BRISTOL-MYERS SQUIBB COMPANY

Belatacept

Final Clinical Study Report for Study IM103010

Belatacept Conversion Trial in Renal Transplantation

Indication:	Renal Transplant
Phase:	2
Study Initiation Date:	12-Jan-2007
Study Completion Date:	Last 12-month visit 03-Jun-2009
Report Date:	08-Oct-2009
Document Control Number:	930039173
Previous Version(s) of this Report:	None

THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:

[redacted]

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Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient: Belatacept		

SYNOPSIS

Clinical Study Report for Study IM103010

TITLE OF STUDY: Belatacept Conversion Trial in Renal Transplantation

INVESTIGATORS/STUDY CENTERS: 34 investigators at 34 sites

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 12-Jan-2007 **CLINICAL PHASE:** 2

Study Completion Date: 03-Jun-2009

OBJECTIVES: The primary objective was to assess the effects of a belatacept-based immunosuppressive regimen relative to a CNI regimen on the change in calculated GFR (cGFR) from baseline to 12 months post-randomization.

Secondary objectives assessed the following effects in belatacept as compared with CNI-treated subjects:

- The incidence and severity of acute rejection (AR) at 6 and 12 months post-randomization
- The change in calculated GFR from baseline to 6 months
- The incidence of discontinuation of study medication or dose alteration due to declining renal function at 6 and 12 months
- The incidence of death and graft loss at 6 and 12 months
- The change in serum creatinine (SCr) from baseline to 6 and 12 months
- The incidence of new onset diabetes at 6 and 12 months
- The incidence of human leukocyte antigen (HLA) antibodies at baseline (randomization) and at 6 and 12 months
- Quality of Life (QoL) at baseline (randomization) and at 6 and 12 months
- Overall safety and tolerability of a belatacept-based immunosuppressive regimen

METHODOLOGY: This was a randomized, open-label, active-controlled, parallel-group study of renal transplant subjects on a CNI-based regimen, randomized to treatment with either belatacept or continued treatment with their established CNI. All subjects also received background maintenance immunosuppression with 1 of the following: mycophenolate mofetil (MMF) or mycophenolic acid (MPA), sirolimus (SRL), or azathioprine (AZA) with optional adjunctive corticosteroids, according to their immunosuppressive regimen at the time of enrollment. Doses of MMF, MPA, SRL, or AZA were to remain

stable throughout the study. Subjects who were receiving corticosteroids at the time of enrollment were to be maintained on a stable dose of corticosteroids during the next 12 months of the study unless a change in the medical condition of the subject warranted adjustment.

The duration of the study was 12 months with a subsequent 8-week follow-up period for safety evaluations. All subjects who completed the 12 month phase of the initial study, and met inclusion criteria and provided consent to continue, were eligible to participate in a long-term extension (LTE). Summaries of these data and by-subject listings of events are included in the body of this clinical study report (CSR). A future study report for the post-Month 12, LTE period will more completely describe these data.

NUMBER OF SUBJECTS (Planned and Analyzed):

Approximately 170 subjects on a CNI-based regimen (approximately equal numbers of subjects on TAC-based and on CsA-based regimens, with no more than 100 subjects on either agent) were to be randomized in a 1:1 ratio to treatment with either belatacept or continued treatment with their established CNI. One hundred and seventy-three subjects received a transplant and were treated in the 2 arms (belatacept 84; CNI 89).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

The study population included male and female (≥18 years of age) recipients of a renal allograft from a living donor or a deceased donor at least 6 months, but not longer than 36 months, prior to randomization. Subjects at low to moderate immunological risk were eligible. The study excluded subjects of greatest immunological risk as identified by prior graft loss due to AR, recent (< 3 months) AR, or Banff 97 Grade IIA or greater AR since transplantation of current allograft.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Subjects randomized to belatacept received IV belatacept 5 mg/kg on Days 1, 15, 29, 43, and 57, and then every 28 days thereafter.

