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

Final Clinical Study Report: Study IM103045

TITLE OF STUDY: Evaluation of Belatacept as First-line Immunosuppression in De Novo Liver Transplant Recipients

INVESTIGATORS/STUDY CENTERS: Subjects were enrolled at 39 sites worldwide

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 22-Jan-2008 (First Subject First Visit)

Study Completion Date: 22-Jul-2010 (Last Subject Last Visit for Month 12)

CLINICAL PHASE: 2

OBJECTIVES:

Primary Objective - To evaluate the effects of belatacept, relative to tacrolimus, on the incidence of acute rejection (AR), graft loss and death by 6 months in subjects receiving an orthotopic liver transplant (OLT).

Key Secondary Objectives - To evaluate the effects of belatacept relative to tacrolimus, on:

- The composite of subject and graft survival by 6 and 12 months
- The triple composite of AR, graft loss and death by 12 months
- Incidence, severity, treatment and outcome of AR by 3, 6 and 12 months
- Change in renal function over time
- Pharmacokinetic (PK) characteristics of belatacept
- Incidence of Hepatitis C virus (HCV) recurrence by 6 and 12 months
- Incidence of metabolic and cardiovascular comorbidity (post-transplant diabetes mellitus [PTDM], dyslipidemia, hypertension) by 12 months
- Overall safety of belatacept based regimens

METHODOLOGY: Randomized, partially blinded, active-controlled, parallel-group, multi-center clinical trial. The trial was fully blinded with respect to belatacept dosing regimen [More Intensive (MI) or Less Intensive (LI)] and basiliximab assignment, open-label with respect to allocation to belatacept or tacrolimus and open-label between the two tacrolimus groups.

Subjects were randomized (stratified by HCV-infection status) in equal numbers to the following groups:

Group 1): Basiliximab + Belatacept (MI) + MMF (mycophenolate mofetil)

Group 2): Belatacept (MI) + MMF

Group 3): Belatacept (LI) + MMF

Group 4): Tacrolimus + MMF

Group 5): Tacrolimus

For the first 45 subjects randomized to receive belatacept, intensive PK samples were collected for full characterization of belatacept PK at 10 mg/kg. Blood samples were collected between Weeks 12 and 16 at pre-dose, 30 minutes after the end of infusion, and at 1, 7, 14, 21, and 28 days following the Week 12 infusion. In addition, PK samples were collected at 96 hours post-dose on Day 9, to provide exposure information during post-transplant period. For Cmax evaluation, post-infusion (30 minutes after end of infusion) samples were collected on Days 1 and 5 and Weeks 12, 16, 28 and 48. As a part of PK sampling schedule from all subjects randomized to receive belatacept, pre-dose (trough) samples were collected on Day 5 and Weeks 2, 4, 8, 12, 16, 24, 36, 48 and 52. In Years 2 and 3, PK samples are to be collected every 6 months.

Ascites fluid was collected for a maximal duration of 2 weeks, when available.

NUMBER OF SUBJECTS: Of the 260 randomized subjects, 250 received a liver transplant (Intent-to-treat [ITT] population). All 250 randomized and transplanted subjects were treated.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

1) First time recipient of a primary de novo orthotopic liver allograft from a deceased donor
2) Male or female (not nursing, not pregnant) subjects ≥ 18 years of age
3) Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 56 days after the last dose of investigational product in such a manner that the risk of pregnancy is minimized.
4) Willing to provide signed, written informed consent

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Belatacept was administered over 30 minutes via intravenous (IV) infusion according to the following regimens (Day 1 was the day of transplant):

More Intensive (MI) regimen: Patients received 10 mg/kg on Days 1, 3 and 5, and at Weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24. After 6 months (Week 24), subjects received a maintenance dose of 5 mg/kg every 4 weeks through the completion of the trial at 12 months.

Less Intensive (LI) regimen: Patients received 10 mg/kg on Days 1, 3 and 5, and at Weeks 2, 4, 8 and 12. After 3 months (Week 12), subjects received a maintenance dose of 5 mg/kg every 4 weeks through the completion of the trial at 12 months. Blinding between the LI and MI groups was preserved with the use of placebo infusions in the LI treatment group at Week 6 and Week 10.

