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 (12-Month Results) for Study IM103034

TITLE OF STUDY: A Randomized, Open-Label, Multicenter, Parallel-Group Study of Belatacept-Based Corticosteroid-Free Regimens in Renal Transplant

INVESTIGATORS/STUDY CENTERS: 24 investigators at 25 sites

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 11-Jul-2007 **CLINICAL PHASE:** 2
Study Completion Date: 04-May-2009
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INTRODUCTION: IM103034 assessed the safety and efficacy of different calcineurin-inhibitor (CNI)-free, corticosteroid-avoiding, belatacept-based immunosuppressive regimens in de novo kidney transplant recipients. The primary objective was to assess the rate of acute rejection (AR) by 6 months post-transplantation. Results for the primary objective were previously reported in the 6-month clinical study report (CSR). This CSR presents results at the 12-month time point for all secondary study objectives.

OBJECTIVES: The primary objective was to assess the rate of AR in different corticosteroid-avoiding, belatacept-based immunosuppressive regimens in de novo renal transplant subjects by 6 months post-transplantation.

Secondary objectives were:

- Severity, treatment, and outcome of AR by 6 and 12 months
- Incidence of death and graft loss by 12 months
- Incidence, severity, treatment, and outcome of AR by 12 months
- Incidence of composite endpoint AR, death, and graft loss by 6 and 12 months
- Incidence of metabolic and cardiovascular comorbidity (post-transplant diabetes mellitus [PTDM], dyslipidemias, hypertension) by 12 months
- Renal function (calculated glomerular filtration rate[cGFR]) at 12 months
- Proportion of subjects that remain corticosteroid-free at 12 months
- Incidence of discontinuation of study treatment by 12 months
- Overall safety of a belatacept-based corticosteroid-avoiding immunosuppressive regimen

METHODOLOGY: This was an exploratory, 1-year randomized, open-label, multicenter, parallel-group study. Approximately 90 subjects (n = 30 per group) who received de novo kidney transplants were to be randomized in a 1: 1: 1 ratio to either belatacept + MMF, or belatacept + sirolimus, or tacrolimus + MMF. All subjects received thymoglobulin as an induction agent and 4 associated doses of corticosteroids.

NUMBER OF SUBJECTS (Planned and Analyzed):

The planned enrollment was 90 subjects (30 per group for Bela-MMF, Bela-Siro, and Tac-MMF). The total randomized was 93 subjects (35, 27, and 31, respectively). The total transplanted and treated was 89 subjects (33, 26, and 30, respectively).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

The study population comprised adult, Epstein-Barr virus (EBV)-positive recipients of a renal allograft from a living donor or a deceased donor. Subjects at low to moderate immunological risk were eligible for enrollment. The study excluded subjects of greatest immunological risk as identified by pre-transplant panel-reactive antibodies (PRA) of ≥ 50% or prior graft loss due to AR.

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

All subjects received induction with thymoglobulin at a dose of 1.5 mg/kg for 4 days and 4 corresponding doses of corticosteroids.

Belatacept-MMF: Subjects randomized to belatacept received IV belatacept (10 mg/kg) on Days 1 and 5, and then every other week through Month 3 (Weeks 2, 4, 6, 8, 10, and 12), and then every 4 weeks through Month 6 (Weeks 16, 20, and 24). After 6 months, subjects received belatacept at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial at 12 months. MMF was given 1 g BID. This dose regimen was selected based on the More Intense (MI) regimen being used in ongoing Phase 2 and 3 studies of belatacept.

Belatacept-Siro: Belatacept was administered as described above. Sirolimus was initiated at 5 mg/day on Day 1 (day of transplant) and continued through Day 2. The dosing was adjusted subsequently to keep pre-dose (C_0) levels at 7 to 12 ng/mL for the first 6 months, followed by 5 to 10 ng/mL thereafter.

Batch numbers of study drug are listed in Table 1.

Table 1: Batch Numbers of Study Drug

Belatacept	MMF	Sirolimus	Tacrolimus	Thymoglobulin
6F11441	7B28459	7B28911	0D5196B	7B29517
6F11442	7F31553	7G30704	7B28461	7F31059
6K16271	7G28317	7K29247	7B28462	8B39394
7M23688	7H24239	8C46068	7G21580	8B43491
7M23392	7J21762	D15354	7G21597	-
-	7J31127	-	7J25569	-
-	7L24378	-	7L31782	-
-	8C36418	-	7L31851	-
-	M1163B0	-	8B43856	-
-	U1096	-	8C43084	-

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

All subjects received induction with thymoglobulin at a dose of 1.5 mg/kg for 4 days and 4 corresponding doses of corticosteroids.

