BRISTOL-MYERS SQUIBB COMPANY

BELATACEPT

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:	10-Aug-2011
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:

[redacted]

Bristol-Myers Squibb
Princeton, NJ 08543
USA

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:		

SYNOPSIS

Clinical Study Report Addendum for Study IM103010

TITLE OF STUDY: Belatacept Conversion Trial in Renal Transplantation

INVESTIGATORS/STUDY CENTERS: 34 investigators at 34 sites

PUBLICATIONS: Rostaing L, Massari P, Garcia VD, et al. Switching from Calcineurin Inhibitor-based Regimens to a Belatacept-based Regimen in Renal Transplant Recipients: A Randomized Phase II Study. Clin J Am Soc Nephrol 2011.

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

Study Completion Date: 10-Aug-2011

OBJECTIVES:

Long-term safety and tolerability of belatacept in subjects who have completed 12 months of treatment in the main study and entered the long-term extension (LTE).

Efficacy, pharmacokinetics (PK), immunogenicity (which will be reported on separately) and patient-reported outcomes of belatacept.

METHODOLOGY:

Study IM103010 was a Phase 2 randomized, open-label, active-controlled, parallel-group study of renal transplant subjects (≥18 years of age), currently on a CNI-based immunosuppressive regimen (Cyclosporine A [CsA] and tacrolimus [TAC]) between 6 and 36 months post-transplant, who were randomized 1:1 to conversion to belatacept-based immunosuppressive regimen (84 subjects) or to continue treatment with CNI-based immunosuppressive regimen (89 subjects). All subjects received stable background maintenance immunosuppression and optional adjunctive corticosteroids. Subjects who completed the 12-month treatment period could participate in a long-term extension (LTE) phase. The primary objective was to assess the effects of a belatacept-based immunosuppressive regimen relative to a CNI regimen on the change in calculated glomerular filtration rate (cGFR) from baseline to 12 months post-randomization. This addendum presents the safety and efficacy results through Month 36 or to database lock (11-Aug-2011) for the subjects who enrolled in the LTE.

During the LTE, eligible subjects continued in their original treatment group assignment, so that subjects initially randomized to belatacept continued to intravenous (IV) belatacept (5 mg/kg) every 28 days. Subjects randomized to CNIs in the main study continued to receive their CNI-based regimen.

Subjects treated with CNI who had completed 12 months of treatment and entered the LTE were allowed to switch from their CNI to belatacept.

All subjects continued a background maintenance immunosuppressive regimen of mycophenolate mofetil (MMF), mycophenolic acid (MPA), sirolimus (SRL), or azathioprine (AZA), with or without adjunctive corticosteroids.

NUMBER OF SUBJECTS (Planned and Analyzed):

Of the 173 CNI subjects (76 on CsA and 97 on tacrolimus TAC) randomized 1:1 in the initial study, 84 were assigned to switch to belatacept (37 from CsA, 47 from TAC), and the other 89 subjects continued their baseline CNI (39 CsA, 50 TAC). After 12 months, 81 subjects in each group entered the LTE.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects who completed 12 months of treatment and consented entered the LTE.

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

Subjects randomized to belatacept received intravenous (IV) belatacept 5 mg/kg every 28 days. Batch numbers were: 0C60503; 0E56759; 0E61426; 4E82288; 6D19912; 6F11426; 6F11441; 6F11442; 6K16271; 7G27486; 7M23392; 7M23688; 9A99996; 9A99997; 9A99998; 9M37711.

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

Subjects randomized to CNI in the main study continued to receive their CNI-based regimen in accordance with local practice and the package insert.

CRITERIA FOR EVALUATION:

Safety assessments during the LTE included adverse events (AEs), clinically significant changes in vital signs, physical examination, and laboratory test abnormalities.

Efficacy variables included acute rejection (AR), graft loss and death, cGFR, lipids, new-onset diabetes mellitus (NODM).

