviewer's Comment: Although the duration of the trial was 36 months, 12 months was the primary time point for assessing efficacy. Therefore, the trial was still ongoing at the time of BLA submission. During the review, the 24 month study reports were submitted with the 120-day safety update. This review will focus on the analyses at 12 months with the exception of analyses of calculated GFR, PTLD, and patient and graft survival which will also look at 24 month data.

The primary analysis population for all efficacy endpoints was the intent-to-treat (ITT) population. The ITT population included all randomized and transplanted subjects. The per-protocol population included all randomized and transplanted subjects who did not have a relevant protocol deviation. The as treated population included all randomized and transplanted subjects who received at least 1 dose of study medication. The per-protocol and as treated populations were used for secondary summaries of the data.

Reviewer's Comment: This review will focus on analyses of the ITT population.

A sequential testing procedure was employed for testing the 3 co-primary endpoints and key secondary hypotheses, as specified in the protocol, according to the following hierarchy:
- Assessment of non-inferiority for the difference between belatacept and CsA in patient and graft survival at 12 months,
- Test of the difference between belatacept and CsA on the composite renal impairment endpoint at 12 months,
- Assessment of non-inferiority for the difference between belatacept and CsA in acute rejection experienced by 12 months,
- Test of difference between belatacept and CsA on the incidence of CAN by 12 months.

The test of the other key secondary endpoint of measured GFR at Month 12 was performed to support the co-primary renal impairment endpoint and was therefore not part of the sequential testing procedure. Overall, it was estimated that 220 patients per treatment group would provide 93% power to detect 1 belatacept regimen that met all co-primary endpoints with overall Type I error controlled at the 0.05 significance level. The nominal type I error was set at 0.027 for each belatacept treatment group versus CsA using Dunnett's adjustment for multiple treatment comparisons. A sample size of 220 patients per treatment group provides 95% power to ascertain that the lower bound of the 97.3% 2-sided confidence interval for the difference between each belatacept regimen and CsA in patient and graft survival does not exceed -10%, assuming a patient and graft survival rate at Month 12 of 92%. For the renal function endpoint, the sample size of 220 patients per group provided 99% power to detect a decrease of 25% in the proportion of patients meeting the composite renal impairment endpoint, assuming 75% of CsA subjects met the composite endpoint and 25% drop-outs per treatment group. For the acute rejection endpoint, 220 patients per group provided 99% power to ascertain that the upper bound of the 97.3% 2-sided confidence intervals for the difference would not exceed 20% assuming the rate of acute rejection by 12 months was 15%.

Reviewer's Comment: See Section 5.1 for discussion of the non-inferiority margins for acute rejection (20% justified from a data driven standpoint) and patient and graft survival (unable to justify a margin from a data driven standpoint). Please also refer to Section 5.1 regarding the

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choice of endpoints for assessing and proving the efficacy of belatacept. Due to issues discussed in Section 5.1, proof of efficacy of belatacept will be based on the endpoint of the incidence of biopsy proven acute rejection, graft loss, death, or loss to follow-up at Month 12 (a variation of the Applicant's defined acute rejection endpoint).

The endpoint of patient and graft survival was summarized within each treatment group using point estimates of the proportion of patients surviving with a functioning graft. Two-sided 97.3% confidence intervals were calculated for the difference between each belatacept regimen and CsA. If the lower bound of the confidence interval (belatacept –CsA) was > -10% then the corresponding belatacept regimen was considered to be non-inferior to CsA. In the Applicant's analyses, any patient with unknown status at Month 12 was imputed to have had a graft loss or died if one of various unfavorable events were met during 12 months post-transplantation. In the analyses presented in this review, all patients with unknown status at Month 12 will be imputed as having a graft loss or died.

A continuity corrected Chi-square test at a significance level of 0.027 was performed on the composite renal impairment endpoint. Measured GFR at 12 months was analyzed using analysis of variance. Missing observations of Month 3 or Month 12 measured GFR were imputed based on a linear extrapolation and quartile algorithm. Calculated GFR was summarized descriptively at Months 1 and Months 3 to 36 in increments of 3 months. For all analyses of calculated GFR, if a subject died or had a graft loss then a value of 0 was imputed for a missing calculated GFR. For an analysis of calculated GFR at Month 12 by acute rejection status, a last observation carried forward was used to impute additional missing observations. To assess the trend in renal function, a linear mixed model was used to analyze the calculated GFR values with terms for treatment and month.

Acute rejection, defined as a clinico-pathological event requiring clinical evidence and biopsy confirmation by central pathologist, by 12 months was summarized within each treatment group using point estimates of the proportion of patients who experienced acute rejection by 12 months. Two-sided 97.3% confidence intervals were calculated for the difference between each belatacept regimen and CsA. If the upper bound of the confidence interval (belatacept –CsA) was < 20% then the corresponding belatacept regimen was considered to be non-inferior to CsA.

Reviewer's Comment: *The endpoint of biopsy proven acute rejection, graft loss, death, or lost to follow-up was analyzed in a similar fashion as acute rejection.*

3.1.1.2   Patient Demographics

Of the 686 patients randomized into the study, 666 were transplanted (belatacept MI 219, belatacept LI 226, and CsA 221) and make up the ITT population. Of the 666 randomized and transplanted patients, 660 were treated (6 CsA patients were not treated). All belatacept patients received treatment because treatment with belatacept was required at the time of transplant whereas treatment with CsA could be delayed up to 7 days due to post-operative impairment of allograft function. The proportion of patients who discontinued treatment during the first 12 months was comparable across treatment groups. The primary reason for discontinuation from

treatment, however, was different. In the belatacept treatment groups, the most common reason for discontinuation of treatment was due to lack of efficacy. For the CsA treatment group, adverse event was the most common reason for discontinuation of treatment.

Table 1
Patient Randomization and Treatment Discontinuation within 12 months
IM103008

	Belatacept MI	Belatacept LI	CsA
Randomized and transplanted (ITT)	219	226	221
Randomized, transplanted and treated	219	226	215
Number discontinuing treatment	46 (21.0)	45 (19.9)	42 (19.5)
Adverse event	9 (4.1)	12 (5.3)	20 (9.3)
Lack of efficacy	26 (11.9)	24 (10.6)	10 (4.7)

Table 2 summarizes the demographic and baseline characteristics of the ITT population. There were no significant differences across treatment groups. Overall, 69% of the study population was male and 61% was white. The mean age of the patients was 43 years. Approximately 42% of the patients were enrolled at sites in North America. Fifty-eight percent of donors were living and 42% were deceased. EBV-serostatus of the recipient was positive in over 85% of the patient population.

Table 2
Demographic and Baseline Characteristics (ITT)
IM103008

	Treatment Group		
	Belatacept MI	Belatacept LI	CsA
# Patients	219	226	221
Gender			
Male	151 (68.9)	146 (64.6)	165 (74.7)
Female	68 (31.1)	80 (35.4)	56 (25.3)
Age mean (SD)	43.6 (14.6)	42.6 (13.4)	43.5 (14.3)
Min, max	18, 77	18, 71	18, 75
Race			
White	132 (60.3)	133 (58.8)	139 (62.9)
Black	15 (6.8)	23 (10.2)	17 (7.7)
Asian	27 (12.3)	29 (12.8)	27 (12.2)
Other	45 (20.6)	41 (18.2)	38 (17.2)
Region			
North America	95 (43.4)	92 (40.7)	94 (42.5)
South America	35 (16.0)	36 (15.9)	33 (14.9)
Europe	55 (25.1)	64 (28.3)	58 (26.2)
Rest of World (Asia/Pacific)	32 (14.6)	33 (14.6)	34 (15.4)
Africa	2 (0.9)	1 (0.4)	2 (0.9)
Type of Transplant			
Living-related	91 (41.6)	99 (43.8)	91 (41.2)
Living- unrelated	41 (18.7)	30 (13.3)	33 (14.9)
Cadaveric	87 (39.7)	97 (42.9)	97 (43.9)
Recipient EBV serology			
Positive	194 (88.6)	199 (88.1)	184 (83.3)
Negative	25 (11.4)	27 (11.9)	37 (16.7)

3.1.1.3 Efficacy Results

Patient and graft survival at 12 months is presented in Table 3. The rates of patient and graft survival at 12 months were 95%, 96.5%, and 93.2% in the belatacept MI, belatacept LI, and CsA treatment groups respectively. The lower bound of the 97.3% confidence interval about the difference between belatacept regimen and CsA was greater than -5% for both belatacept regimens.

Table 3
Patient and Graft Survival at 12 months
IM103008

	Belatacept MI	Belatacept LI	CsA
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)	

Reviewer's Comment: This analysis, as compared to that presented by the Applicant, includes one fewer belatacept MI patient as surviving with a functioning graft since all patients with unknown status at 12 months were imputed as having a graft loss or died and not just those who met various other unfavorable events during 12 month post-transplantation.

The confidence intervals reported in this review are slightly different than those reported in the Applicant's study report due to slightly different computation methods. The conclusions drawn, however, are the same.

The proportion of patients meeting the composite renal impairment endpoint as well as the reasons for meeting the composite endpoint is presented in Table 4. The difference in the proportion of patients meeting the composite endpoint was statistically significantly fewer for both belatacept vs. CsA comparisons. The majority of the patients who met the composite endpoint met the endpoint due to their measured GFR being less than 60 mL/min/1.73 m^2 at Month 12. It should be noted that the analyses presented here are slightly different from that presented by the Applicant in that patients with missing measured GFR for reasons other than death or graft loss are also included as failures of the endpoint whereas they were excluded from the Applicant's analysis. The conclusions drawn, however, are not different.

Table 4
Composite Renal Function at 12 months
IM103008

	Belatacept MI (n=219)	Belatacept LI (n=226)	CsA (n=221)
Met composite endpoint	125 (57.1)	128 (56.6)	174 (78.7)
Reason for meeting composite:			
M12 < 60 and Decrease ≥ 10 from M3 to 12	33	34	52
M12 < 60 only	58	58	92
Decrease ≥ 10 from M3 to M12 only	15	16	8
Imputed due to GL or death	9	8	14
Missing	10	12	8
p-value	<0.0001	<0.0001	

Reviewer's Comment: *Refer to Section 5.1 for a discussion regarding the difficulty in the interpretation of this endpoint as proof of efficacy of belatacept.*

Table 5 summarizes the incidence of acute rejection at 12 months, as defined by the Applicant. Non-inferiority of the belatacept LI regimen compared to CsA based on a 20% non-inferiority margin was shown, as demonstrated by an upper bound of the 97.3% confidence interval less than 20%. However, it should be noted that there were significantly more acute rejections in the belatacept treated patients than in the CsA treated patients. For both of the belatacept comparisons to CsA, the lower bound of the 97.3% confidence interval was above zero, indicating a significant increase in the number of acute rejections compared to CsA. Additionally, the severity of the acute rejections was greater in the belatacept groups.