The following belatacept batch numbers were used in the study: 4E82288, 6D19912, 6F11426, 6F11441, 6F11442, 6K16271, 7M23392.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

CsA doses were to be adjusted to maintain a range of trough serum concentrations of 100-250 ng/mL as determined by local laboratory assessment and methodology.

TAC was administered according to the package insert. TAC doses were to be adjusted to maintain a range of trough serum concentrations of 5-10 ng/mL as determined by local laboratory assessment and methodology.

CRITERIA FOR EVALUATION:

Efficacy: GFR at 3, 6, 9 and 12 months was calculated based upon SCr using the Modification Diet in Renal Disease (study) formula.

A subject was determined to have an episode of AR if either one of the following conditions (a) or (b) below was satisfied:

(a) the reason for clinical suspicion was reported to be any one of the reasons in Table 1 and the episode was a case of biopsy proven AR (AR of Banff histopathologic classification grade IA or higher as assessed by the blinded central pathologist)

(b) the reason for clinical suspicion was reported to be something other than those in Table 1, the episode was a case of biopsy proven AR, and the subject was treated for this episode.

Table 1: Criteria for Clinically Suspected AR

1. An unexplained rise of serum creatinine ≥ 25% from baseline creatinine
2. An unexplained decreased urine output
3. Fever and graft tenderness

Graft loss was defined as either functional loss or physical loss. Functional loss was defined as either:

- A sustained level of SCr ≥ 6.0 mg/dL (530 μmol/L) for ≥ 4 weeks as determined by the local laboratory
- Regularly scheduled dialysis treatments over a period of 56 days
- Impairment of renal function to such a degree that the subject undergoes retransplantation.

Safety: Safety assessments included AEs, clinically significant changes in vital signs, physical examination, and laboratory test abnormalities. The investigator determined the severity of each AE as mild, moderate, severe, or very severe. In addition, the investigator determined the relationship of the AE to the administration of the study drug.

Pharmacokinetics: Sparse pharmacokinetic (PK) samples were collected from all belatacept-treated subjects pre-dose at Weeks 4, 24, and 52. In addition, samples were collected 30 minutes after the end of infusion (EOI, 1 hour after start of infusion) at Week 20, and at the time of a suspected AR episode.

STATISTICAL CONSIDERATIONS: The primary objective was to estimate the effects of conversion from a CNI-based to a belatacept-based maintenance immunosuppression regimen on change in cGFR from baseline to 12 months post-randomization. The sample size was determined in order to provide a reasonable precision of the effect to be estimated. The estimate of the treatment effect was given by the mean difference of change from baseline to 12 months post-randomization between belatacept and CNI group. With 85 subjects per treatment group the half-width of a two-sided 95% confidence interval for the difference in mean changes in calculated GFR between the belatacept group and the CNI group was estimated to be 5.71 mL/min/1.73 m^2, assuming a standard deviation of 19 mL/min/1.73 m^2.

The proportion of subjects who had at least 1 AR up to Month 6 post-randomization was summarized within each treatment group using point estimates and the corresponding 95% CIs. Two-sided 95% CI was also generated for the difference between the belatacept-based regimen and CNI-based regimen. The severity of AR was summarized descriptively for each treatment group by Month 6 and Month 12.

The proportions of subjects surviving with a functioning graft by 6 and 12 months were summarized within each treatment group using point estimates and the corresponding 95% CIs. Two-sided 95% CIs were also generated for the difference between belatacept-based regimen and CNI-based regimen.

The proportion of subjects who died, the proportion of subjects who had a graft loss, and the proportion of subjects who died with a functioning allograft were all summarized by Months 6 and 12, using point estimates and 95% CI within each treatment group.

All AEs and SAEs, and marked laboratory abnormalities (MA) were descriptively summarized by treatment group.