In addition, PK and patient-reported outcomes were assessed.

STATISTICAL CONSIDERATIONS:

All analyses of efficacy and safety endpoints were summarized descriptively by treatment groups. No statistical testing was performed.

Efficacy measures were summarized for the ITT-LT population starting from the randomization (Day 1) unless specified otherwise.

The events of death, graft loss, and AR are defined as outcome measures of efficacy rather than safety variables.

All safety summaries were based on the ITT-LT population, starting from the first dose date after randomization, unless otherwise specified. The frequencies and incidence rates with exposure starting from the first dose after randomization were summarized by treatment groups up to the Month-36 database lock.

Datasets:

Intent-to-Treat (ITT) population: all patients randomized. The Month-12 primary efficacy analyses were performed on the ITT population. All Month-12 safety analyses were performed based on all randomized and treated subjects.

Intent-to-Treat-Long Term Extension (ITT-LT) population: all randomized and treated patients who completed 12 months of study treatment, consented to continue in the LTE, and received at least one dose of belatacept or CNI after 12 months post-randomization. Subjects were grouped according to the treatment to which they were randomized (belatacept or CNI), regardless of whether they later switched from CNI to belatacept. Subjects who discontinued treatment or died during the first 12 months post-randomization are not included in this population.

Intent-to-Treat-Switch from CNI to Belatacept (ITT-SW) population: ITT-LT subjects who converted from CNI to belatacept during the LTE. Subjects were grouped into one single treatment group, belatacept. Day of conversion is defined as the first belatacept infusion day.

PK analysis population: subjects who received at least one dose of belatacept.

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 1. A total of 16 subjects in the CNI group switched to belatacept during the LTE period.

Table 1: Subject Disposition by Database Lock

	Belatacept	CNI
Number of subjects who completed 12 months	81	86
Number of subjects entering LTE, N	81	81
Number discontinued treatment up to database lock, N (%)	3 (3.7)	11 (13.6)
Adverse event	1 (1.2)	2 (2.5)
Withdrawal of consent	0 (0.0)	4 (4.9)
Pregnancy	0 (0.0)	1 (1.2)
Administrative reason	0(0.0)	1 (1.2)
Death	1 (1.2)	0 (0.0)
Lack of efficacy	0 (0.0)	1 (1.2)
Other	1 (1.2)	2 (2.5)
Number continued treatment up to database lock, N (%)	78 (96.3)	70 (86.4)

Overall, the 2 treatment groups were balanced in baseline demographic characteristics (Table 2).

Table 2: Baseline Demographic Characteristics

Parameter	Belatacept N = 81	CNI N = 81
Age (years)		
Mean (SD)	45.0 (13.6)	44.0 (12.8)
Range	19.0 - 72.0	18.0 - 71.0
Gender, N (%)		
Male	64 (79.0)	54 (66.7)
Female	17 (21.0)	27 (33.3)
Race, N (%)		
White	43 (53.1)	46 (56.8)
Black or African-American	5 (6.2)	4 (4.9)
Asian	15 (18.5)	11 (13.6)
Native Hawaiian or Other Pacific Islander	1 (1.2)	1 (1.2)
Other	17 (21.0)	19 (23.5)

Table 2: Baseline Demographic Characteristics

Parameter	Belatacept N = 81	CNI N = 81
Geographic Region		
North America	27 (33.3)	24 (29.6)
South America	28 (34.6)	30 (37.0)
Europe	14 (17.3)	18 (22.2)
Asia/Pacific	12 (14.8)	9 (11.1)
Previous number of transplants, N		
0	71 (87.7)	71 (87.7)
1	10 (12.3)	9 (11.1)
2	0	1 (1.2)

Efficacy Results:

A summary of calculated GFR for the ITT-LT population is presented in Table 3. The cGFR analyses are based on imputed values.