Tac-MMF: The recommended total initial dose of tacrolimus was 0.1 mg/kg/day in 2 divided doses orally. Tacrolimus could be initiated any time within 24 hours post-transplantation or when renal function showed acceptable improvement; i.e., the serum creatinine (SCr) concentration decreased to 4 mg/dL in the absence of dialysis. The initial targeted trough level of tacrolimus was 8 - 12 ng/mL for Days 1 through 30 with dose reduction to achieve a 12-hour trough target of 5 - 10 ng/mL thereafter. MMF was given at a dose of 1 g BID. Batch numbers are listed in the table, above.

CRITERIA FOR EVALUATION:

Efficacy: The incidence of AR by Month 6 was assessed when rejection was clinically suspected as specified by the protocol and confirmed by a central histopathologist using the Banff 97 working classification of kidney transplant pathology.

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 had to undergo retransplant.

Glomerular filtration rate (GFR) was calculated based upon SCr using the Modification Diet in Renal Disease (study) formula.

Safety: Safety was assessed by the review of adverse events and laboratory test results.

Pharmacokinetics: Trough concentrations of belatacept were determined and summarized over time.

Pharmacodynamics: An exploratory determination of the co-stimulation blockade biomarker, CD86 receptor occupancy was evaluated over time using a CD86 receptor competition assay in peripheral blood in subjects receiving belatacept only. Results for anti-donor human leukocyte antigen (HLA) antibodies and leukocyte phenotyping are also reported.

STATISTICAL CONSIDERATIONS:

AR was summarized within each treatment group using point estimates of the proportion of subjects who had at least 1 AR up to Month 12 and the corresponding 95% confidence intervals (CIs). In addition, 2-sided 95% CIs were also generated for the difference between each of the belatacept regimens and tacrolimus. The upper 95% CI bounds excluded a 30% rate of rejection with either belatacept regimen, a rate that would have been considered unacceptable on clinical grounds.

Subject and graft survival by 12 months were summarized using the similar method as for the incidence of AR. Point estimates of the proportion of subjects who survived with functioning grafts by 12 months for each treatment group and the corresponding 95% CIs were provided. Two-sided 95% CIs were also generated for the differences between each of the belatacept regimens and tacrolimus.

Calculated GFR at various time points post-transplant and changes from Month 3 to Month 12 were summarized by treatment group.

All adverse events (AEs) and serious adverse events (SAEs) were summarized by treatment group by 12 months. Laboratory marked abnormalities were also descriptively summarized.

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 with belatacept or tacrolimus are summarized in Table 2. Subjects who were unable to tolerate MMF or sirolimus could switch to the alternative background immunosuppressant. Two subjects in the Bela-MMF (none in the Tac-MMF group) discontinued MMF and switched to sirolimus. Ten subjects in the Bela-Siro group discontinued sirolimus and switched to MMF. The total number of subjects who discontinuation from any part of the protocol-prescribed regimen (belatacept, tacrolimus, MMF or sirolimus) was 8 (24%), 12 (46%), and 2 (7%) subjects in the Bela-MMF, Bela-Siro, and Tac-MMF groups, respectively.

Table 2: Reasons for Treatment Discontinuation after Randomization and Transplantation Up to Month 12

Reason	Bela-MMF[a] N = 33	Bela-Siro[b] N = 26	Tac-MMF N = 30
Number (%) discontinued belatacept or tacrolimus	6 (18.2)	5 (19.2)	2 (6.7)
Adverse event	2 (6.1)	5 (19.2)	0
Withdrew consent	0	0	1 (3.3)
Lack of efficacy	4 (12.1)	0	0
Unknown	0	0	1 (3.3)

[a] 2 additional subjects discontinued MMF and switched to sirolimus

[b] 10 additional subjects discontinued sirolimus and switched to MMF

The majority of subjects were white, male, and age 46 to 65 years (Table 3). Subjects were well balanced across treatment groups with respect to age and gender. There were more black or African-American subjects in the Bela-MMF group compared with the other 2 groups.