Table 5
Acute Rejection at 12 months (as defined by Applicant)
IM103008

	Belatacept MI	Belatacept LI	CsA
Acute Rejection	49/219 (22.4)	39/226 (17.3)	16/221 (7.2)
Mild IA	7	4	3
Mild IB	3	8	5
Moderate IIA	17	16	6
Moderate IIB	20	10	2
Severe III	2	1	0
Difference from CsA (97.3% CI)	15.2 (7.4, **23.0**)	10.1 (2.9, **17.3**)	

Most of the episodes of acute rejection occurred by 6 months. Only 1 belatacept LI and 4 CsA patients experienced an episode of acute rejection between 6 and 12 months. Few patients experienced more than 1 episode of acute rejection during the first 12 months. Six patients in the belatacept MI group, 3 patients in the belatacept LI group, and 2 patients in the CsA group experienced 2 episodes of acute rejection in the first 12 months. An additional belatacept LI patient experienced 3 episodes of acute rejection in the first 12 months.

Traditionally, the Medical Division's assessment of acute rejection is based on a combined endpoint of biopsy proven acute rejection (BPAR), graft loss, death, or loss to follow-up. This

endpoint is only slightly different from that of the Applicant in that BPAR includes all central biopsy confirmed rejections not just those accompanied by clinical signs and symptoms. Inclusion of graft loss, death, or loss to follow-up is a way to handle patients who have missing information with respect to the endpoint of acute rejection at 12 months. The results of this assessment are presented in Table 6. Using a non-inferiority margin of 20%, non-inferiority of both belatacept regimens to CsA is shown (upper bound of the 97.3% confidence interval is less than 20%). The upper bound of the belatacept MI comparison, however, is approaching 20%.

Table 6
Biopsy Proven Acute Rejection, Graft Loss, Death, or Loss to Follow-up at 12 Months
IM103008

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

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

Reviewer's Comment: *The assessment of biopsy proven acute rejection, graft loss, death, or lost to follow-up constitutes the primary proof of efficacy of belatacept from the Medical Division's standpoint. See Section 5.1 for further discussion and justification of the 20% non-inferiority margin from a data driven standpoint.*

Mean measured GFR at Month 3 and Month 12 is presented in Table 7. The mean measured GFR was significantly higher for both belatacept regimens compared to CsA at both timepoints.

Table 7
Measured GFR at Month 3 and Month 12
IM103008

	Belatacept MI n=219	Belatacept LI n=226	CsA n=221
Month 3			
Mean (sd)	59.9 (28.5)	61.7 (25.4)	51.9 (21.1)
# in analysis	209	215	201
Belatacept –CsA (97.3% CI)	8.0 (2.4, 13.5)	9.8 (4.3, 15.3)	
p-value	0.0015	<0.0001	
Month 12			
Mean (sd)	65.0 (30.0)	63.4 (27.7)	50.4 (18.7)
# in analysis	200	206	199
Belatacept –CsA (97.3% CI)	14.6 (8.9, 20.4)	13.0 (7.3, 18.7)	
p-value	<0.0001	<0.0001	

Reviewer's Comment: *As discussed in Section 5.1, proof of efficacy of belatacept can not be claimed based on differences in GFR due to known hemodynamic effects of CsA (i.e. lack of a toxicity related to the control cannot prove the efficacy of the new product without the toxicity).*

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However, since it is known that belatacept does not have the same hemodynamic effects as CsA, differences in GFR would be anticipated.

Mean calculated GFR at months 1, 3, 12, and 24 is presented in Table 8 and depicted in Figure 1. Differences in renal function for the belatacept regimens compared to CsA were apparent in the first month after transplant and maintained up to 24 months (the latest time point of the study for which complete follow-up on all patients was available by the 120-day safety update for the BLA submission). Slopes of the calculated GFR curves from Month 3 (the time when post-transplant GFR appeared to stabilize) to Month 24 were calculated and are summarized in Table 9. For the CsA group, the slope was -1.7 mL/min/1.73m^2/year indicating a slight annual decline in renal function. For the belatacept regimens, the slopes were positive. However, the 95% confidence intervals about the slopes do not exclude 0 indicating that there may not be any improvement but only maintenance of calculated GFR over time.

Table 8
Mean (standard deviation) Calculated GFR
IM103008

	Belatacept MI	Belatacept LI	CsA
Month 1	63.6 (23.3)	61.5 (24.5)	48.1 (18.9)
	n=214	n=220	n=214
Month 3	63.1 (22.4)	63.6 (22.9)	51.0 (19.0)
	n=207	n=211	n=201
Month 12	65.2 (23.5)	65.4 (22.9)	50.1 (21.1)
	n=201	n=200	n=199
Month 24	65.5 (24.9)	65.4 (25.2)	47.9 (23.0)
	n=191	n=201	n=182

Figure 1
Mean Calculated GFR through 24 months
IM103008

Error bars represent the 95% confidence interval about the mean

Table 9
Slope for Calculated GFR from Month 3 to 24
IM103008

	Belatacept MI	Belatacept LI	CsA
Slope* (standard error)	0.96 (0.71)	1.19 (0.70)	-1.73 (0.79)
95% Confidence Interval	(-0.43, 2.36)	(-0.18, 2.57)	(-3.16, -0.30)

*mL/min/1.73 m²/year

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

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remained on study therapy for the entire 12 months and those who didn't may have switched to a regimen containing a calcineurin inhibitor; and these subsets of patients are based on an outcome variable that is affected by treatment.

Table 10
Calculated GFR at 12 Months by Rejection Status at 12 months
IM103008

Acute Rejection Status by Month 12		Belatacept MI	Belatacept LI	CsA
AR	Mean (sd) at Month 12	58.2 (23.3)	48.0 (21.6)	44.3 (17.8)
	95% CI	(51.5, 64.9)	(41.0, 55.0)	(34.8, 53.8)
	# in analysis	49	39	16
No AR	Mean (sd) at Month 12	66.2 (23.0)	67.7 (21.7)	49.8 (21.5)
	95% CI	(62.7, 69.7)	(64.5, 70.9)	(46.8, 52.7)
	# in analysis	170	184	203

Missing GFR at 12 months imputed as 0 if graft loss or death within first 12 months and last observation carried forward otherwise.

3.1.2   IM103027

3.1.2.1   Study Design

IM103027 was similar to that of IM103008 in many aspects of study design and conduct, including belatacept dosing, background immunosuppressive regimen, comparator agent, and study endpoints (aside from the designation of acute rejection as a primary endpoint in IM103008 and as a secondary endpoint in IM103027). The distinguishing feature of the 2 studies was characteristics of the donors. IM103027 enrolled recipients of organs from deceased donors who met the extended donor criteria. These criteria were based in part on those issued by the United Network of Organ Sharing (UNOS) and also included other features widely used to identify potentially compromised organs, such as those from donors with cardiac death or with prolonged cold ischemia time. Due to these similarities, the reader is referred to Section 3.1.1.1 for the discussion of the study design elements.

Patients were enrolled at 79 sites worldwide: 28 in the United States, 9 in France, 6 in Brazil, 5 each in Germany, Argentina, and Spain, 4 in Canada, 3 in Italy, 2 each in Hungary, Austria, and Poland, and 1 each in Belgium, Chile, Czech Republic, Norway, South Africa, Sweden, United Kingdom, and Australia.

A sequential testing procedure was employed for testing the co-primary endpoints and key secondary hypotheses, as specified in the protocol, according to the following hierarchy:
- Assessment of non-inferiority for the difference between belatacept and CsA in patient and graft survival at 12 months,
- Test of the difference between belatacept and CsA on the composite renal impairment endpoint at 12 months,
- Test of difference between belatacept and CsA on the incidence of CAN by 12 months.

The test of the other key secondary endpoint of measured GFR at Month 12 was performed to support the co-primary renal impairment endpoint and was therefore not part of the sequential

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testing procedure. Overall, it was estimated that 180 patients per treatment group would provide 80% power to detect 1 belatacept regimen that met both co-primary endpoints with overall Type I error controlled at the 0.05 significance level. The nominal type I error was set at 0.027 for each belatacept treatment group versus CsA using Dunnett's adjustment for multiple treatment comparisons. A sample size of 180 patients per treatment group provides 83% power to ascertain that the lower bound of the 97.3% 2-sided confidence interval for the difference between each belatacept regimen and CsA in patient and graft survival does not exceed -10%, assuming a patient and graft survival rate at Month 12 of 80% for the CsA regimen and 83% for each belatacept regimen. For the renal function endpoint, the sample size of 180 patients per group provided 98% power to detect a decrease of 25% in the proportion of patients meeting the composite renal impairment endpoint, assuming 75% of CsA patients met the composite endpoint and 25% drop-outs per treatment group.

Reviewer's Comment: *See Section 5.1 for discussion of the non-inferiority margins for acute rejection (20% justified from a data driven standpoint) and patient and graft survival (unable to justify a margin from a data driven standpoint). Please also refer to Section 5.1 regarding the choice of endpoints for assessing and proving the efficacy of belatacept. Due to issues discussed in Section 5.1, proof of efficacy of belatacept will be based on the endpoint of the incidence of biopsy proven acute rejection, graft loss, death, or loss to follow-up at Month 12 (a variation of the Applicant's acute rejection endpoint).*

3.1.2.2 Patient Demographics

Of the 578 patients randomized into the study, 543 were transplanted (belatacept MI 184, belatacept LI 175, and CsA 184) and make up the ITT population. Of the 543 randomized and transplanted patients, 536 were treated (1 belatacept MI, 1 belatacept LI, and 5 CsA patients were not treated). The first dose of belatacept was intended to be given at the time of transplant; however, the first dose of CsA could be delayed up to day 7 until there was evidence of adequate renal function. The proportion of patients who discontinued treatment during the first 12 months was comparable across treatment groups. The most common reasons for treatment discontinuation during the first 12 months were adverse events and lack of efficacy.