Table 3: Summary of Calculated GFR (mL/min/1.73 $m^{2)}$ Based on Imputed Values at Specified Time Points (ITT-LT Subjects)

	Belatacept N = 81	CNI N = 81
Baseline		
N	81	81
Mean (SD)	53.2 (10.52)	55.0 (10.39)
Month 12 (Week 52)		
N	81	81
Mean (SD)	60.3 (16.15)	57.8 (13.57)
Change from baseline		
Mean (SD)	7.1 (12.02)	2.8 (9.70)
Month 24 (Week 100)		
N	81	77
Mean (SD)	62.0 (17.70)	55.4 (16.63)
Change from baseline		
Mean (SD)	8.8 (13.77)	0.3 (14.57)
Month 36 (Week 148)		
N	72	69
Mean (SD)	61.4 (19.77)	56.6 (18.71)
Change from baseline		
Mean (SD)	8.2 (16.13)	1.4 (16.88)

In the ITT-LT population, 8 ARs were reported up to Month 36: 5 with belatacept and 3 with CNI. Therefore, the rate of acute rejection was 5 of 81 subjects (6%; 4 subjects in the first 12 months and 1 subject from Month 12 to Month 36) for belatacept and 3 of 81 subjects (4%; all from Month 12 to Month 36) for CNI. All biopsies were confirmed by a blinded central pathologist. For belatacept, the readings

showed Banff grades of the episodes were IB -IIB. For CNI, Banff grades were IB - IIA (2 subjects). There were no Grade III episodes in either group.

Of the subjects with AR, 2 (1 in the belatacept group and 1 in the CNI group) had graft loss by Month 36. One subject had graft loss after Month 36.

By Month 36 (ITT-LT cohort), there were 4 cases of NODM in the belatacept group (7%) and 3 in the CNI group (5%). HbA1c values at Month 36 were similar between groups for those subjects with diabetes at baseline.

There were no clinically meaningful differences from baseline to Month 36 between belatacept and CNI with respect to serum lipids.

Subgroup Analyses (cGFR)

By baseline CsA or TAC: changes from baseline suggested that, over time, cGFR values increased more in the belatacept group than in the CNI group, regardless of initial CNI.

By baseline GFR: changes from baseline by baseline GFR suggested that, over time, cGFR values increased more in the belatacept group than in the CNI group, regardless of baseline GFR, most markedly in subjects with baseline GFR ≥45 ml/min/1.73 m^2.

By prerandomization diabetes status: In diabetics, changes in cGFR were similar between CNI and belatacept. In nondiabetics, cGFR changes from baseline were higher with belatacept than with CNI over Months 12, 24, and 36.

Safety Results:

From first dose after randomization to the Month-36 database lock (for the ITT-LT populations), there were 2 deaths, both in the belatacept group (Table 4) and both judged unrelated to treatment. The frequencies of serious adverse events (SAEs) were similar for belatacept and CNI (46% and 44%, respectively). Almost all subjects had an AE during the study (98% for belatacept and 95% for CNI). For belatacept, 43% of the AEs were judged related to treatment, compared with 51% for CNI. Three subjects discontinued because of an AE (2 for belatacept and 1 for CNI). The system organ class (SOC) with the highest frequency of adverse events for both groups (85% for belatacept and 72% for CNI) was Infections and Infestations. The next most common SOCs were Gastrointestinal Disorders (59% for belatacept and 52% for CNI), General Disorders/Administration Site Conditions (56% for belatacept and 37% for CNI), Metabolism and Nutrition Disorders (52% for belatacept and 47% for CNI), and Musculoskeletal Disorders (48% for belatacept and 26% for CNI). Most of the AEs were non-serious and did not lead to discontinuation.