For subjects in both the MI and LI regimens who experienced significant blood loss (> 3L) and/or drainage of ascites (> 4L) during the intraoperative and the postoperative period between Day 1 (day of transplant) and Day 14, one additional 10 mg/kg dose of belatacept was to be administered. This dose was to be held if a scheduled dose was due for administration within 24 hours.

The following batches of belatacept were used in this study: 6F11441, 6F11442, 6K16271, 6K20505, 7M23392, 7M23688, 8B41775, 9A99996, 9A99998, 9A99999, and 9M37711.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Subjects randomized to tacrolimus (Groups 4 and 5) received oral tacrolimus twice daily (bid). The initial dose was given no sooner than 6 hours post transplant, but no later than Day 7 to achieve a stable 12-hour trough level of 6 - 12 ng/mL.

INDUCTION THERAPY: Subjects in Group 1 received basiliximab (20 mg IV) on Day 1 and Day 5. Groups 2 and 3 received 2 respective placebo infusions.

ADJUVANT THERAPY: Subjects in Groups 1, 2, 3 and 4 received MMF, starting at 1 g bid (i.e., a total of 2 g daily) starting on Day 1. MMF was reduced after 3 months. All subjects received corticosteroids that could be tapered or discontinued after Month 3 according to institutional practice.

CRITERIA FOR EVALUATION:

Efficacy: The primary endpoint was the incidence of AR, graft loss and death by 6 months post transplantation. Any AR that was clinically suspected and biopsy proven (by central pathologist) was included in the primary endpoint. All biopsies for suspected AR were assessed by a blinded central histopathologist using the Banff schema for grading of liver transplant rejection and rejection activity index (RAI) for staging. Graft loss was defined as impairment of liver function to such a degree that the subject died or underwent re-transplantation.

Secondary efficacy endpoints included subject and graft survival, AR, renal function, HCV recurrence, and metabolic and cardiovascular endpoints. Renal function was evaluated via the assessment of measured glomerular filtration rate (GFR), calculated GFR, serum creatinine (SCr) and serum cystatin C. Measured GFR was assessed using a true measure of glomerular filtration via iothalamate clearance test. Calculated GFR was calculated based upon SCr using the Modification of Diet in Renal Disease (MDRD) formula.

HCV recurrence was defined as histologic confirmation on liver biopsy by the Ishak (modified Knodell) system and required both a score of ≥ 5 out of a total of 18 on modified Histological Activity Index (HAI) grading and a Fibrosis Score (FS) ≥ 2 out of 6 on modified staging.

Safety: Safety endpoints included the frequency of adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs, as well as results for electrocardiogram (ECG) abnormalities, clinically significant changes in vital signs, physical examination, laboratory test abnormalities, and neurologic assessment. 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: PK parameters (Cmax, Cmin, Tmax, AUC(TAU), T-HALF, CLT, and Vss) were derived from serum concentration versus time data between Weeks 12 (Day 84) and 16 (Day 112). Additional Cmax and Cmin concentrations were collected at designated time points on other study days. Amount of belatacept excreted in ascites fluid (Ae, asc) was estimated from the ascites drug concentrations and volumes within a collection interval.

STATISTICAL CONSIDERATIONS (Primary and Key Secondary Endpoints):

The proportion of subjects with the triple composite endpoint of AR, graft loss and death by 6 months was summarized within each treatment group using point estimates and corresponding 95% CIs. The proportion included all subjects who experienced at least one episode of AR, graft loss, or death up to Month 6. Similar methods were used to summarize this composite endpoint by Month 12.

Subject and graft survival was summarized within each treatment group using point estimates of the proportion of subjects surviving with a functioning graft and corresponding 95% CIs. The proportion of subjects who died, the proportion of subjects who experienced graft loss, and the proportion of subjects who died with a functioning allograft by 6 months were also summarized. Similar methods were used to summarize this composite endpoint at Month 12.

The incidence of AR by Months 3, 6, and 12 was summarized within each treatment group using point estimates and corresponding 95% CIs. The proportion included all subjects who had at least one AR episode. The primary analysis of the incidence of AR utilized the Banff grading by the central histopathologist.