Table 3: Baseline and Demographic Characteristics

Parameter	Bela-MMF N = 33	Bela-Siro N = 26	Tac-MMF N = 30
Age (Years)			
Mean (SD)	49.2 (11.1)	52.7 (10.8)	53.6 (13.2)
Range	24 - 65	25 - 69	23 - 70
Gender, N (%)			
Male	25 (75.8)	20 (76.9)	22 (73.3)
Female	8 (24.2)	6 (23.1)	8 (26.7)
Race, N (%)			
White	24 (72.7)	23 (88.5)	23 (76.7)
Black or African-American	8 (24.2)	3 (11.5)	5 (16.7)
American Indian/Alaskan Native	0 (0.0)	0 (0.0)	1 (3.3)
Asian	1 (3.0)	0 (0.0)	1 (3.3)
Geographic Region			
North America	22 (66.7)	16 (61.5)	20 (66.7)
Europe	11 (33.3)	10 (38.5)	10 (33.3)

Baseline disease characteristics of the transplant donors were balanced across treatment groups. The cause of death in the deceased donors, the most recent SCr value, and the type of transplant were generally balanced across the treatment groups. Approximately half of the transplants came from deceased donors. The cold ischemia time was similar across treatment groups. All subjects were EBV positive as required by the protocol. Nearly half of all subjects were cytomegalovirus (CMV) positive, with a lower proportion of subjects in the Bela-MMF group being positive.

Efficacy Results:

Following randomization, subjects were monitored for graft and vital status and some key safety events, regardless of whether study treatment had been discontinued. This information was collected for every subject through Month 12.

At Month 6, AR was reported for 4 subjects in the Bela-MMF group, 1 in the Bela-Siro group, and 1 in the Tac-MMF group (Table 4). At Month 12, AR was reported for 1 additional subject in the Bela-MMF group. The proportion of subjects who were alive with a functioning graft at Month 12 was 91%, 92%, and 100% in the Bela-MMF, Bela-Siro and Tac-MMF groups, respectively.

Mean calculated GFR was 8 to 10 mL/min higher in the belatacept groups than in the Tac-MMF group. The proportion of subjects who were steroid-free was 73%, 77%, and 93% in the Bela MMF, Bela-Siro, and Tac-MMF groups, respectively. The proportion of subjects who were both CNI- and steroid-free was 73% and 69% in the belatacept groups, respectively.

Table 4: Summary of Key Efficacy Outcomes

	Bela-MMF N = 33	**Bela-Siro N = 26**	**Tac-MMF N = 30**
AR at Month 6, N (%)	4 (12.1)	1 (3.8)	1 (3.3)
Difference from tacrolimus, % (95% CI)	8.8 (-6.6, 24.9)	0.5 (-14.5, 16.7)	---
AR at Month 12, N (%)	5 (15.2)	1 (3.8)	1 (3.3)
Difference from tacrolimus, % (95% CI)	11.8 (-4.1, 28.7)	0.5 (-14.5, 16.7)	---
Subject and graft survival at Month 12, N (%)	30 (90.9)	24 (92.3)	30 (100)
Difference from tacrolimus, % (95% CI)	-9.1 (-23.6, 2.8)	-7.7 (-24.1, 4.1)	---
AR, death, or graft loss by Month 12, N (%)	7 (21.2)	3 (11.5)	1 (3.3)
Calculated GFR mL/min/1.73 m^2 at Month 12, mean (SD)	63.6 (27.3)	61.8 (30.7)	54.0 (15.0)
Steroid-free at Month 12, N (%)	24 (73)	20 (77)	28 (93)
CNI- and steroid-free at Month 12, N (%)	24 (73)	18 (69)	1 (3)

GFR = glomerular filtration rate, SD = standard deviation, CI = confidence interval

Safety Results:

All subjects had at least 1 AE by Month 12. The frequency of SAEs was higher in the Bela-Siro group (62%) compared with the Bela-MMF and Tac-MMF groups (58% and 53%, respectively). Few SAEs resulted in study treatment discontinuation. The frequency of AEs leading to treatment discontinuation by Month 12 was higher in the Bela-Siro compared with the Bela-MMF group (19.2% vs 12.1%, respectively) and was higher in both belatacept groups compared with the Tac-MMF group (0 subjects) One death was reported in this study through 12 months of follow-up: a subject in the Bela-MMF group died of pneumonia

and related complications on Day 21 (received 3 doses of belatacept). AEs judged to be at least possibly related to study drug by the investigator were reported with similar frequency across the 3 treatment groups.

Table 5: Summary of Subjects with Adverse Events Reported after Randomization Up to Month 12: All Randomized and Transplanted Subjects (ITT)

	Number of Subjects (%)		
Event	**Bela-MMF N = 33**	**Bela-Siro N = 26**	**Tac-MMF N = 30**
Deaths	1 (3.0)	0	0
SAEs	19 (57.6)	16 (61.5)	16 (53.3)
Related SAEs	6 (18.2)	3 (11.5)	5 (16.7)
Discontinued due to SAE	4 (12.1)	2 (7.7)	0
AEs	33 (100.0)	26 (100.0)	30 (100.0)
Related AEs	21 (63.6)	19 (73.1)	23 (76.7)
Discontinued due to AE	4 (12.1)	5 (19.2)	0

Note: Related AE or SAE defined as certain, probable, possible or missing

Malignant neoplasms were reported for 2 subjects (1 Bela-Siro, 1 Tac-MMF). The belatacept-treated subject had facial skin cancer and right ear skin cancer, with an onset at Week 10, judged unrelated to study treatment. The Tac-treated subject had squamous cell carcinoma of the forehead, judged mild but possibly related to study drug and subsequently had malignant melanoma in situ.