Table 11
Patient Randomization and Treatment Discontinuation within 12 months
IM103027

	Belatacept MI	Belatacept LI	CsA
Randomized and transplanted (ITT)	184	175	184
Randomized, transplanted and treated	183	174	179
Number discontinuing treatment	50 (27.3)	45 (25.9)	54 (30.2)
Adverse event	22 (12.0)	27 (15.5)	31 (17.3)
Lack of efficacy	16 (8.7)	15 (8.6)	14 (7.8)

Table 12 summarizes the demographic and baseline characteristics of the ITT population. There were no significant differences across treatment groups. Overall, 67% of the study population

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was male and 75% was white. The mean age of the patients was 56 years. Approximately 25% of the subjects were enrolled at sites in North America and 49% were enrolled at sites in Europe. Approximately half of the donor organs met the extended donor criteria of age >60. EBV serostatus of the recipient was positive in over 90% of the patient population.

Table 12
Demographic and Baseline Characteristics (ITT)
IM103027

	Treatment Group		
	Belatacept MI	**Belatacept LI**	**CsA**
# Patients	184	175	184
Gender			
Male	119 (64.7)	129 (73.7)	116 (63.0)
Female	65 (35.3)	46 (26.3)	68 (37.0)
Age mean (SD)	56.7 (12.6)	56.1 (12.4)	55.7 (12.2)
Min, max	21, 80	21, 79	24, 79
Race			
White	137 (74.5)	134 (76.6)	137 (74.5)
Black	25 (13.6)	24 (13.7)	22 (12.0)
Asian	7 (3.8)	3 (1.7)	4 (2.2)
Other	14 (7.6)	14 (8.0)	21 (11.4)
Missing	1 (0.5)	0	0
Region			
North America	49 (26.6)	40 (22.9)	45 (24.5)
South America	45 (24.5)	47 (26.9)	50 (27.2)
Europe	89 (48.4)	86 (49.1)	89 (48.4)
Rest of World (Asia/Pacific)	1 (0.5)	1 (0.6)	0
Africa	0	1 (0.6)	0
Extended Donor Criteria			
Age ≥ 60	94 (51.1)	79 (45.1)	93 (50.5)
Age 50 to 59 with complications	34 (18.5)	43 (24.6)	40 (21.7)
Donor Cardiac Death	15 (8.2)	16 (9.1)	14 (7.6)
Anticipated CIT ≥ 24 hours	38 (20.7)	34 (19.4)	36 (19.6)
None	3 (1.6)	3 (1.7)	1 (0.5)
Recipient EBV serology			
Positive	169 (91.8)	156 (89.1)	168 (91.3)
Negative	14 (7.56)	19 (10.9)	16 (8.7)
Unknown	1 (0.5)	0	0

3.1.2.3   Efficacy Results

Patient and graft survival at 12 months is presented in Table 13. The rates of patient and graft survival at 12 months were 85.9%, 88.6%, and 84.8% in the belatacept MI, belatacept LI, and CsA treatment groups respectively. These rates are lower than those seen in IM103008 but are as might be expected for recipients of extended criteria donor kidneys. The lower bounds of the 97.3% confidence intervals about the difference between the belatacept regimens and CsA were -4.7% and -7.6% for belatacept LI and belatacept MI, respectively.

Table 13
Patient and Graft Survival at 12 months
IM103027

	Belatacept MI	Belatacept LI	CsA
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)	

Reviewer's Comment: This analysis, compared to that presented by the Applicant, includes one fewer belatacept MI patient as surviving with a functioning graft since all patients with unknown status at 12 months were imputed as having a graft loss or died and not just those who met various other unfavorable events during 12 month post-transplantation..

The proportion of patients meeting the composite renal impairment endpoint as well as the reasons for meeting the composite endpoint is presented in Table 14. The difference in the proportion of patients meeting the composite endpoint was statistically significantly fewer for only the belatacept MI vs. CsA comparison. The majority of the patients who met the composite endpoint met the endpoint due to their measured GFR being less than 60 mL/min/1.73 m^2 at Month 12. It should be noted that the analyses presented here are slightly different from that presented by the Applicant in that patients with missing measured GFR for reasons other than death or graft loss are also included as failures of the endpoint, whereas they were excluded from the Applicant's analysis. The conclusions drawn, however, are not different.

Table 14
Composite Renal Function at 12 months
IM103027

	Belatacept MI (n=184)	Belatacept LI (n=175)	CsA (n=184)
Met composite endpoint	132 (71.7)	135 (77.1)	157 (85.3)
Reason for meeting composite: M12 < 60 and Decrease ≥ 10 from M3 to 12	27	41	37
M12 < 60 only	71	64	83
Decrease ≥ 10 from M3 to M12 only	4	6	7
Imputed due to GL or death	22	19	24
Missing	8	5	6
p-value	.0022	.0575	

Reviewer's Comment: Refer to Section 5.1 for a discussion regarding the difficulty in the interpretation of this endpoint as proof of efficacy of belatacept.

Table 15 summarizes the incidence of acute rejection at 12 months, as defined by the Applicant. Non-inferiority of both belatacept regimens compared to CsA based on a 20% non-inferiority margin was shown, as demonstrated by an upper bound of the 97.3% confidence interval less than 20%. However, it should be noted that there were numerically more acute rejections in the

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belatacept treated patients than in the CsA treated patients. Severity of the acute rejection episodes were similar between the belatacept LI and CsA groups.

Table 15
Acute Rejection at 12 months (as defined by Applicant)
IM103027

	Belatacept MI	Belatacept LI	CsA
Acute Rejection	33/184 (17.9)	31/175 (17.7)	26/184 (14.1)
Mild IA	0	4	2
Mild IB	7	2	2
Moderate IIA	10	17	17
Moderate IIB	16	8	5
Severe III	0	0	0
Difference from CsA (97.3% CI)	3.8 (-5.2, **12.8**)	3.6 (-5.5, **12.7**)	

Most of the episodes of acute rejection occurred by 6 months. Only 2 belatacept LI and 1 CsA patients experienced an episode of acute rejection between 6 and 12 months. Few patients experienced more than 1 episode of acute rejection during the first 12 months. Five patients in the belatacept MI group and 2 patients in the CsA group experienced 2 episodes of acute rejection in the first 12 months. An additional belatacept LI patient experienced 3 episodes of acute rejection in the first 12 months.

As stated for IM103008, the Medical Division's traditional assessment of acute rejection is based on a combined endpoint of biopsy proven acute rejection (BPAR), graft loss, death, or loss to follow-up. The results of this assessment are presented in Table 16. Using a non-inferiority margin of 20%, non-inferiority of both belatacept regimens to CsA is shown (upper bound of the 97.3% confidence interval is less than 20%).

Table 16
Biopsy Proven Acute Rejection, Graft Loss, Death, or Loss to Follow-up at 12 Months
IM103027

	Belatacept MI	Belatacept LI	CsA
Met Endpoint	62/184 (33.7)	51/175 (29.1)	52/184 (28.3)
Biopsy Proven Acute Rejection	40	37	34
Graft Loss	14	11	12
Death	6	3	5
Unknown	2	0	1
Difference from CsA (97.3% CI)	5.4 (-5.8, **16.6**)	0.8 (-10.3, **11.9**)	

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

Reviewer's Comment: *The assessment of biopsy proven acute rejection, graft loss, death, or lost to follow-up constitutes the primary proof of efficacy of belatacept from the Medical Division's standpoint. See Section 5.1 for further discussion.*

Mean measured GFR at Month 3 and Month 12 is presented in Table 17. The mean measured GFR was numerically higher for both belatacept regimens compared to CsA at both time points.

Table 17
Measured GFR at Month 3 and Month 12
IM103027

	Belatacept MI n=184	Belatacept LI n=175	CsA n=184
Month 3			
Mean (sd)	46.9 (22.2)	51.0 (25.9)	43.1 (23.3)
# in analysis	165	156	160
Belatacept –CsA (97.3% CI)	3.8 (-2.1, 9.6)	8.0 (2.0, 13.9)	
p-value	0.1513	0.0031	
Month 12			
Mean (sd)	52.1 (21.9)	49.5 (25.8)	45.2 (21.1)
# in analysis	154	151	154
Belatacept –CsA (97.3% CI)	6.9 (1.1, 12.7)	4.3 (-1.5, 10.2)	
p-value	0.0089	0.0995	

Reviewer's Comment: *As discussed in Section 5.1, proof of efficacy of belatacept can not be claimed based on differences in GFR due to known hemodynamic effects of CsA (i.e. lack of a toxicity related to the control cannot prove the efficacy of the new product without the toxicity). However, since it is known that belatacept does not have the same hemodynamic effects as CsA, differences in GFR would be anticipated.*

Mean calculated GFR at months 1, 3, 12, and 24 is presented in Table 18 and is depicted in Figure 2. Differences in renal function for the belatacept regimens compared to CsA were apparent in the first month after transplant and maintained up to 24 months (the latest time point of the study for which complete follow-up on all patients was available by the 120-day safety update for the BLA submission). Slopes of the calculated GFR curves from Month 3 (the time when post-transplant GFR appeared to stabilize) to Month 24 were calculated and are summarized in Table 19. For the CsA group, the slope was -1.88 mL/min/1.73m^2/year indicating a slight annual decline in renal function. For the belatacept regimens, the slopes were also negative but to a lesser extent.