For each of the above endpoints, two-sided 95% CIs, adjusted for stratification [HCV-infection status (yes/no)], were also generated for the difference between each of the belatacept treatment groups and each of the tacrolimus treatment groups.

Summary statistics were tabulated for the PK parameters. To assess the attainment of steady state, geometric mean Cmin were plotted by study day.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics: A total of 250 randomized subjects received a liver transplant (ITT population). All 250 randomized and transplanted subjects were treated, of whom 164 completed 12 months of treatment (62%, 60%, and 53% of the subjects in the basiliximab + belatacept MI, belatacept MI, and belatacept LI groups and 87% and 64% of the subjects in the tacrolimus + MMF and tacrolimus groups, respectively). In the belatacept groups, the most common reasons for discontinuing treatment were AE and lack of efficacy. In the tacrolimus groups, all treatment discontinuations were due to AEs.

Baseline demographics of transplant recipients were generally similar across treatment groups (Table 1).

Baseline pre-transplant and disease characteristics of transplant recipients were generally similar across treatment groups. The mean Model for End-Stage Liver Disease (MELD) score in each group was between 21 and 24 and the most common cause of end-stage liver disease (ESLD) was non-cholestatic cirrhosis. Few subjects entered the study with hepatorenal syndrome. Hypertension and diabetes were common in the study population.

Table 1: Baseline Demographic Characteristics of Transplant Recipients - All Randomized and Transplanted Subjects (ITT)

Baseline Characteristics	Basi + Bela MI + MMF (N=50)	Bela MI +MMF (N=48)	Bela LI + MMF (N=49)	Tac + MMF (N=53)	Tac (N=50)
Mean Age, years	54.0	53.4	55.2	53.0	54.7
Gender (n, %)					
Male	39 (78.0)	34 (70.8)	31 (63.3)	46 (86.8)	42 (84.0)
Female	11 (22.0)	14 (29.2)	18 (36.7)	7 (13.2)	8 (16.0)
Race (n, %)					
White	44 (88.0)	40 (83.3)	46 (93.9)	49 (92.5)	43 (86.0)
Black/African American	4 (8.0)	3 (6.3)	1 (2.0)	3 (5.7)	2 (4.0)
American Indian/ Alaska Native	0	1 (2.1)	0	0	0
Asian	1 (2.0)	0	2 (4.1)	0	0
Other	1 (2.0)	4 (8.3)	0	1 (1.9)	5 (10.0)
Ethnicity (n, %)					
US-Hispanic or Latino	5 (10.0)	7 (14.6)	3 (6.1)	3 (5.7)	4 (8.0)
US-Not Hispanic or Latino	28 (56.0)	16 (33.3)	11 (22.4)	22 (41.5)	23 (46.0)
Not applicable[a]	17 (34.0)	25 (52.1)	35 (71.4)	28 (52.8)	23 (46.0)

[a] Ethnicity data collected in compliance with the 2005 Food and Drug Administration (FDA) Guidance for Industry for subjects enrolled in the United States (US) only.

Note: basiliximab, belatacept, and tacrolimus are abbreviated Basi, Bela, and Tac, respectively, in all table header rows.

Extent of Exposure: The mean duration of exposure to belatacept up to Month 12 was 262, 251, and 239 days in the basiliximab + belatacept MI, belatacept MI, and belatacept LI groups, respectively. The mean duration of exposure to tacrolimus was 326 and 268 days in the tacrolimus + MMF and tacrolimus groups, respectively.

Efficacy Results: The efficacy results up to Month 12 are summarized in Tables 2 and 3.

Subject and graft status was known for 98% and 97% of subjects at Months 6 and 12, respectively. Biopsies were available for central reading in 97% of the clinically suspected episodes of AR. Mean mGFR values were available for 78% of subjects who were alive at Month 12.