Table 4: Number (%) of Subjects with Adverse Events Up to Database lock (ITT-LT Subjects)

Event	Belatacept N = 81	CNI N = 81
Deaths	2 (2.5)	0
SAEs	37 (45.7)	36 (44.4)
Related SAEs	15 (18.5)	13 (16.0)
Discontinued due to SAEs	2 (2.5)	1 (1.2)
AEs	79 (97.5)	77 (95.1)
Related AEs	35 (43.2)	41 (50.6)
Discontinued due to AEs	2 (2.5)	1 (1.2)

Up to the Month-36 database lock (ITT-LT population), the incidence rates for malignancy were 2.89/100 p-y for belatacept and 2.62/100 p-y. for CNI. No subject in either group had an event of post-transplant lymphoproliferative disorder.

Up to the Month-36 database lock (ITT-LT population), the frequency of infections was higher in the belatacept group than in the CNI group (85% vs 72% with incidence rates of 72.41/100 p-y and 42.72/10, respectively). However, the frequency of serious infections was similar for the 2 treatment groups (27% for belatacept and 28% for CNI). The incidence rate of serious infections was 9.02/100 p-y for belatacept and 9.58 /100 p-y for CNI. More subjects treated with belatacept had serious urinary tract infections (9%) than subjects treated with CNI (1%). Serious gastroenteritis was also more frequent with belatacept (6%) than with CNI (3%).

In the ITT-LT population, more subjects treated with belatacept had viral infections (36%) than subjects treated with CNI (27%) for an incidence rate of 12.60/100 p-y and 10.03/100 p-y, respectively. Herpes, cytomegalovirus (CMV) and polyoma infections occurred in more belatacept-treated subjects than CNI treated subjects (4.9%, 6.2%, and 3.7%, respectively, vs 2.5%, 2.5%, and 0). There was no additional case of serious viral infection between the Month-12 and Month-36 database lock for belatacept. There were 3 additional SAEs of serious viral infections in the CNI group (viral infection, viral infection of unknow etiology, and papilloma viral infection).

More subjects in the belatacept group (25%) had fungal infections than in the CNI group (7%), for incidence rates of 8.15/100 p-y and 2.32/100 p-y, respectively, for belatacept and CNI. Most fungal infections involved nails and skin and none was considered serious or resulted in discontinuation of study drug

No new cases of tuberculosis were reported (one subject had tuberculosis in the first 12 months of the study). Two subjects treated with belatacept experienced thrombotic events, both considered unrelated to study drug. Twenty-seven subjects in the belatacept group had an acute peri-infusional event. None of these events was considered serious or led to discontinuation from study drug. One subject in the study experienced an autoimmune disease, namely psoriasis, which occurred in the belatacept group. No laboratory test showed a proportion of subjects with markedly abnormal values above 10% in either treatment group.

Up to the Month-36 database lock (ITT-LT population), one subject in the belatacept group had congestive heart failure in the 13th month of treatment that was considered unlikely related to study therapy.

Quality of Life

At Month 36, no clinically meaningful differences were observed between belatacept and CNI in terms of the SF-36 subscale scores or the physical and mental component summaries.

Results in SW Population

The safety profile of belatacept in the 16 patients who switched from CNI to belatacept was generally consistent with that observed by the ITT-LT population. One of these 16 subjects had AR without graft loss after switching to belatacept.

Pharmacokinetic Results

The serum belatacept trough concentration data in the LTE period indicated that the exposure to belatacept was achieved as targeted, suggesting that belatacept PK are predictable in kidney transplant subjects switched from a CNI-based regimen to a belatacept-based regimen.

CONCLUSION:

During the long-term extension of this open-label Phase 2 study among stable kidney-transplant recipients, switching from CNI-based therapy to belatacept appears to be well tolerated and safe, although the rate of nonserious viral and fungal infections was higher with belatacept than with CNI. Furthermore, conversion from a CNI-based immunosuppressive regimen to a belatacept-based immunosuppressive regimen may

result in improvement in renal function that is sustained up to 36 months, which may help preserve allograft function and lead to better long-term outcomes.

DATE OF REPORT: 14-Feb-2012