BRISTOL-MYERS SQUIBB COMPANY

BELATACEPT

Closeout Clinical Study Report for Study IM103010

BELATACEPT CONVERSION TRIAL IN RENAL TRANSPLANTATION

Indication:	Renal Transplantation
Phase:	2
Study Initiation Date:	04-Jan-2007
Study Completion Date:	07-Jun-2013
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

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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: Nulojix®		
Name of Active Ingredient: belatacept		

SYNOPSIS

Closeout Clinical Study Report for Study IM103010

TITLE OF STUDY: Belatacept Conversion Trial in Renal Transplantation

INVESTIGATORS/STUDY CENTERS: 34 Investigators/34 sites

PUBLICATIONS:

Grinyo J, Alberu J, Contieri F, Manfro R, Mondragon G, Nainan, G, del C. Rial M, Steinberg S, Vincenti F, Dong Y, Thomas D, Kamar N. Improvement in Renal Function in Kidney Transplant Recipients Switched from Cyclosporine or Tacrolimus to Belatacept: 2-Year Results from the Long-Term Extension of a Phase II Study. Transplant International, European Society for Organ Transplantation 2012.

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: 04-Jan-2007 **CLINICAL PHASE:** 2

Study Completion Date: 07-Jun-2013

OBJECTIVES:

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

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 calcineurin inhibitor (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 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 closeout clinical study report (CSR) presents the safety and efficacy results through database lock for the subjects who enrolled in the LTE.

During the LTE, eligible subjects continued their original treatment group assignment (belatacept or CNI). Subjects on belatacept received the maintenance phase dose (5 mg/kg IV every 28 days). Subjects on CNI continued on their current dose. 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. Subjects on CNI were allowed to switch to belatacept after Month 24.

In October 2011, the CNI arm was discontinued after completing the Year-3 follow-up. If CNI subjects did not convert to belatacept, the subjects were removed from study participation.

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. A total of 38 subjects switched from CNI treatment to belatacept during 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; 1A65453; 1E64044; 1E64086; 2K71389; 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. The CNI arm was discontinued in October 2011.

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.

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.

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 final database lock.

Datasets:

Intent-to-Treat-Long Term Extension (ITT-LT) population: all randomized and treated subjects 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.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

The number of subjects in each treatment group and their reasons for not completing treatment are summarized in Table -1.

Table -1: Subject Disposition by Database Lock

	Belatacept	CNI	Total
Number of subjects who completed 12 months	81	86	167
Number of subjects entering LTE, N[a]	81	81	162
Number of subjects who discontinued treatment up to database lock, N (%)	11 (13.6)	17 (21.0)	28
Adverse event	1 (1.2)	5 (6.2)	6
Withdrawal of consent	4 (4.9)	7 (8.6)	11
Pregnancy	0 (0.0)	1 (1.2)	1
Lost to follow-up	1 (1.2)	0 (0.0)	1
Death	4 (4.9)	0 (0.0)	4
Lack of efficacy	0 (0.0)	2 (2.5)	2
Other	1 (1.2)	2 (2.5)	3
Number completed treatment up to database lock, N (%)	70 (86.4)	64 (79.0)	134

[a] 38 subjects randomized to CNI switched to belatacept during the LTE.

Overall, the baseline demographic characteristics were balanced across the 2 groups, as shown in Table -2. (The baseline demographic characteristic information was provided in the Month 36 CSR Addendum.)

Table -2: Baseline Demographic Characteristics

Parameter	Belatacept N = 81	CNI N = 81	Total
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)	118
Female	17 (21.0)	27 (33.3)	44
Race, N (%)			
White	43 (53.1)	46 (56.8)	89
Black or African-American	5 (6.2)	4 (4.9)	9
Asian	15 (18.5)	11 (13.6)	26
Native Hawaiian or Other Pacific Islander	1 (1.2)	1 (1.2)	2
Other	17 (21.0)	19 (23.5)	36
Geographic Region			
North America	27 (33.3)	24 (29.6)	51
South America	28 (34.6)	30 (37.0)	58
Europe	14 (17.3)	18 (22.2)	32
Asia/Pacific	12 (14.8)	9 (11.1)	21
Previous number of transplants, N			
0	71 (87.7)	71 (87.7)	142
1	10 (12.3)	9 (11.1)	19
2	0	1 (1.2)	1

Efficacy Results

In the ITT-LT population, 9 ARs were reported up to final database lock: 5 with belatacept and 4 with CNI. Therefore, the rate of AR was 5 of 81 subjects (6.2%; 4 subjects in the first 12 months and 1 subject from Month 12 to Month 36) for belatacept and 4 of 81 subjects (4.9%; all from Month 12 to Month 48) for CNI. All biopsies were confirmed by a blinded central pathologist. 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. The subject in the belatacept group had polyoma (BK) nephropathy, and was diagnosed with chronic renal failure. Dialysis therapy was instituted. For the subject in the CNI group, a renal allograft biopsy was performed and interpreted locally as showing moderate AR (Banff Grade IIA), chronic rejection, and severe tubular atrophy. Both subjects met the protocol-specified definition of functional graft loss since both of the subjects received dialysis for ≥ 56 days.

Safety Results:

The safety results are provided on the ITT-LT population from first dose (Day 1) after randomization through the final database lock. The exposure to belatacept was approximately 4.5 years.