Table 2: Summary of Key Efficacy Results Up to Month 12 - All Randomized and Transplanted Subjects (ITT)

Parameter	Basi + Bela MI + MMF (N=50)	Bela MI +MMF (N=48)	Bela LI + MMF (N=49)	Tac + MMF (N=53)	Tac (N=50)
Composite AR/Death/Graft loss by Month 6, n (%) Difference from Tac + MMF, % (95% CI for the diff)	24 (48.0) 32.9 (16.1, 49.8)	20 (41.7) 26.6 (9.6, 43.5)	23 (46.9) 31.8 (14.8, 48.5)	8 (15.1) NA	19 (38.0) NA
Difference from Tac, % (95% CI for the diff)	10.0 (-8.7, 29.6)	3.7 (-15.3, 23.2)	8.9 (-9.8, 28.4)	NA	NA
Composite AR/Death/Graft loss by Month 12, n (%)	26 (52.0)	23 (47.9)	26 (53.1)	10 (18.9)	20 (40.0)
Acute Rejection by Month 12, n (%) Grade: I II III	22 (44.0) 15 (30.0) 7 (14.0) 0	16 (33.3) 7 (14.6) 8 (16.7) 1 (2.1)	16 (32.7) 7 (14.3) 8 (16.3) 1 (2.0)	7 (13.2) 6 (11.3) 1 (1.9) 0	15 (30.0) 7 (14.0) 6 (12.0) 2 (4.0)
Subject and Graft survival, n (%) Difference from Tac + MMF (95% CI for the diff)	45 (90.0) -2.5 (-12.9, 8.7)	40 (83.3) -9.1 (-18.1, 5.4)	33 (67.3) -25.1 (-38.9, -9.5)	49 (92.5) NA	44 (88.0) NA
Difference from Tac (95% CI for the diff)	2.0 (-9.9, 14.4)	-4.7 (-15.5, 10.7)	-20.7 (-35.5, -4.1)	NA	NA
Death or graft loss, n[a]	5	8	16	4	6
Death, n	4	7	10	1	4
Graft loss, n	2	2	8	4	4

Table 2: Summary of Key Efficacy Results Up to Month 12 - All Randomized and Transplanted Subjects (ITT)

Parameter	Basi + Bela MI + MMF (N=50)	Bela MI +MMF (N=48)	Bela LI + MMF (N=49)	Tac + MMF (N=53)	Tac (N=50)
cGFR (mL/min/1.73m^2): Mean					
Baseline (Day 1)	66.3	77.4	76.6	73.7	80.2
Month 2	86.1	96.6	105.8	76.3	66.9
Month 12	83.8	97.7	85.6	68.4	63.8
mGFR as observed (mL/min/1.73m^2): Mean					
Month 2	72.4	86.6	98.6	65.9	58.5
Month 12	88.9	93.1	73.1	75.2	70.5

AR = acute rejection; CI = confidence interval; mGFR = measured glomerular filtration rate; cGFR = calculated glomerular filtration rate; NA = not applicable

[a] Subjects may have experienced both death and graft loss.

Table 3: Summary of Metabolic and Cardiovascular Endpoints Up to Month 12 - All Randomized and Transplanted Subjects (ITT)

Parameter	Basi + Bela MI + MMF (N=50)	Bela MI +MMF (N=48)	Bela LI + MMF (N=49)	Tac + MMF (N=53)	Tac (N=50)
Incidence of NODM, n/N[a] (%)	11/31 (35.5)	5/32 (15.6)	5/36 (13.9)	9/38 (23.7)	14/37 (37.8)
Hypertension-related Endpoints					
Blood Pressure (mmHg), Mean (SD)					
SBP	125.8 (12.8)	127.0 (17.0)	121.2 (13.1)	137.0 (18.1)	138.0 (18.7)
DBP	76.5 (9.4)	78.5 (11.4)	74.5 (8.5)	80.3 (10.2)	79.5 (11.2)
MAP	93.0 (8.6)	94.6 (11.9)	90.1 (8.9)	99.2 (11.6)	99.0 (12.1)

Table 3: Summary of Metabolic and Cardiovascular Endpoints Up to Month 12 - All Randomized and Transplanted Subjects (ITT)