Table 18
Mean (standard deviation) Calculated GFR
IM103027

	Belatacept MI	Belatacept LI	CsA
Month 1	41.0 (21.0) n=182	39.6 (173) n=173	31.8 (16.1) n=184
Month 3	45.1 (21.7) n=177	45.3 (19.3) n=168	37.8 (19.2) n=172
Month 12	44.3 (22.8) n=165	44.5 (21.8) n=158	36.5 (21.1) n=159
Month 24	44.4 (26.7) n=152	42.8 (24.1) n=158	34.9 (21.6) n=154

Figure 2
Mean Calculated GFR through 24 months
IM103027
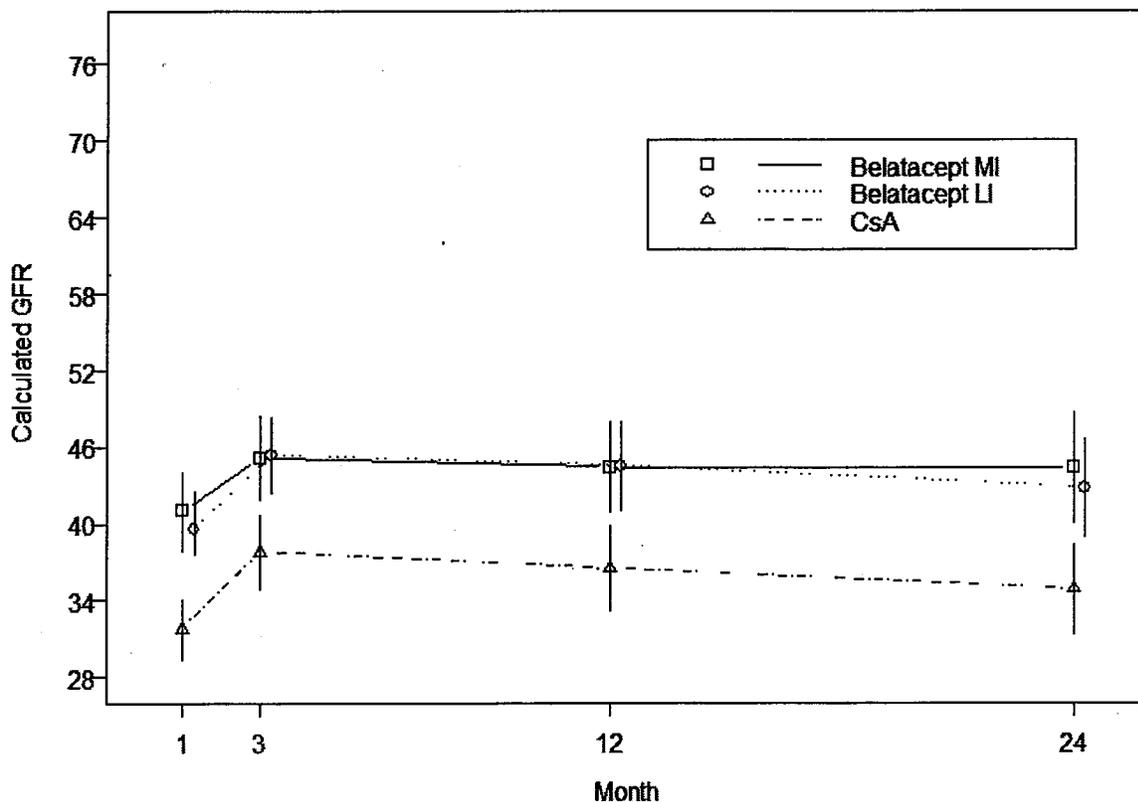
Error bars represent the 95% confidence interval about the mean

Table 19
Slope for Calculated GFR from Month 3 to 24
IM103027

	Belatacept MI	Belatacept LI	CsA
Slope* (standard error)	-0.74 (0.78)	-0.93 (0.77)	-1.88 (0.78)
95% Confidence Interval	(-2.28, 0.79)	(-2.44, 0.58)	(-3.40, -0.34)

*mL/min/1.73 m²/year

Table 20 presents the mean calculated GFR at 12 months for patients who experienced an acute rejection and for those who didn't. In patients with acute rejection and in subjects without acute rejection, mean calculated GFR was higher in the belatacept groups than in the CsA group. Mean calculated GFR was lower for patients who experienced an acute rejection compared to those who did not experience an acute rejection. The differences in calculated GFR for those

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

Table 20
Calculated GFR at 12 Months by Rejection Status at 12 months
IM103027

Acute Rejection Status by Month 12		Belatacept MI	Belatacept LI	CsA
Acute Rejection	Mean (sd) at Month 12	36.1 (17.0)	38.9 (20.5)	25.2 (18.8)
	95% CI	(30.0, 42.1)	(31.4, 46.5)	(17.6, 32.8)
	# in analysis	33	31	26
No Acute Rejection	Mean (sd) at Month 12	44.3 (22.7)	45.0 (21.5)	37.6 (20.3)
	95% CI	(40.7, 48.0)	(41.4, 48.5)	(34.4, 40.7)
	# in analysis	150	144	158

Missing GFR at 12 months imputed as 0 if graft loss or death within first 12 months and last observation carried forward otherwise.

3.2 Evaluation of Safety

Nearly all patients experienced 1 or more adverse event during the first 12 months of the Phase 3 trials. In IM103008, serious adverse events up to month 12 were reported for 51% belatacept MI patients, 44% belatacept LI patients, and 57% CsA patients. In IM103027, serious adverse events up to 12 months were reported for 70% belatacept MI patients, 65% belatacept LI patients, and 71% CsA patients. For a detailed review of adverse events and serious adverse events, refer to the clinical review written by Patrick Archdeacon, M.D.

Table 21
Overall Adverse Events
IM103008 and IM103027

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

AE= adverse event

Table 22 summarizes the total number of deaths and/or graft losses observed up to 12 months and up to 24 months in the Phase 3 trials. Overall, the total number of deaths up to 24 months

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were 19 (4.0%) in the belatacept LI group, 20 (5.0%) in the belatacept MI group, and 25 (6.2%) in the CsA group. Overall, the total number of graft losses up to 24 months were 25 (6.2%) in the belatacept LI group, 25 (6.2%) in the belatacept MI group, and 30 (7.4%) in the CsA group.

Table 22
Graft Loss and/or Death
IM103008 and IM103027

	IM103008			IM103027		
	Belatacept MI (n=219)	Belatacept LI (n=226)	CsA (n=221)	Belatacept MI (n=184)	Belatacept LI (n=175)	CsA (n=184)
Death/Graft Loss						
Up to Month 12	10	8	14	23	20	25
Up to Month 24	13	12	20	29	28	30
Death						
Up to Month 12	6	4	7	8	5	8
Up to Month 24	7	8	13	13	11	12
Graft Loss						
Up to Month 12	4	5	8	17	16	20
Up to Month 24	7	5	8	18	20	22

Hypertension, dyslipidemias, and new onset diabetes after transplantation (NODAT) are class effects of calcineurin inhibitors (e.g. CsA). Therefore, the Applicant prospectively studied these endpoints to support the benefits of belatacept. Table 23 summarizes the mean systolic and diastolic blood pressure at Month 12 for both studies. Mean systolic and diastolic blood pressures were significantly lower for patients in both belatacept groups relative to the CsA group in both studies.

Table 23
Mean Blood Pressure at Month 12
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	Systolic Blood Pressure	132.7 (16.2)* n=191	131.4 (16.5)* n=193	138.7 (20.0) n=187
	Diastolic Blood Pressure	79.3 (11.5)* n=191	78.7 (10.9)* n=193	81.9 (11.1) n=187
027	Systolic Blood Pressure	141.4 (21.3)* n=137	140.9 (21.1)* n=140	149.5 (19.8) n=124
	Diastolic Blood Pressure	77.8 (13.8)* n=137	78.3 (10.6)* n=140	81.8 (11.7) n=124

Mean (standard deviation)
Number in analysis
*comparison of mean value of belatacept regimen to CsA p-value<0.027

Mean non-HDL cholesterol and mean triglyceride levels at Month 12 were significantly lower for patients in both belatacept groups relative to the CsA group in both studies. The differences in non-HDL cholesterol between the belatacept and CsA groups appears to be driven by the contribution of triglycerides, as the LDL levels at Month 12 were more similar across groups.

Table 24
Serum Lipids at Month 12
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	Non-HLD cholesterol	131.7 (36.8)* n=192	131.5 (38.2)* n=195	144.1 (47.3) n=189
	LDL cholesterol	100.8 (29.5) n=183	102.1 (33.4) n=186	107.3 (39.6) n=187
	Triglycerides	155.0 (85.1)* n=183	149.4 (87.3)* n=186	184.6 (106.4) n=187
027	Non-HLD cholesterol	135.9 (46.3)* n=144	134.4 (41.1)* n=142	153.0 (46.3) n=133
	LDL cholesterol	105.5 (38.8) n=133	102.5 (37.2) n=135	109.8 (40.9) n=124
	Triglycerides	169.6 (120.8)* n=134	152.9 (67.2)* n=135	211.3 (120.6) n=124

Mean (standard deviation)
Number in analysis
*comparison of mean value of belatacept regimen to CsA p-value<0.027

NODAT was defined in the trials as the use of an antidiabetic agent for more than 30 days or at least two fasting plasma glucose values greater than or equal to 126 mg/dL in a subjects who was not diabetic at study entry. Across all treatment groups relatively few patients developed NODAT by Month 12. Numerically fewer belatacept treated patients compared to CsA treated patients developed NODAT.

Table 25
New Onset Diabetes Mellitus After Transplantation
IM103008 and IM103027

Study	Belatacept MI	Belatacept LI	CsA
008	11/156 (7.1)	7/168 (4.2)	16/162 (9.9)
027	3/133 (2.3)	7/136 (5.1)	11/118 (9.3)
Pooled	14/289 (4.8)	14/304 (4.6)	27/280 (9.6)

Denominator is number of subjects with out diabetes at transplant

Post transplant lymphoproliferative disorder (PTLD) was found to be observed at an increased frequency in the belatacept arms in the 3 core belatacept trials (IM103008, IM103027, and IM103100). PTLD is a composite term encompassing the following MedDRA preferred terms: lymphoproliferative disorder, hematological malignancy, lymphoma, CNS lymphoma, hepatosplenic t-cell lymphoma, EBV-associated lymphoproloferative disorder, and b-cell lymphoma. Up to 14-Dec-2009, there were 8 cases (1.7%) of PTLD in the belatacept MI group, 6 cases (1.3%) in the belatacept LI group, and 2 cases (0.4%) in the CsA group. Nine of the 16 cases presented with CNS involvement (6 belatacept MI, 3 belatacept LI and 0 CSA). The distribution of PTLD cases across the trials was as follows:

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

EBV-negative status of the recipient is a known and the most significant risk factor for the development of PTLD. Table 26 summarizes the PLTD cases observed in the belatacept core trials by recipient EBV status and CNS or non-CNS involvement. While EBV-negative patients make up 12% of the trial population across the belatacept treatment groups, half of the PTLD cases were in EBV-negative patients.