Four (12%), 2 (8%), and 6 (20%) subjects in the Bela-MMF, Bela-Siro, and Tac-MMF groups, respectively, had at least 1 viral infection reported through Month 12. None of the viral infections resulted in discontinuation of study treatment.

Fungal infections were reported for 8 subjects through 12 months of treatment (5, 15.2% Bela-MMF, 1, 3.8% Bela-Siro, and 2, 6.7% Tac-MMF). All were mild, non-serious mucosal or skin infections, except for SAEs of meningococcal/fungal meningitis in 1 subject. None resulted in study drug discontinuation, including the meningitis.

No subject had an acute peri-infusional event (i.e., any one of a prespecified list) that occurred within 1 hour of an infusion). Peri-infusional events (i.e., any pre-specified AE reported from 0 to 24 hours after the end of IV study drug) were reported in the majority of subjects in the 2 belatacept treatment groups: 21 (64%) in the Bela-MMF group and 21 (81%) in the Bela-Siro group. None of the peri-infusional events resulted in treatment discontinuation and only 1 event, pyrexia, was serious.

Nearly all subjects in the study had lymphocyte counts below the normal range at some point during treatment. Low hemoglobin at Month 12 was reported for 12%, 27%, and 10% in the Bela-MMF, Bela-Siro, and Tac-MMF groups, respectively. The proportions with white blood cell counts below normal range were 8% to 12% across all treatment groups.

Pharmacokinetic Results: The geometric mean trough serum concentrations (Cmin) of belatacept were consistent with those previously reported for the dose regimens of belatacept.

Pharmacodynamic Results: On Day 5 following the initial 10 mg/kg infusion of belatacept, the CD86 receptors appeared to be nearly fully saturated (minimum saturation ~94%). The receptor saturation decreased slightly as the interval between dosing increased. At Weeks 2, 4, 12, 24 and 52, the pre-infusion mean receptor saturations observed were approximately 88, 86, 75, 67, and 65%, respectively, likely due to

lower belatacept concentrations at these time points. No differences were observed between the 2 belatacept treatment groups with respect to changes in free and total CD86 receptor expression.

Following transplantation and thymoglobulin treatment, total T cells, CD4+ T cells, CD8+ T cells, and NK cells were markedly decreased (> 10-fold) in all treatment groups on Day 5. The Bela-Siro subjects appeared to recover their total T cell, CD4+ T cell, and CD8+ T cell numbers more slowly than subjects in the other 2 groups. The NK cells appeared to recover in all groups at approximately the same rate. In contrast, B cells were not dramatically affected by the thymoglobulin treatment in any group as decreases were <2-fold on Day 5 and levels appeared to recover completely by the end of the study.

Six subjects tested positive for anti-donor HLA antibodies at any time during the study. Two of these subjects, 1 in the Bela-MMF group and 1 in the Tac-MMF group, tested positive at baseline for anti-donor HLA antibodies and both continued to test positive through Month 12. Following transplantation, 4 subjects in the Bela-MMF group who were negative at baseline subsequently tested positive for anti-donor HLA antibodies at or before Month 6.

CONCLUSIONS:

This exploratory study in a small number of subjects, evaluating CNI-free, steroid-avoiding, belatacept-based regimens for 12 months, suggests the following:

- Belatacept may enable CNI-free and steroid-avoiding immunosuppression in recipients of living and deceased standard criteria donor kidneys, with acceptable rates of AR. The rate of AR was somewhat greater with a belatacept-MMF regimen than with a tacrolimus-MMF regimen at 6 months. There was some suggestion of better renal function with the belatacept-based regimen at Month 12.
- Based on rates of discontinuation of the protocol-prescribed regimen, the belatacept-MMF regimen may be better tolerated than a belatacept-sirolimus regimen.
- The belatacept dosing regimens showed no important differences compared with the tacrolimus-based regimen for metabolic and cardiovascular comorbidity (post-transplant diabetes mellitus, dyslipidemias, and hypertension) by Month 12.
- Belatacept dosing regimens used in this study provided sufficient levels of drug to fully saturate the target initially and maintained relatively high saturation thereafter.

Longer-term follow-up is ongoing to help determine whether the effects and safety profile are sustained.

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