Parameter	Basi + Bela MI + MMF (N=50)	Bela MI +MMF (N=48)	Bela LI + MMF (N=49)	Tac + MMF (N=53)	Tac (N=50)
Use of any anti-hypertension medications, n/N[b] (%)	20/41 (48.8)	19/39 (48.7)	14/36 (38.9)	26/48 (54.2)	21/42 (50.0)
1 medication, n	13	16	8	17	12
≥ 2 medications, n	7	3	6	9	9
Dyslipidemia-related Endpoints					
Median Change from baseline to Month 12 (mg/dL)					
Total Cholesterol	75.0	57.0	64.5	54.5	43.5
LDL-C	35.5	55.0	41.5	23.0	14.0
HDL-C	12.0	7.0	5.5	7.5	6.0
Non-HDL	55.0	63.0	57.0	42.5	40.0
Triglycerides	55.5	37.0	62.0	85.0	82.0
Use of antihyperlipidemic medications, n/N[b] (%)	5/41 (12.2)	2/39 (5.1)	3/36 (8.3)	6/48 (12.5)	2/42 (4.8)

NODM = new onset diabetes mellitus; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; SD = standard deviation; LDL-C = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol

[a] Among subjects who did not have diabetes at baseline.

[b] Based on all subjects who had been followed up at least 364 days after transplantation

The primary and key secondary efficacy outcomes are summarized below (Table 3):

Primary (Month 6)

- The incidence of the composite endpoint of AR, graft loss, and death by Month 6 (primary endpoint) in the 3 belatacept-containing groups was similar or higher (42% to 48%) compared to the tacrolimus group (38%) and higher compared to the tacrolimus + MMF group (15%).

Secondary (Month 12)

- The incidence of the composite endpoint of AR, graft loss, and death by Month 12 increased across all treatment groups compared to Month 6 with similar patterns observed.
- The rate of subject and graft survival was highest in the tacrolimus + MMF group and lowest in the belatacept LI group.
  - Within the first 6 weeks, the number of deaths was higher in the basiliximab + belatacept MI (n = 3) and belatacept LI (n = 4) groups, and the number of graft loss was higher in the belatacept LI group (n = 5). The causes of death and graft loss in this period were mostly due to post-operative complications and did not appear to be related to study drug.
  - Between Week 6 and Month 6, the number of deaths (n = 1 to 3) and graft loss (n = 1 to 2) were similar across all treatment groups. Sepsis was the most common cause of death and variable causes of graft loss were noted.
  - Between Month 6 and Month 12, the number of deaths was higher in the belatacept MI (n = 3) and belatacept LI (n = 4) groups and the number of graft loss (n = 2) was higher in the belatacept LI group compared to the other groups. Of the 3 deaths in the belatacept MI group, 2 died at home (cause unknown) and 1 was due to progressive multifocal leukoencephalopathy (PML). Of the 4 deaths in the belatacept LI group, 1 was due to post-transplant lymphoproliferative disorder (PTLD) and 3 were due to multi-organ failure (2 HCV recurrence and 1 sepsis leading to multi-organ failure. Of the 2 graft loss, 1 was due to hepatic artery thrombosis leading to multiple liver abscesses and 1 was due to AR/HCV recurrence. A total of 5 patients in the belatacept MI group and 4 in the belatacept LI group who had an event (death or graft loss) had discontinued belatacept >56 days prior to the event.
- The rate of AR was highest (44%) in the basiliximab + belatacept MI group, 33% in the belatacept MI and belatacept LI groups, 30% in the tacrolimus alone group, and lowest (13%) in the tacrolimus + MMF group; most AR were Banff grade I or II. One subject in each group who experienced AR subsequently had a graft loss or death, except in the belatacept LI group where there were 3 subjects with AR who experienced death and 3 subjects who experienced graft loss. The causes of death were multi-organ failure, acute hepatic failure, and PTLD and the causes of graft loss were sepsis, bile duct stenosis, and AR/HCV recurrence. Of these 6 subjects in the belatacept LI group, only 2 received steroid treatment for AR. Upon detailed review of the cases, there appears to be no clear relationship between AR and the events of death and graft loss however, it cannot be definitively ruled out.
- The mean cGFR was ~ 15 to 34 mL/min/1.73 m^2 higher in the 3 belatacept groups compared to the 2 tacrolimus groups.
- The incidence of new onset diabetes mellitus (NODM) was lower in the belatacept MI and LI groups compared to the 2 tacrolimus groups.
- Systolic blood pressure (SBP) was 10 to 17 mmHg lower and diastolic blood pressure (DBP) was 1 to 6 mmHg lower in the 3 belatacept groups compared to the 2 tacrolimus groups.
- Lipid parameters increased from baseline in all treatment groups.
  - Triglyceride levels: increased in all treatment groups, but increased more in the tacrolimus groups.
  - Low-density lipoprotein (LDL) cholesterol levels: increased in all treatment groups, but increased more in the belatacept groups.