Table 26
Summary of PTLD Cases
IM103008, IM103027, and IM103100

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

*The belatacept LI regimen studied in IM103100 is non-identical to that studied in IM103008 and IM103027
Ω = Patient alive; † = Patient dead in first 24 months; ‡ = Patient died after first 24 months

Another known risk factor for the development of PTLD is the use of lymphocyte depleting agents. Since there was a higher incidence of acute rejection and subsequent use of lymphocyte depleting agents to treat the episode of acute rejection in the belatacept arms, it was hypothesized that the increased incidence of PTLD seen in the belatacept arms was due to the use of a lymphocyte depleting agent rather than belatacept. However, when one looks at the incidence of PTLD by lymphocyte depleting agent use or not, the increased risk of PTLD is seen with belatacept compared to CsA, regardless.

Table 27
Lymphocyte Depleting Agent Use and PTLD
IM103008, IM103027, and IM103100

		Belatacept MI	Belatacept LI	CsA
All patients	Lymphocyte depleting agent not used	4/407 (0.98%) 3 of 4 were CNS	6/422 (1.42%) 3 of 6 were CNS	2/417 (0.48%) 0 of 2 were CNS
	Lymphocyte depleting agent used	4/70 (5.7%) 3 of 4 were CNS	0/50 (0%)	0/59 (0%)
EBV +	Lymphocyte depleting agent not used	1/344 1 of 1 was CNS	4/359 (1.1%) 2 of 4 were CNS	0/349
	Lymphocyte depleting agent used	1/60 1 of 1 was CNS	0/42	0/50
EBV-	Lymphocyte depleting agent not used	2/39 2 of 2 were CNS	2/46 1 of 2 was CNS	1/50 0 of 1 was CNS
	Lymphocyte depleting agent used	3/6 2 of 3 were CNS	0/5	0/7

The Applicant conducted a multivariate analysis to identify independent risk factors for the development of PTLD and CNS PTLD in belatacept treated patients. The analysis included known risk factors such as recipient EBV serostatus, the use of lymphocyte-depleting therapies, cytomegalovirus (CMV) disease, and age greater than 60 years as well as gender, belatacept dose, and recipient CMV status at the time of transplantation. The results of these analyses are presented in Table 28. The most significant risk factor for the development of PTLD or CNS PTLD was recipient EBV-negative status. In addition, lymphocyte depleting therapy prior to PTLD was identified as a significant risk factor for the development of PTLD or CNS PTLD and CMV infection prior to PTLD was identified as a significant risk factor for the development of CNS PTLD. These 2 factors, however, are those that occurred during treatment with belatacept not those that were baseline factors. Based on these results, the Applicant has determined and the Medical Division agrees that if approved, belatacept should be contraindicated for EBV-negative patients and labeled for EBV-positive patients only.

Table 28
Multivariate Risk Factor Assessment for PTLD in Belatacept-treated Patients

	All Belatacept PTLD		Belatacept CNS PTLD	
Risk Factor	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Age ≥ 60	2.402	0.777, 7.426	3.395	0.855, 13.487
Gender (female vs. male)	0.347	0.07, 1.604	All cases male	
Recipient EBV status (- vs. +)	10.346	3.255, 32.889	13.042	3.261, 52.152
Lymphocyte depleting therapy prior to PTLD (yes vs. no)	3.58	1.064, 12.049	4.622	1.072, 19.94
Recipient CMV status (- vs. +)	1.804	0.591, 5.507	1.708	0.431, 6.761
CMV infection prior to PTLD (yes vs. no)	2.74	0.825, 9.097	5.634	1.411, 22.487
Belatacept dosing regimen (LI vs. MI)	0.879	0.296, 2.612	0.540	0.13, 2.233

There has been discussion as to whether CMV serostatus of the recipient should be another factor to consider before treating with belatacept. In the above multivariate risk factor assessment, CMV serostatus of the recipient appears to have less independent association for an increased risk when the other variables are taken into account. When examined individually (Table 29), it appears that CMV negative serostatus may be a predictive factor overall and within the EBV-positive serostatus group. However, two of the PTLD cases in EBV-positive / CMV-negative patients were not confirmed as cases of PTLD by a review of a blinded central pathologist. If these two cases are excluded, there is still an increased risk but the significance of this increased risk is questionable.

Table 29
CMV serostatus and PTLD in Belatacept-treated Patients

		Belatacept MI	Belatacept LI	All Belatacept	Odds Ratio (95%CI)
All patients	CMV +	4/337 (1.2)	2/336 (0.6)	6/673 (0.9)	
	CMV -	4/138 (2.9)	4/134 (3.0)	8/272 (2.9)	3.37 (1.16, 9.8)*
EBV +	CMV +	1/291 (0.34)	1/301 (0.33)	2/593 (0.34)	
	CMV -	1/111 (0.9)	3/98 (3.1)	4/209 (1.9)	5.76 (1.05, 31.7)**
EBV-	CMV +	2/24 (8.3)	1/23 (4.4)	3/47 (6.4)	
	CMV -	1/28 (3.6)	3/21 (14.3)	4/29 (8.2)	1.3 (0.28, 6.2)

* Excluding 2 CMV- PTLD cases, Odds Ratio 2.5 and 95% CI (0.80, 7.8)
** Excluding 2 EBV+/CMV- PTLD cases, Odds Ratio 2.85 and 95% CI (0.40, 20.4)

4.   FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Results of patient and graft survival at 12 months, biopsy proven acute rejection, graft loss, death, or lost to follow-up at 12 months, and measured GFR at 12 months are presented by gender, age, and race in the following tables for both Phase 3 trials. For many of the subgroups, the results should be interpreted with caution due to small sample sizes. In IM103008, results for gender are fairly consistent with those seen for the overall population with the exception of female CsA patients who have slightly worse patient and graft survival at 12 months and higher biopsy proven acute rejection, graft loss, death, or loss to follow-up at 12 months compared to belatacept females and their male CsA counterparts. In IM103027, female belatacept patients have lower patient and graft survival at 12 months and higher biopsy proven acute rejection, graft loss, death, or loss to follow-up at 12 months than female CsA patients. In IM103008, there were too few patients ≥ 65 to make and meaningful comparisons with respect to age groups. In IM103027, patient and graft survival is slightly lower for patients ≥ 65 than patients < 65. There appears to be a larger difference between age groups for the belatacept LI group than the belatacept MI and CsA groups and belatacept LI patients ≥ 65 have the lowest patient and graft survival at 12 months.. Biopsy proven acute rejection, graft loss, death, or lost to follow-up at 12 months is fairly similar between age groups for the belatacept MI and CsA groups but is greatest for patients ≥ 65 in the belatacept LI group. As for measured GFR at 12 months, older patients tend to have lower GFR but the difference between treatment groups is consistent for both age groups. In general where the sample sizes are sufficient, the results for race are consistent with those seen for the overall population.

Table 30
Patient and Graft Survival at 12 Months
By Gender, Age, and Race
IM103008 and IM103027

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

*Includes 1 patient who experienced GL prior to death
^Includes 2 patients who experienced GL prior to death
**Includes 3 patients who experienced GL prior to death

Table 31
Biopsy Proven Acute Rejection, Graft Loss, Death, or Lost to Follow-up at 12 Months
By Gender, Age, and Race
IM103008 and IM103027

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

Table 32
Measured GFR at 12 Months
By Gender, Age, and Race
IM103008 and IM103027

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

Subgroup analyses by gender, age, and race are uninformative for the incidence of PTLD. For the cases of PTLD, there were 2 females (1 belatacept MI and 1 belatacept LI) and the rest were males; 1 Asian (belatacept MI), 1 other race (belatacept LI), and the rest were white; and 4 patients ≥ 65 years (2 belatacept MI and 2 belatacept LI) and the rest were < 65 years of age.

4.2 Other Special/Subgroup Populations

Both Phase 3 trials were multi-regional trials. Therefore, results for patient and graft survival at 12 months, biopsy prove acute rejection, graft loss, death, or lost to follow-up at 12 months, and measured GFR at 12 months are presented by region in the following tables. The rates of patient and graft survival as well as the differences between belatacept LI and CsA appear to be fairly

consistent across regions. The rate of biopsy proven acute rejection, graft loss, death, or lost to follow-up, which was driven by acute rejection, appears to differ for the belatacept regimens depending on region. The treatment differences between belatacept LI and CsA vary from 10 to 17% in favor of CsA for North America, 7 to 11% in favor of belatacept LI for South America, and little to no difference for Europe. In both studies, the rates of the belatacept LI group in North America are higher than the remaining regions. Even though the rates are higher for the belatacept LI group in North America when compared to the other regions, there are no differences across the regions in the distribution of the severity of acute rejections, which contributes the most to the composite endpoint. Measured GFR at 12 months appears to vary depending on region but measured GFR is consistently higher for the belatacept groups compared to CsA.