The proportions of subjects who had anti-donor HLA antibodies at baseline, and by Months 6 and 12, were assessed using point estimates within each treatment group. The proportions of anti-donor HLA antibodies, stratified by subjects' AR status within Year 1, were also assessed. At baseline, subjects who had a non-missing test result were included in the analysis. For subsequent time points, subjects who had at least one

non-missing test result after baseline up to that time point were included in the analysis. Analyses were performed using data from the randomized (intent to treat, ITT) population.

ATP data were summarized using means and standard deviations. Differences between the 2 treatment regimens at various times were assessed using a two-way linear mixed effects model with a spatial-exponential covariance structure. The time by treatment interaction effect p-value was used to test whether there was a difference over time between the 2 arms of the trial. If this p-value was not significant, then a model without the time by treatment interaction was fit to test whether there was an effect of time.

Summary statistics were tabulated for the serum concentration of belatacept by study day.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

The number of subjects in each treatment group and their reasons for not completing 12 months of treatment are summarized in Table 2.

Table 2: Subject Disposition by Month 12

	Belatacept	**CNI**
Number randomized, N	84	89
Number randomized and not treated, N	1	1
Number discontinued treatment, N (%)	2 (2.4)	2 (2.3)
Death	0	1 (1.1)
Lack of efficacy	2 (2.4)	0
Other	0	1 (1.1)
Number continued treatment on or beyond Day 365	81 (97.6)	86 (97.7)

Baseline demographic characteristics were well balanced between treatment groups (Table 3).

Table 3: Baseline Demographic Characteristics

Parameter	Belatacept N = 84	CNI N = 89
Age (Years)		
Mean (SD)	45.3 (13.5)	44.3 (13.0)
Range	19.0 - 72.0	18.0 - 71.0
Gender, N (%)		
Male	66 (78.6)	60 (67.4)
Female	18 (21.4)	29 (32.6)
Race, N (%)		
White	44 (52.4)	53 (59.6)
Black or African-American	6 (7.1)	4 (4.5)
Asian	16 (19.0)	12 (13.5)
Native Hawaiian or Other Pacific Islander	1 (1.2)	1 (1.1)
Other	17 (20.2)	19 (21.3)
Geographic Region		
North America	28 (33.3)	25 (28.1)
South America	28 (33.3)	31 (34.8)
Europe	15 (17.9)	22 (24.7)
ROW (Asia/Pacific)	13 (15.5)	11 (12.4)
Previous Number of Transplants, N		
0	74 (88.1)	77 (86.5)
1	10 (11.9)	10 (11.2)
2	0	2 (2.2)

Baseline disease characteristics of the transplant donors were well balanced between treatment groups, including the cause of death in the deceased donors, baseline cGFR values, and the time from transplant to randomization. Approximately half of the transplants came from deceased donors. The number of human leukocyte antigen (HLA) mismatches between donor and recipient were similar and balanced between groups. The EBV status at baseline was balanced but there were more CMV-positive subjects in the CNI group than in the belatacept group.

Efficacy Results: At Month 12, the mean (SD) cGFR values were 60.5 (16.2) for belatacept and 56.5 (14.4) for the CNI group, with the mean change from baseline being 7.0 (12.0) and 2.1 (10.3) mL/min/1.73 m^2 (Table 4).

At Month 12 post-randomization, 6 subjects (7%) in the belatacept group had AR compared to none in the CNI group (Table 4). Blinded central pathology reading showed Banff grades of the episodes were 1 each for IA and IB, 3 for IIA, and 1 for IIB; there were no Grade III episodes.

All of the belatacept-treated subjects survived and had a functioning graft at Month 12. One subject in the CNI group died (due to a myocardial infarction [MI]) with a functioning graft. There were no functional graft losses reported in either treatment arm up to Month 12.