Safety Results: Safety results up to Month 12 are summarized in Tables 4 and 5.

Table 4: Summary of Adverse Events Up to Month 12 - All Randomized and Transplanted Subjects (ITT)

AE Parameter	Number (%) of Subjects				
	Basi + Bela MI + MMF (N=50)	**Bela MI +MMF (N=48)**	**Bela LI + MMF (N=49)**	**Tac + MMF (N=53)**	**Tac (N=50)**
Deaths[a]	4 (8.0)	4 (8.3)	9 (18.4)	1 (1.9)	4 (8.0)
SAEs	28 (56.0)	29 (60.4)	37 (75.5)	40 (75.5)	35 (70.0)
Related SAEs	12 (24.0)	11 (22.9)	14 (28.6)	16 (30.2)	19 (38.0)
Discontinued due to SAEs	7 (14.0)	6 (12.5)	11 (22.4)	4 (7.5)	13 (26.0)
AEs	50 (100)	48 (100)	48 (98.0)	53 (100)	50 (100)
Related AEs	45 (90.0)	34 (70.8)	33 (67.3)	42 (79.2)	42 (84.0)
Discontinued due to AEs	7 (14.0)	7 (14.6)	12 (24.5)	7 (13.2)	18 (36.0)

[a] Deaths up to Month 12 summarized in this table occurred within 56 days after discontinuation of study medication. Deaths up to Month 12 summarized in Table 2 include all deaths irrespective of treatment discontinuation.

AE = adverse event; SAE = serious adverse event.

Table 5: Events of Special Interest Up to Month 12 - All Randomized and Transplanted Subjects (ITT)

Parameter	Number (%) of Subjects				
	Basi + Bela MI + MMF (N=50)	**Bela MI +MMF (N=48)**	**Bela LI + MMF (N=49)**	**Tac + MMF (N=53)**	**Tac (N=50)**
Malignancies	1 (2.0)	0	2 (4.1)	2 (3.8)	2 (4.0)
PTLD[a,b]	0	0	1 (2.0)	0	0
All Infections	32 (64.0)	39 (81.3)	30 (61.2)	31 (58.5)	29 (58.0)
Bacterial	5 (10.0)	11 (22.9)	11 (22.4)	6 (11.3)	13 (26.0)
Fungal	6 (12.0)	9 (18.8)	14 (28.6)	6 (11.3)	5 (10.0)
Viral	10 (20.0)	11 (22.9)	14 (28.6)	9 (17.0)	7 (14.0)
CMV Infection	5 (10.0)	4 (8.3)	10 (20.4)	4 (7.5)	1 (2.0)
Polyoma virus	0	1 (2.1)[c]	0	0	0
Herpes infections	3 (6.0)	3 (6.3)	4 (8.2)	3 (5.7)	2 (4.0)
HCV Recurrence[d]	14/23 (60.9)	7/23 (30.4)	6/21 (28.6)	13/25 (52.0)	9/24 (37.5)
Serious Infections	11 (22.0)	12 (25.0)	13 (26.5)	12 (22.6)	12 (24.0)

Table 5: Events of Special Interest Up to Month 12 - All Randomized and Transplanted Subjects (ITT)

Parameter	Number (%) of Subjects				
	Basi + Bela MI + MMF (N=50)	**Bela MI +MMF (N=48)**	**Bela LI + MMF (N=49)**	**Tac + MMF (N=53)**	**Tac (N=50)**
Autoimmune events	0	0	1 (2.0)	0	2 (4.0)
Acute peri-infusional events[e]	5 (10.0)	1 (2.1)	0	NA	NA
Thrombotic and embolic events	3 (6.0)	3 (6.3)	7 (14.3)	10 (18.9)	5 (10.0)

[a] One subject in the basiliximab + belatacept MI group had PTLD after Month 12.