Table 33
Patient and Graft Survival at 12 Months
By Region
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	**Region**			
	North America	92/95 (96.8)	88/92 (95.7)	86/94 (91.5)
		1 GL, 1 Died, 1 Missing	2 GL, 3 Died*	4 GL, 3 Died, 1 Missing
	South America	29/35 (82.9)	35/36 (97.2)	30/33 (90.9)
		2 GL, 4 Died	1 Died	2 GL, 1 Died
	Europe	54/55 (98.2)	63/64 (98.4)	56/58 (96.6)
		1 GL	1 GL	2 GL, 1 Died*
	Rest of World	33/34 (97.1)	32/34 (94.1)	34/36 (94.4)
		1 Died	2 GL	2 Died
027	**Region**			
	North America	43/49 (87.8)	34/40 (85.0)	38/45 (84.4)
		4 GL, 2 Died*, 1 Missing	6 GL	5 GL, 2 Died
	South America	39/45 (86.7)	42/47 (89.4)	40/50 (80.0)
		3 GL, 3 Died	4 GL, 2 Died*	6 GL, 4 Died*, 1 missing
	Europe	75/89 (84.3)	77/86 (89.5)	78/89 (87.6)
		10 GL, 3 Died*, 2 missing	6 GL, 3 Died	9 GL, 2 Died^, 2 Missing
	Rest of World	1/1	2/2	-
		-	-	

Table 34
Biopsy Proven Acute Rejection, Graft Loss, Death, or Lost to Follow-up at 12 Months
By Region
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	**Region**			
	North America	29/95 (30.5)	25/92 (27.2)	16/94 (17.0)
	South America	13/35 (37.1)	4/36 (11.1)	6/33 (18.2)
	Europe	15/55 (27.3)	12/64 (18.8)	10/58 (17.2)
	Rest of World	3/34 (8.8)	8/34 (23.5)	5/36 (13.9)
027	**Region**			
	North America	18/49 (36.7)	18/40 (45.0)	13/45 (28.9)
	South America	10/45 (22.2)	9/47 (19.2)	15/50 (30.0)
	Europe	33/89 (37.1)	24/86 (27.9)	24/89 (27.0)
	Rest of World	1/1	0/2	-

Table 35
Measured GFR at 12 Months
By Region
IM103008 and IM103027

Study		Belatacept MI	Belatacept LI	CsA
008	**Region**			
	North America	69.1 (24.9) n=88	68.2 (24.2) n=80	52.8 (16.3) n=86
	South America	73.4 (37.0) n=29	63.4 (29.0) n=35	49.3 (17.1) n=30
	Europe	63.0 (29.6) n=50	61.3 (31.6) n=61	53.9 21.9) n=50
	Rest of World	49.6 (31.7) n=33	54.8 (24.7) n=30	39.6 (17.4) n=33
027	**Region**			
	North America	53.8 (20.2) n=42	52.4 (26.1) n=33	45.6 (17.0) n=37
	South America	53.8 (25.9) n=39	48.3 (19.0) n=42	48.8 (23.6) n=41
	Europe	50.3 (20.7) n=73	49.5 (29.1) n=74	43.1 (21.4) n=76

As discussed in the safety section, belatacept treated patients are at increased risk for developing PTLD. Additionally, it is known that EBV-negative patients are also at increased risk for developing PTLD. In order to minimize the risk for PTLD, the Applicant is proposing to contraindicate the use of belatacept in EBV-negative patients. Therefore, analyses by EBV serostatus were conducted for the endpoints of patient and graft survival at 12 months, biopsy prove acute rejection, graft loss, death, or lost to follow-up at 12 months, and measured GFR at 12 months. Treatment comparisons are presented for the EBV-positive group only since this is the population of patients for which belatacept may receive approval. In IM103027, there is 1 belatacept MI patient who had unknown EBV status and is not presented in any of the tables. The conclusions drawn for the EBV-positive patients are similar to those drawn for the overall population. Additional analyses by EBV status were conducted and are presented in the appendix to this review.

Table 36
Patient and Graft Survival at 12 months by EBV Serostatus
IM103008 and IM103027

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

Table 37
Biopsy Proven Acute Rejection, Graft Loss, Death at 12 months
By EBV Serostatus
IM103008 and IM103027

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

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

Table 38
Measured GFR at Month 12
By EBV Serostatus
IM103008 and IM103027

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

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

<u>Non-Inferiority Margin</u>

Two objectives of the belatacept Phase 3 program were to demonstrate that at least one of the belatacept treatment regimens was non-inferior to the CsA regimen. The first was with respect to patient and graft survival at 12 months and the second was with respect to the frequency of acute rejection at 12 months. The sponsor had specified a margin of 10% for the endpoint of patient and graft survival and a margin of 20% for the endpoint of acute rejection in both studies.

As with all non-inferiority trials, it is necessary to determine how the efficacy of the new drug can be determined based on the results of the non-inferiority trial. This is done by providing a justification of the non-inferiority margin used to assess the results for the trial. Regarding choosing a margin, the ICH guidance document E10: Choice of Control Group and Related Issues in Clinical Trials, states the margin:
- "cannot be greater than the *smallest effect size that the active drug would be reliably expected to have* compared with placebo in the setting of the planned trial" (M1) and
- "is based on both statistical reasoning and clinical judgment, should reflect uncertainties in the evidence on which the choice is based, and should be suitably conservative."[1]

In the setting of a multi drug regimen, the non-inferiority margin chosen should not be larger than the amount of efficacy the control arm has over the putative placebo (i.e. the appropriate

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[1] International Conference on Harmonisation. Guidance for Industry: E 10 Choice of control group and related issues in clinical trials. Food and Drug Administration, DHHS, 2001.

placebo arm if one were included in the trial). The control effect needs to be determined by assessing the difference between the putative placebo and the control arm using data from previously conducted clinical trials. For the current trials, the treatment arms are as follows:

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

The ideal way to assess the effect of the control regimen over the putative placebo (i.e., estimate M1) would be based on obtaining a treatment effect from multiple randomized trials that compared these two regimens. However, there are no trials available which allow for the direct comparison of the control arm to the putative placebo. Since this information is not available, the next step would be to estimate the efficacy of the putative placebo and the efficacy of the control regimen from separate sources and compare them.

There is only one published study (Vincenti, 2001)[2] available which studied a regimen similar to the putative placebo. In this study, patients received daclizumab (D) instead of basiliximab in addition to MMF and corticosteroids. The rate of biopsy proven acute rejection at 12 months in this study was 53% (52/98) with a 95% confidence interval of (42.7, 63.2). If graft losses, deaths, and patients who are lost to follow-up are considered events as well, referred to as efficacy failure here, efficacy failure at 12 months in the Vincenti study would be 58.2% (57/98) with a 95% confidence interval of (47.9, 68.4).

Six studies were found that contained 7 randomized treatment arms of CsA + basiliximab + MMF + corticosteroids similar to the control arm for the current trial. Table 39 contains the results of the acute rejection endpoint from these studies. A 95% CI from pooling acute rejection from these 6 studies is (13.8, 20.4). A conservative estimate (high estimate) for this regimen is therefore, 20.4%. Comparing this to a conservatively low estimate from the Vincenti study 42.7%, leads to a difference of 22.3% (42.7 – 20.4). Thus, based on the limited amount of data available for assessing the effect of CsA in a regimen that also contains basiliximab, MMF and corticosteroids with respect to the rate of acute rejection, a non-inferiority margin no greater than approximately 20% would be acceptable from a data driven point of view.

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

Table 39
12-Month Acute Rejection and Efficacy Failure Rates from Literature

Study	Treatment arm	Acute Rejection	Efficacy Failure
Budde (2006)[3]	CS + B + CsA + MMF	8/45 (17.8%)	9/45 (20%)
Silva (2007)[4]	CS + B + CsA + MMF	29/212 (13.7%)	36/212 (17%)
Kamar (2005)[5]	CS + B + CsA + MMF	26/100 (26.0%)	29/100 (29%)
	CS + B + CsA + MMF	15/97 (15.5%)	23/97 (23.7%)
Sollinger (2001)[6]	CS + B + CsA + MMF	13/70 (18.6%)	15/70 (21.4%)
Pescovitz (2003)[7]	CS + D + CsA + MMF	7/50 (14%)	n/a
Lawen (2003)[8]	CS + B + CsA + MMF	12/59 (20.3%)	n/a
Random Effect C.I[*]		(13.8, 20.4)	(17.0, 26.0)

* DerSimonian and Laird Method

The Medical Division's preferred assessment of acute rejection is based upon the endpoint of efficacy failure which is defined as the incidence of biopsy proven acute rejection, graft loss, death, or lost to follow-up. This analysis of acute rejection considers missing data due to graft loss, death, or lost to follow-up as events in the analysis. Four studies were found that considered efficacy failure at 12 month for the treatment regimen of CsA + basiliximab + MMF + corticosteroids. A 95% CI from pooling efficacy failure from these 4 studies is (17.0, 26.0). A conservative estimate (high estimate) of this regimen is 26.0%. Comparing this to a conservatively low estimate from the Vincenti study 47.9%, leads to a difference of 21.9% (47.9 − 26.0). Based on this data, with respect to the rate of acute rejection, where graft losses, deaths and losses to follow-up are considered as events, a non-inferiority margin no greater than approximately 20% would be acceptable from a data driven point of view.

In efforts to find additional information to support the justification of the non-inferiority margin, the results of a previously conducted literature search and mixed effects modeling approach were used to estimate the effects of the control and putative placebo rates. The previously conducted literature search identified all relevant randomized clinical trials (RCTs) in de novo kidney transplantation, excluding trials conducted in special populations (e.g. pediatrics, delayed graft function only, non-heart beating donor). The search yielded 47 relevant clinical trials published between 1996 and 2008. No studies were identified that evaluated the use of B+CS+MMF (the putative placebo) in renal transplantation, many studies did not include a 12-month efficacy endpoint, and several studies did not report the incidence of the composite endpoint used by the

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[3] Budde K et al (2007) Reduced-exposure cyclosporine is safe and efficacious in de novo renal transplant recipients treated with enteric-coated mycophenolic acid and basiliximab. Clin Nephrol;67(3):164-75.

[4] Silva, HT et al (2007) One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. Am J Transplant; (7):595-608.

[5] Kamar N et al (2006) Impact of early or delayed cyclosporine on delayed graft fuctio in renal transplant recipients: a randomized, multicenter study. Am J Transplant;6(5 Pt 1):1042-8.

[6] Sollinger H et al. Basiliximab versus antithymocyte globulin for prevention of acute renal allograft rejection. Transplantation 2001; 72 (12) 1915-1919.

[7] Pescovitz MD et al (2003) Pharmacokinetics of daclizumab and mycophenolate modetil with cyclosprorine and steroids in renal tranaplantation. Clin Transplant; 17(6):511-7.

[8] Lawen JG et al (2003) Randomized double-blind study of immunoprophylaxis with basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in combination with mycophenolate mofetil-containing triple therapy in renal transplantation. Transplantation; 75(1):37-43.

Medical Division. Therefore the acute rejection endpoint was used as surrogate while assuming no major differences in treatment effects between acute rejection alone versus the composite endpoint. Lastly, there was considerable variation in treatment regimens (i.e. drugs used and doses) used in the identified studies. Therefore, for simplicity each calcineurin-inhibitor (CNI) was categorized into 'reduced (r)' or 'standard (s)' drug exposure categories.