Table 4: Summary of Key Efficacy Results at Month 12

	Belatacept N = 84	CNI N = 89
Mean (SD) cGFR* with Imputed Values n subjects	60.5 (16.2) 82	56.5 (14.4) 87
Mean (SD) Change from Baseline in Imputed cGFR*	7.0 (12.0)	2.1 (10.3)
Mean (SD) cGFR* with Observed Values n subjects	60.5 (16.2) 82	57.1 (13.6) 86
Mean (SD) Change from Baseline in Observed cGFR*	7.0 (11.99)	2.6 (9.49)
Acute Rejection	6 (7.1)	0
Banff Grade, n (%)		
Mild Acute (IA)	1 (1.2)	0
Mild Acute (IB)	1 (1.2)	0
Moderate Acute (IIA)	3 (3.6)	0
Moderate Acute (IIB)	1 (1.2)	0
Severe Acute (III)	0	0
Subject and Graft Survival	84 (100)	88 (98.9)

*mL/min/1.73 m^2

Safety Results:

There was 1 death in this study through Month 12: a subject in the CNI group died (with a functioning graft) due to an MI on day 142.

Similar proportions of subjects had SAEs in each treatment group, and only 1 of these SAEs (belatacept group) resulted in study treatment discontinuation. The proportion of subjects with AEs was higher in the belatacept group; however, the proportion of subjects judged to have had related AEs was similar between groups (Table 5).

Table 5: Number (%) of Subjects with Adverse Events Up to Month 12; All Randomized and Treated Subjects

Event	Belatacept N = 83	CNI N = 88
Deaths	0	1 (1.1)
SAEs	20 (24.1)	17 (19.3)
Related SAEs	9 (10.8)	4 (4.5)
Discontinued due to SAEs	1 (1.2)	0
AEs	78 (94.0)	73 (83.0)
Related AEs	24 (28.9)	27 (30.7)
Discontinued due to AEs	1 (1.2)	0

Two subjects in the belatacept group and 2 subjects in the CNI group had malignancies reported up to Month 12. All subjects remained on-treatment. With the exception of 1 subject (belatacept group) with Kaposi's Sarcoma, all malignancies were non-melanoma skin cancer.

No subject had an event of post transplant lymphoproliferative disorder (PTLD).

The proportion of subjects with a viral infection through Month 12 was comparable for the 2 treatment groups (13% in both). The most frequent viral infection reported in both treatment arms was influenza (belatacept 4.8%, CNI 8%). CMV infection or viremia was reported in 2 subjects in each group; BK nephropathy was reported in 3 subjects in the belatacept group and none in the CNI group. One subject in the belatacept group had an SAE of polyomavirus-associated nephropathy and discontinued study drug. The subject continued in the study and the event was reported as continuing at data base lock.

There was a greater proportion of subjects with fungal infections in the belatacept group (13%) than in the CNI group (3%). Most were transient skin or oral infections; none were considered serious or resulted in discontinuation of study drug; and all were mild or moderate in severity.

I subject had an event of tuberculosis (belatacept group). The event resolved, no changes were made in belatacept dosing, and the subject continued in the study.

Peri-infusional events were reported in 16 (19%) belatacept-treated subjects. The most frequently reported event was hypertension in 6 subjects, due to worsened, pre-existing hypertension. None of the peri-infusional events resulted in treatment discontinuation and none were serious. The majority were transient and resolved with treatment, when given. Other than hypertension that was reported on Day 1 and 31 in 1 subject, no event occurred more than once in any given subject.

There were 3 belatacept subjects that had an acute peri-infusional event (ie, occurring within 1 hour of infusion); all were considered non-serious.

CONCLUSIONS:

- Conversion from a CNI to belatacept resulted in improved renal function.
- Conversion resulted in a rate of AR of 7%; all cases were mild or moderate in intensity.
- The safety experiences of subjects who remained on CNIs or converted to belatacept were similar.
- The study appeared to identify a suitable dose regimen for conversion from a CNI to belatacept.

DATE OF REPORT: 08-Oct-2009