[b] Both cases of PTLD involved the liver and neither involved the CNS.

[c] Progressive multifocal leukoencephalopathy (PML).

[d] Among subjects who were HCV positive at baseline, n/N (%). HCV recurrence was pre-specified in the protocol as HAI score of ≥ 5 out of 18 and a fibrosis score of ≥ 2 (Ishak Scoring system) as assessed by the central pathologist on any liver biopsy done during the study including the Month 12 biopsies.

[e] Occurring within 1 hour after belatacept infusion.

PTLD = post-transplant lymphoproliferative disorder; CMV = cytomegalovirus; HCV = hepatitis C virus; NA = not applicable; HAI = Histological Activity Index

Additional safety findings were:

- The rate of SAEs was comparable across all 5 treatment groups.
- Among the belatacept groups, there was 1 case of progressive multifocal leukoencephalopathy (PML) (belatacept MI) and 2 cases of post-transplant lymphoproliferative disorder (PTLD) (1 in the belatacept LI group prior to Month 12 and 1 in the basiliximab + belatacept MI group after Month 12). The case of PML occurred in a subject who received an extra dose of belatacept MI due to massive fluid loss and 3 to 4 g/day MMF dose due to transaminitis. Both cases of PTLD involved the liver and neither involved the CNS.
- The rate of serious infections was similar across all 5 treatment groups.
- Higher rates of viral and fungal infections were reported in the belatacept LI group; most were non-serious.
- The incidence of HCV recurrence was lower in the belatacept MI and LI groups compared to the other 3 treatment groups.
- Fewer events of neurotoxicity were observed in the belatacept groups than in the tacrolimus groups (e.g., headache: 20%, 17%, and 10% in the belatacept groups and 26% and 28% in the tacrolimus groups; tremor: 4%, 4%, and 8% in the belatacept groups and 32% and 26% in the tacrolimus groups).

Pharmacokinetic Results: The PK parameters of belatacept after Day 84 dosing (Week 12) are summarized by treatment in Table 6.

The PK of belatacept suggested a relatively low variability of the exposure to belatacept after IV infusion (CV% for Cmax and AUC(TAU) was in the range of 20 to 29% and 21 to 44%, respectively). The T-HALF of belatacept was approximately 10 days after IV infusion in liver transplant subjects. The Vss of belatacept was low at 0.08 to 0.11 L/kg, indicating that the distribution of belatacept is restricted to the extra-cellular fluid volume. The AUC(TAU) of belatacept from the MI regimens (calculated over two weeks), is similar to the AUC(TAU) of belatacept from the LI regimen (calculated over four weeks). Hence the exposure of belatacept from the MI regimen is approximately twice that from the LI regimen during Months 2 and 3 when the MI regimen had double dosing frequency at 10 mg/kg as compared to the LI regimen.

Table 6: Summary Statistics of Belatacept Pharmacokinetic Parameters Following an IV infusion Dose of 10 mg/kg on Day 84 (Week 12)

Treatment	Cmax (µg/mL) Geo. Mean [N] (CV%)	Tmax (h) Median [N] (min-max)	AUC(TAU)[a] (µg•h/mL) Geo. Mean [N] (CV%)	Cmin (µg/mL) Geo. Mean [N] (CV%)	T-HALF (h) Mean [N] (SD)	CLT (mL/h/kg) Geo. Mean [N] (CV%)	Vss (L/kg) Mean [N] (SD)
BASI + Bela MI + MMF	221.3 [12] (29)	1.00 [12] (0.5-1.67)	19865 [10] (21)	23.63 [13] (30)	240.80 [10] (47.82)	0.45 [10] (28)	0.09 [10] (0.02)
Bela MI + MMF	227.6 [11] (23)	1.08 [11] (0.75-1.50)	21526 [5] (44)	27.20 [11] (37)	227.74 [5] (56.15)	0.41 [5] (46)	0.08 [5] (0.04)
Bela LI + MMF	205.4 [11] (20)	1.00 [11] (0.83-1.17)	19730 [6] (22)	5.91 [12] (50)	207.88 [7] (31.66)	0.45 [6] (22)	0.11 [6] (0.03)