For the ITT-LT population, there were 4 deaths in the belatacept group, and no deaths were reported in the CNI group (Table -3). The 4 subjects who died were randomized to the belatacept treatment group on Day 1. Two of the deaths occurred prior to Month 36 CSR Addendum database lock (11-Aug-2011), on days 794 and 1200 after approximately 3 years of belatacept treatment. The causes of death were reported as sudden death of unknown etiology and myocardial ischemia, respectively. The other 2 deaths occurred after approximately 4.5 years of belatacept treatment on days 1739 and 1851. The causes of death were reported as sepsis and brain abscess, respectively.

Serious adverse events (SAEs) occurred in 56% of subjects in the belatacept group compared to 49% in the CNI treatment group (Table -3). For AEs, the number of subjects who reported an AE was 98% for belatacept group and 95% for the CNI group.

The system organ class (SOC) with the highest rate of serious adverse events (SAEs) for both groups (26 subjects in the belatacept group, 24 subjects in the CNI group) was Infections and Infestations, with an incidence rate of 7.86/100 patient-years (p-y) for belatacept and 10.09/100 p-y for CNI.

Table -3: Number (%) of Subjects with Adverse Events Up to Database lock (ITT-LT Subjects)

Event	Belatacept N = 81	CNI N = 81	Total
Deaths	4 (4.9)	0	4
SAEs	45 (55.6)	40 (49.4)	85
Related SAEs	18 (22.2)	14 (17.3)	32
Discontinued due to SAEs	1 (1.2)	2 (2.5)	3
AEs	79 (97.5)	77 (95.1)	156
Related AEs	38 (46.9)	43 (53.1)	81
Discontinued due to AEs	1 (1.2)	3 (3.7)	4

- Eight subjects (10%) in the belatacept group, incidence rate of 2.05/100 p-y, and 9 subjects (11%) in the CNI group, incidence rate of 2.68/100 p-y, had a malignancy.
- No subject had an event of post-transplant lymphoproliferative disorder (PTLD).
- The frequency of serious infections for both treatment groups was the same at 32%. The incidence rate of serious infections was 7.85/100 p-y for belatacept and 8.83 /100 p-y for CNI. More subjects treated with belatacept had serious urinary tract infections (10%) than subjects treated with CNI (1%). Serious gastroenteritis was reported in 6% of belatacept subjects vs. 3% of CNI subjects.
- More belatacept-treated subjects had viral infections (40%) versus (vs.) subjects treated with CNI (32%), and the majority of events were reported for Infections and Infestations: 31 (38%) subjects in the belatacept group,

incidence rate of 9.99/100 p-y compared to subjects treated with CNI (21 [26%] subjects), incidence rate of 8.97/100 p-y. The most frequent viral infection in both treatment arms was influenza (belatacept 14%, CNI 12%, with incidence rates of 2.91/100 p-y and 3.83/100 p-y, respectively).

- The frequency of herpes virus infections was 14% for belatacept, incidence rate of 2.94/100 p-y, and 11% for CNI, incidence rate 3.40/100 p-y.
- The frequency for cytomegalovirus (CMV) viremia was 6.2% (incidence rate of 1.25/100 p-y) for belatacept and 0 for CNI. CMV infection was 3% for belatacept and 3% for CNI, with an incidence rate of 0.48/100 p-y and 0.72/100 p-y, respectively.
- Three belatacept-treated subjects (4%, incidence rate of 0.73/100 p-y) developed a polyoma virus infection. One of these subjects had apolyoma virus-associated nephropathy, considered very severe, and had subsequent graft loss. Two subjects had reported BK infections that were considered mild to moderate in intensity. No polyoma virus infections were reported in the CNI group.
- More subjects in the belatacept group (21 subjects, 26%) had fungal infections than in the CNI group (7 subjects, 9%), incidence rates of 6.20/100 p-y and 2.56/100 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.
- There were two SAEs of tuberculosis in the belatacept group (2.5%, incidence rate of 0.49/100 p-y), and no cases in the CNI group.
- Three belatacept subjects had thrombolic/embolic events (vs. none for CNI): two SAEs of arteriovenous fistula thrombosis and one AE of thrombophlebitis.
- Thirty-seven subjects (46%) had peri-infusional events (defined as any prespecified event reported within 24 hours after an infusion), and 5 subjects (6%) had an acute peri-infusional event (defined as events occurring within 1 hour after study drug infusion). The events reported included: eyelid oedema, pyrexia, arthralgia, headache and hypertension.
- Two subjects (3%) in the belatacept group had an event of reported for autoimmune diseases: one event was dry eye (1%, incidence rate of 0.24/100 p-y) and one event was psoriasis (1%, incidence rate of 0.24/100p-y). For the CNI group, 1 subject (1%) had an event of dry eye (0.35/100 p-y).
- Three subjects (4%) in the belatacept group and 2 subjects (3%) in the CNI group had a pulmonary edema event and/or a congestive heart failure event.
- No laboratory test showed a proportion of subjects with markedly abnormal values above 10% in either treatment group.

Results in SW Population

The safety profile of belatacept in the 38 subjects who switched from CNI to belatacept was generally consistent with that observed by the ITT-LT population.

CONCLUSIONS:

During the LTE of this open-label Phase 2 switch study in stable kidney-transplant recipients with an average exposure of approximately 4 and a half years, the safety of belatacept was consistent with the known profile and no new findings were identified. There are limitations of interpreting the study results due to the discontinuation of the CNI treatment arm and the decrease in the number of subjects over time in the control arm.

DATE OF REPORT: 05-Jan-2015