Given the lack of any RCTs evaluating the efficacy of the putative placebo in renal transplant patients, a mixed effects model (MEM) was used to estimate the contribution of each of the immunosuppressant drugs to the combination therapy event rate. These models assume additive drug effects in a combination therapy on a log-odds scale. The model was used to estimate the combined effect of the three immunosuppressant drugs (B+CS+MMF) for the putative placebo group and of the four immunosuppressant drugs (B+CS+CsA(s)+MMF) for the control group.

The mathematical model is as follows:

Let $Y_{ij} \sim Binomial(N_{ij}, \pi_{ij})$ where Y_{ij} is the number of events in study i and treatment arm j N_{ij}, is the number of patients and π_{ij} is the event rate in study i and treatment arm j.

The log-odds of the event rate is related to the study effects based on a linear model with the random study effect:

logit $(\pi_{ij}) = \mu + \delta_i + x_{ij}\beta$ where the intercept and effects of the immunosuppressant drugs and covariates are μ and β respectively, the random effect $\delta_i \sim N(0, \sigma^2)$, vector x_{ij} includes indicators for presence or absences of each of the immunosuppressant drugs and covariates.

The model was fit using the maximum-likelihood method (PROC NLMIXED in SAS). Based on this modeling approach, the estimated failure rate of the control group (B+CS+CsA(s)+MMF) is 19.3%, 95% CI (16.7, 21.8) and that for the putative placebo (B+CS+MMF) is 63.4%, 95% CI (55.1, 71.7) and an estimated difference in event rates (B+CS+MMF - B+CS+CsA(s)+MMF) of 44.1% (36.2, 52.1).

While this modeling approach includes several assumptions, this approach seems reasonable given the absence of comparative (concurrent) clinical data. The lower bound around the estimated difference in failure rates is 36.2% (e.g. the minimum (estimated) amount that active control is better than putative placebo in terms of efficacy failure). Thus, providing additional support of a margin of 20%.

Therefore, from a data driven point of view, a 20% non-inferiority margin for the endpoint of acute rejection (as defined by the Applicant or per the Medical Division) is acceptable to demonstrate an effect of belatacept over placebo if a placebo was included in the current trials. However, the 20% non-inferiority margin may not be acceptable from a clinical standpoint for assessing the potential loss of efficacy compared to the standard of care. This determination is left to the clinical reviewer.

With respect to the endpoint of patient and graft survival, the size of the effect of CsA given the current standard regimen including induction, corticosteroids, and MMF cannot be estimated based on historical data. Therefore, a non-inferiority margin cannot be defined. However, in the past the 10% margin has been used to rule out a regimen that would not be considered any further.

Reviewer's comment: During End of Phase 2 discussions, the Applicant was informed that if the confidence interval of the difference in patient and graft survival was within a 5% margin that this would demonstrate strong support of the non-inferiority of belatacept, however if the difference was outside the 5% range but still within in the 10% margin then establishing efficacy would be based on an assessment of the totality of the data. These statements were not based on a data driven estimate of the effect of CsA.

Choice of Endpoints

The co-primary endpoints for assessing the efficacy of belatacept as specified in the protocols were the composite of patient and graft survival at 12 months and the composite renal impairment endpoint. The incidence of acute rejection by 12 months was a third co-primary endpoint for IM103008 and a secondary endpoint for IM103027. These endpoints were agreed to in principle during End of Phase 2 discussions in 2004 and a Special Protocol Assessment of IM103008 in 2005. During both of these time periods, belatacept was reviewed by the office that at the time was specific to biologics products and not the current Division of Special Pathogen and Transplant Products.

Patient and graft survival is an important endpoint for assessing any immunosuppressant product. However in the modern transplant era, one can no longer depend on patient and graft survival at 12 months to demonstrate the efficacy of newer regimens by comparison to a regimen reflecting standard of care, since the rate of short-term (1 year) patient and graft survival is high. As mentioned above, the effect of CsA on patient and graft survival given in the current standard regimen including induction, corticosteroids, and MMF cannot be easily estimated, and therefore a data driven non-inferiority margin cannot be defined. Thus, patient and graft survival at 12 months cannot be used for the proof of efficacy of belatacept. Patients and graft survival is still important to make sure that there is not an unacceptable loss of efficacy and for assessing safety.

The composite renal impairment endpoint was defined as measured GFR < 60 mL/min/1.73 m^2 at Month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73 m^2 from Month 3 to Month 12. However, based on further clinical considerations the usefulness of this endpoint to prove the efficacy of belatacept has been called into question. CsA, the control drug, causes vasoconstriction of the afferent renal artery which leads to a physiologic decrease in GFR. Belatacept is not known to have this same toxic effect. Therefore, differences in GFR may simply be due to the toxicity profile of CsA rather than any effect of belatacept especially since differences in GFR were seen from the first measurable time points of renal function (see Figures 1 and 2). Most patients who met the composite renal impairment endpoint did so due to a GFR less than 60mL/min at Month 12. The selection of 60 mL/min was based on a retrospective study of registry data which suggested better outcomes among renal transplant patients whose serum creatinine at 1 year was less than 1.5 mg/dL. These results are based on a population of

patients who were maintained on calcineurin inhibitor containing regimens and therefore had comparable renal hemodynamics allowing for meaningful comparisons of GFR as a surrogate of kidney allograft function and structure. It is less clear what the impact of this cutoff implies about the expected outcomes for belatacept treated patients. Furthermore, patients in IM103027, which enrolled recipients of extended criteria donor kidneys, rarely achieved a GFR greater than 60 mL/min even from the start. Therefore, given the limitations of the composite renal impairment endpoint in the setting of incomparable renal hemodynamics across treatment groups and the limitations of the endpoint in the setting of extended criteria donor kidneys, it is difficult to use this endpoint for proof of efficacy of belatacept. GFR is still an important measure of renal function and the higher GFR's exhibited by patients maintained on belatacept may translate into important clinical benefits. Thus, the difference in mean GFR was given consideration as both a secondary efficacy endpoint and a safety endpoint by the Medical Division.

The Applicant defined acute rejection as central biopsy proven rejection that was either clinically suspected by protocol defined reasons or clinically suspected by other reasons and treated. As previously stated, acute rejection by 12 months was a third co-primary endpoint for IM103008 but only a secondary endpoint for IM103027. The traditional assessment of acute rejection, however, has been based on any biopsy proven acute rejection, regardless of the reason for performing the biopsy. Additionally, patients who experience graft loss, death, or are lost to follow-up are not considered as having a positive outcome (i.e. no rejection). The Medical Division's assessment of acute rejection has been referred to as the efficacy failure endpoint which is the composite of biopsy proven acute rejection, graft loss, death, or lost to follow-up. As discussed above, a non-inferiority margin of 20% was able to be justified from a data driven standpoint for an assessment of acute rejection.

Thus, given the limitation in the ability to justify a non-inferiority margin for patient and graft survival at 12 months and the limitations regarding the use of the composite renal impairment endpoint (or any assessment of GFR, in general) for proving the efficacy of belatacept, the Medical Division is using acute rejection as traditionally assessed (i.e. efficacy failure) as the primary proof of efficacy of belatacept for both Phase 3 trials. Acute rejection has been the traditional endpoint used by the Medical Division to assess the efficacy of other products for the indication of prophylaxis of rejection in kidney transplant recipients and has a non-inferiority margin which can be used to demonstrate the efficacy of belatacept that can be supported from previous kidney transplant studies.

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

There were similar rates of patient and graft survival at 12 month between the belatacept regimens and CsA in both trials. In IM103008, the rates of patient and graft survival at 12 months were 93 to 96%. In IM103027, the rates were slightly lower, 85 to 88%, but as may be expected for a trial of extended criteria donor kidneys. The lower bounds of the confidence

interval about the difference in the rate of patient and graft survival (belatacept- CsA) were all greater than -5% with the exception of the belatacept MI vs. CsA comparison in IM103027 which was -7.6%.

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

There were numerically more patients who experienced an acute rejection by 12 months in belatacept treated patients than in CsA treated patients. The severity of rejection was also more severe in the belatacept groups.

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

The results for patient and graft survival at 12 months, biopsy proven acute rejection, graft loss, death, or lost to follow-up at 12 months, and measured GFR at 12 months are consistent for EBV-positive patients only as compared to the overall population.

<u>Summary of Safety</u>
The incidence of PTLD is higher with belatacept compared to CsA. The highest incidence is seen in EBV-negative patients.

There was improved blood pressure, improved non-HDL and triglycerides, and a lower incidence of NODAT seen with belatacept compared to CsA. These are clinically relevant findings for belatacept given the class effects of hypertension, dyslipidemias, and NODAT associated with CsA.

5.2 Conclusions and Recommendations

In two Phase 3 trials, both belatacept regimens were shown to be non-inferior to CsA, based on a non-inferiority margin of 20%, with respect to the incidence of biopsy proven acute rejection, graft loss, death or lost to follow-up at 12 months. If a smaller margin is deemed more appropriate from a clinical stand point, then the belatacept LI regimen would be non-inferior to CsA in both Phase 3 trials based on a 15% margin. This endpoint provides the proof of efficacy for belatacept to support the indication of prophylaxis of organ rejection in adult patients receiving a kidney transplant. Even though belatacept was shown to be non-inferior to CsA with respect to this endpoint, it is important to note that there were numerically more acute rejections seen in the belatacept groups than the CsA group in both trials. Additional evidence of benefit of belatacept is shown based on acceptable and similar rates of patient and graft survival at 12 months, higher GFR through 24 months, and improved blood pressure at 12 months, improved non-HDL cholesterol and triglycerides at 12 months, and lower incidence of NODAT at 12

months. However, the rate of PTLD, a serious adverse event, was higher in the belatacept groups compared to the CsA group and was mainly driven by the event of CNS PTLD. Given the increased risk of PTLD seen for belatacept treated patients as well as the known increased risk for EBV-negative patients in general, use of belatacept is being considered only for EBV-positive patients. Although it appears that the risk of PTLD and CNS PTLD in EBV-positive patients remains higher in the belatacept groups compared to the CsA group, a more favorable risk benefit profile is seen with this subgroup.

6.   APPENDIX

Additional analyses by EBV serostatus

No concerning trends or differences from the overall population were seen for the EBV-positive subgroups for any of the following analyses.