[a] TAU = 4 weeks for LI regimen and 2 weeks for the MI regimen

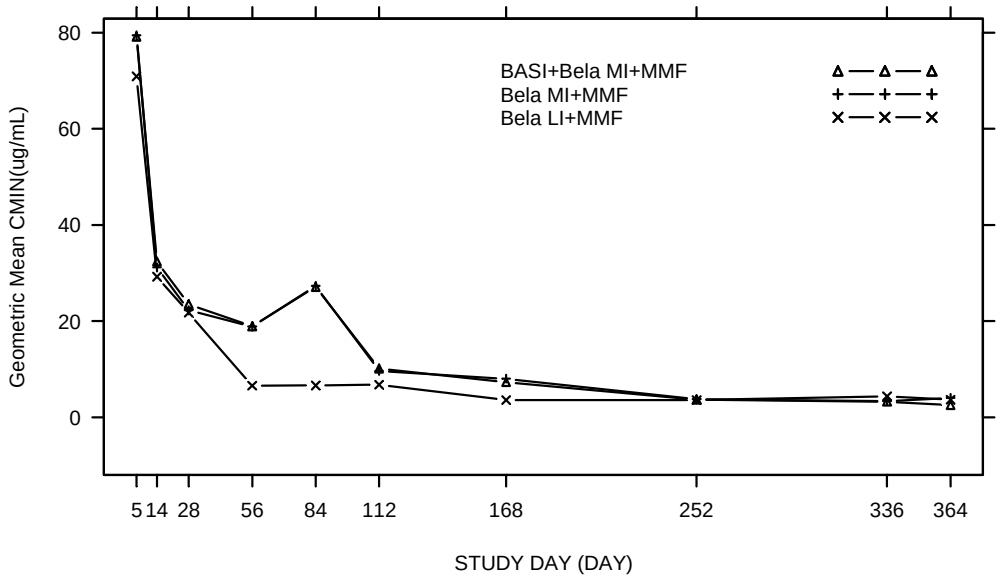
Note: The "N" for AUC(TAU) T-HALF, CLT and Vss is less because some subjects had incomplete PK profiles

As shown in Figure 1, in the MI-regimen, the geometric mean Cmin values of belatacept were highest in the early post transplant period (Study Days 5 and 14) and declined to the steady state concentrations during maintenance phase which were achieved within 252 days. In the LI-regimen, a similar pattern was seen for the early post transplant period (Study Days 5 and 14) but steady state concentrations during maintenance phase were achieved within 168 days. This pattern of Cmin values was consistent with the administered dosing which was constructed to reflect the clinical need to ensure greater immunosuppression in the period immediately post-transplant.

Belatacept Cmin values during months 2 to 6 from the MI regimen were approximately two to four times the Cmin from the LI regimen. Steady state trough serum concentrations of belatacept in the maintenance phase were similar from both the LI and the MI regimens.

Between days 1 to 14, the mean %Ae, asc (percent of dose excreted in ascites fluid) ranged from 1.59 to 2.72% of the belatacept dose administered.

Figure 1: Geometric Mean Belatacept Cmin versus Study Day



Note: Belatacept dosing schedule:
Less Intensive (LI): 10 mg/kg on Days 1, 3, 5, 14, 28, 56 and 84, and 5 mg/kg every 4 weeks starting on Day 112

More Intensive (MI): 10 mg/kg on Days 1, 3, 5, 14, 28, 42, 56, 70, 84, 112, 140 and 168, and 5 mg/kg every 4 weeks starting on Day 196.

CONCLUSIONS:
In conclusion, belatacept dosing regimens studied were comparatively effective in preventing acute rejection relative to the approved regimen of tacrolimus and steroids but were less effective compared to standard of care regimen, tacrolimus + MMF + steroids. Belatacept provided improvements in renal function and avoided the CV/metabolic and neurotoxicities of tacrolimus based regimens. PTLD and PML were observed with belatacept. Further investigation will be needed to evaluate the optimal dose and regimen of belatacept based therapy in liver transplant recipients.

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