Table 40
Composite Renal Function at 12 months
By EBV Serostatus
IM103008 and IM103027

Study			Belatacept MI	Belatacept LI	CsA
008	EBV+		(n=194)	(n=199)	(n=184)
		Composite endpoint	105 (54.1)	108 (54.3)	143 (77.7)
		Reason for meeting composite:			
		-M12 < 60 and Decrease ≥ 10 from M3 to 12	28	31	43
		-M12 < 60 only	46	48	74
		-Decrease ≥ 10 from M3 to M12 only	14	13	7
		-Imputed due to GL or death	8	4	13
		-Missing	9	12	6
		p-value	<0.0001	<0.0001	
	EBV-		(n=25)	(n=27)	(n=37)
		Composite endpoint	20 (80.0)	20 (74.1)	31 (83.8)
		Reason for meeting composite:			
		-M12 < 60 and Decrease ≥ 10 from M3 to 12	5	3	9
		-M12 < 60 only	12	10	18
		-Decrease ≥ 10 from M3 to M12 only	1	3	1
		-Imputed due to GL or death	1	4	1
		-Missing	1	0	2
027	EBV+		(n=169)	(n=156)	(n=168)
		Composite endpoint	121 (71.6)	123 (78.8)	143 (85.1)
		Reason for meeting composite:			
		-M12 < 60 and Decrease ≥ 10 from M3 to 12	26	39	33
		-M12 < 60 only	63	58	76
		-Decrease ≥ 10 from M3 to M12 only	4	5	6
		-Imputed due to GL or death	21	17	23
		-Missing	7	4	5
		p-value	.0026	.1411	
	EBV-		(n=14)	(n=19)	(n=16)
		Composite endpoint	10 (71.4)	12 (63.2)	14 (87.5)
		Reason for meeting composite:			
		-M12 < 60 and Decrease ≥ 10 from M3 to 12	1	2	4
		-M12 < 60 only	7	6	7
		-Decrease ≥ 10 from M3 to M12 only	0	1	1
		-Imputed due to GL or death	1	2	1
		-Missing	1	1	1

Table 41
Acute Rejection at 12 months
By EBV Serostatus
IM103008 and IM103027

Study			Belatacept MI	Belatacept LI	CsA
008	**EBV+**	Acute Rejection	46/194 (23.7)	35/199 (17.6)	13/184 (7.1)
		Mild IA	7	4	1
		Mild IB	3	8	5
		Moderate IIA	15	12	5
		Moderate IIB	20	10	2
		Severe III	1	1	0
		Diff. from CsA (97.3% CI)	16.6 (8.1, **25.1**)	10.5 (2.7, **18.3**)	
	EBV-	Acute Rejection	3/25 (12.0)	4/27 (14.8)	3/37 (8.1)
		Mild IA	0	0	2
		Mild IB	0	0	0
		Moderate IIA	2	4	1
		Moderate IIB	0	0	0
		Severe III	1	0	0
027	**EBV+**	Acute Rejection	30/169 (17.8)	26/156 (16.7)	24/168 (14.3)
		Mild IA	0	3	1
		Mild IB	5	2	2
		Moderate IIA	10	16	16
		Moderate IIB	15	5	5
		Severe III	0	0	0
		Diff. from CsA (97.3% CI)	3.5 (-5.9, **12.9**)	2.4 (-7.1, **11.9**)	
	EBV-	Acute Rejection	3/14 (21.4)	5/19 (26.3)	2/16 (12.5)
		Mild IA	0	1	1
		Mild IB	2	0	0
		Moderate IIA	0	1	1
		Moderate IIB	1	3	0
		Severe III	0	0	0

Table 42
Calculated GFR
By EBV Serostatus
IM103008 and IM103027

Study			Belatacept MI	Belatacept LI	CsA
008	**EBV+**	Month 1	63.4 (23.4)* n=189	61.5 (23.1)* n=193	47.1 (19.2) n=177
		Month 3	62.5 (21.9)* n=183	63.7 (21.7)* n=185	50.0 (18.3) n=168
		Month 12	64.9 (23.4)* n=177	66.1 (20.6)* n=173	50.2 (20.7) n=169
		Month 24	65.2 (2.1)* n=167	66.3 (23.9)* n=175	48.0 (22.6) n=154
	EBV-	Month 1	65.2 (23.4) n=25	61.1 (33.1) n=27	52.6 (16.9) n=37
		Month 3	68.2 (25.9) n=24	62.8 (30.7) n=26	56.0 (22.1) n=33
		Month 12	67.6 (24.9) n=24	60.9 (34.5) n=27	49.6 (23.4) n=30
		Month 24	67.4 (23.9) n=24	59.5 (32.8) n=26	47.2 (25.6) n=28
027	**EBV+**	Month 1	40.4 (21.0)* n=168	39.9 (19.6)* n=154	31.6 (16.3) n=168
		Month 3	44.1 (22.9)* n=153	44.4 (21.4)* n=142	35.9 (20.) n=146
		Month 12	44.3 (22.8)* n=165	44.5 (21.8)* n=158	36.5 (21.1) n=159
		Month 24	43.8 (27.1)* n=141	43.2 (23.8)* n=141	34.3 (21.7) n=141
	EBV-	Month 1	47.5 (20.8) n=13	37.3 (16.5) n=19	33.5 (14.7) n=16
		Month 3	51.3 (17.6) n=13	42.6 (15.3) n=18	39.6 (18.8) n=15
		Month 12	47.8 (22.5) n=11	45.6 (25.7) n=16	43.2 (26.4) n=13
		Month 24	51.2 (22.7) n=10	39.3 (27.0) n=17	41.0 (19.6) n=13

Mean (standard deviation)
Number in analysis
* Comparison to CsA p<0.027 only reported for positive

Table 43
New Onset Diabetes Mellitus After Transplantation
By EBV Serostatus
IM103008 and IM103027

Study	EBV Status Recipient	Belatacept MI	Belatacept LI	CsA
008	EBV+	11/139 (7.9)	5/146 (3.4)	11/132 (8.3)
	EBV-	0/17	2/22 (9.1)	5/30 (16.7)
027	EBV+	2/119 (1.7)	7/121 (5.8)	9/108 (8.3)
	EBV-	1/13 (7.7)	0/15	2/10 (20.0)

Denominator is number of subjects with out diabetes at transplant

Table 44
Mean Blood Pressure at Month 12
By EBV Serostatus
IM103008 and IM103027

Study			Belatacept MI	Belatacept LI	CsA
008	EBV+	Systolic Blood Pressure	132.9 (16.1)* n=168	130.8 (16.6)* n=171	138.1 (19.6) n=157
		Diastolic Blood Pressure	79.2 (11.6) n=168	78.1 (11.0)* n=171	81.6 (11.0) n=157
	EBV-	Systolic Blood Pressure	130.8 (17.2) n=23	136.5 (15.6) n=22	141.9 (22.3) n=30
		Diastolic Blood Pressure	80.5 (11.2) n=23	83.0 (9.5) n=22	83.5 (11.6) n=30
027	EBV+	Systolic Blood Pressure	141.4 (21.6)* n=125	141.2 (21.4)* n=126	149.6 (20.1) n=115
		Diastolic Blood Pressure	77.8 (14.3)* n=125	78.1 (10.7)* n=126	82.1 (11.5) n=115
	EBV-	Systolic Blood Pressure	140.2 (19.2) n=11	138.0 (18.6) n=14	148.7 (16.1) n=9
		Diastolic Blood Pressure	78.6 (7.7) n=11	80.2 (10.0) n=14	78.2 (14.4) n=9

Mean (standard deviation)
Number in analysis
*comparison of mean value of belatacept regimen to CsA p-value<0.027 only reported for Positive

Table 45
Serum Lipids at Month 12
By EBV Serostatus
IM103008 and IM103027

Study			Belatacept MI	Belatacept LI	CsA
008	EBV+	Non-HLD cholesterol	132.1 (36.5)* n=169	133.2 (38.4) n=172	142.8 (47.6) n=158
		LDL cholesterol	101.6 (29.2) n=162	103.2 (33.2) n=164	107.5 (40.5) n=156
		Triglycerides	155.3 (85.1) n=162	151.6 (91.7)* n=164	176.1 (86.7) n=156
	EBV-	Non-HLD cholesterol	128.5 (39.3) n=23	119.0 (34.3) n=23	150.6 (46.2) n=31
		LDL cholesterol	94.5 (31.5) n=21	94.0 (34.9) n=22	106.6 (35.3) n=31
		Triglycerides	152.9 (61.0) n=21	133.4 (39.5) n=22	227.7 (170.7) n=31
027	EBV+	Non-HLD cholesterol	137.6 (47.3)* n=133	133.7 (41.6)* n=128	152.4 (47.2) n=122
		LDL cholesterol	107.0 (39.1) n=123	101.3 (37.4) n=121	109.5 (42.5) n=113
		Triglycerides	171.7 (124.7)* n=124	154.1 (69.7)* n=121	207.2 (117.5) n=113
	EBV-	Non-HLD cholesterol	115.5 (26.6) n=10	141.0 (36.1) n=14	160.3 (35.3) n=11
		LDL cholesterol	86.6 (29.1) n=10	112.6 (35.3) n=14	112.3 (17.0) n=11
		Triglycerides	144.0 (46.6) n=10	142.2 (39.3) n=14	253.6 (148.9) n=11

Mean (standard deviation)
Number in analysis
*comparison of mean value of belatacept regimen to CsA p-value<0.027 only reported for positive

Table 46
Patient and Graft Survival at 24 months
EBV-positive only
IM1030008

	Belatacept MI	Belatacept LI	CsA
Surviving with a functioning graft	180/194 (92.8)	189/199 (95.0)	162/184 (88.0)
Graft Loss	6 (1 died)	1	8 (1 died)
Death w/ functioning graft	6	7	11
Unknown status	2	2	3
Difference from CsA (97.3% CI)	4.8 (-2.4, 12.0)	7.0 (0.2, 13.8)	

Signature Page:

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STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125288   **Applicant:** Bristol-Myers Squibb Co. **Stamp Date:** June 30, 2009

Drug Name: Belatacept   **NDA/BLA Type:** Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	Phase III studies are 3 year studies. However, the primary time for assessing efficacy is 1 year.
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Cheryl A. Dixon   8/10/09
Reviewing Statistician   Date

Karen M. Higgin   8/10/09
Supervisor/Team Leader   Date