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 Addendum for Study IM103045

ABBREVIATED REPORT

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 **CLINICAL PHASE:** 2

Study Completion Date: 02-May-2011

INTRODUCTION: Study IM103045 was a randomized, partially blinded, active-controlled, parallel-group, multicenter Phase 2 study to evaluate the effect of belatacept compared to tacrolimus in subjects receiving an orthotopic liver transplant (OLT). Three belatacept regimens were studied in this trial, representing a stepwise decrease in the level of overall immunosuppression. The belatacept-based regimens were compared to an approved regimen (tacrolimus alone) and the most widely used regimen (tacrolimus + mycophenolate mofetil [MMF]) in OLT.

Towards the end of enrollment in IM103045 (July, 2009), an independent Data Monitoring Committee (DMC) noted an imbalance in death and graft loss in 1 of the 3 belatacept treatment groups, later unblinded as the belatacept less intensive (LI) + MMF group. Although a clear causal relationship to belatacept could not be established, the DMC recommended that enrollment be halted in this group. This was described in the 12-month study report. Subjects already assigned to the belatacept LI + MMF regimen were permitted to continue.

All subjects completed 12 months of follow-up on 22-Jul-2010. The DMC reviewed the safety and efficacy data through that timepoint and recommended that the study be continued unchanged. On 07-Jan-2011, the DMC convened to review data collected beyond Month 12. At that time, a higher number of deaths was evident in 2 of the 3 belatacept groups (belatacept more intensive [MI] + MMF and belatacept LI + MMF) relative to the tacrolimus + MMF standard of care and tacrolimus alone control groups. Following review of the available data, the DMC recommended termination of the long-term extension (LTE) phase of the study in a timely, but non-urgent fashion. Although a clear causal relationship between belatacept and the imbalance in deaths could not be established, Bristol-Myers Squibb (BMS) terminated the LTE phase of Study IM103045 on 18-Jan-2011 and informed the investigators in a letter dated 21-Jan-2011.

The purpose of this abbreviated clinical study report is to provide an overall assessment of key safety and efficacy, pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity data from the 145 subjects

who entered the LTE phase of the IM103045. Cumulative safety and efficacy data (from the time of randomization through the last subject visit date of 02-May-2011) for the intent-to-treat - long-term extension (ITT-LTE) cohort is provided in this report. Due to the imbalance in deaths in 2 of the belatacept-based regimens, which was the primary reason for termination of this study, a comprehensive assessment of all deaths reported in this study is provided as an appendix to the CSR. This death cohort includes all randomized and transplanted subjects in the ITT population who died (N = 40) during the course of the study.

OBJECTIVES: Those protocol-specified objectives analyzed in this abbreviated report include the following:

Primary objective:

To assess the long-term safety and tolerability of a belatacept-based immunosuppressive regimen in subjects who have received a liver transplant and completed study treatment through Week 52.

Secondary objectives:

The following secondary objectives were assessed to evaluate the effects of belatacept, relative to tacrolimus:

- The composite of subject and graft survival
- The triple composite of acute rejection (AR), graft loss, and death
- Incidence, severity, treatment and outcome of AR
- Change in renal function
- PK characteristics of belatacept
- Incidence of hepatitis C virus (HCV) recurrence
- Incidence of discontinuation of study treatment

As this is an abbreviated study report, a complete list of objectives is provided in the protocol.

METHODOLOGY: This was a randomized, partially blinded, active-controlled, parallel-group, multi-center clinical trial in recipients of a primary de novo orthotopic liver allograft from a deceased donor. The trial was fully blinded with respect to the belatacept dosing regimen [MI or LI] and basiliximab assignment, open-label with respect to allocation to belatacept or tacrolimus and open-label between the 2 tacrolimus groups. Subjects were to be randomized (stratified by HCV-infection status) in equal numbers (50 subjects each) to the following groups:

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

Group 2): Belatacept (MI) + MMF

Group 3): Belatacept (LI) + MMF

Group 4): Tacrolimus + MMF

Group 5): Tacrolimus

The duration of the study was 12 months with a subsequent 8-week follow-up period for safety evaluations. At the end of the 12-month treatment period, subjects who had completed study treatment through Week 52 of the main protocol were eligible for the LTE study.

During the LTE, each subject continued on their assigned treatment group as follows:

- Subjects receiving belatacept continued to receive belatacept.
- Subjects receiving tacrolimus continued to receive tacrolimus.

- Subjects in either belatacept or tacrolimus treatment groups receiving MMF continued to receive MMF. Reduction of MMF dose was permitted.

The LTE phase was to continue until the drug was marketed in the respective country or until BMS terminated development of the study drug in this indication, whichever came first.

NUMBER OF SUBJECTS: Of the 250 randomized and transplanted subjects, 164 subjects completed 12 months of treatment and 145 subjects entered the LTE phase of the study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

- Willing to provide signed, written informed consent
- Subject had completed 1 year of study treatment (through Week 52)
- The subject was willing and able to continue therapy with their original assigned study medication (belatacept or tacrolimus)
- Women of childbearing potential 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.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: Subjects assigned to belatacept treatment groups (Groups 1, 2, and 3) were to continue a 5 mg/kg every 4-week intravenous (IV) infusion throughout the LTE until completion of the study.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: Subjects randomized to the tacrolimus arms (Groups 4 and 5) were to receive tacrolimus orally in accordance with local practice and the package insert.

ADJUVANT THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: After Week 52, subjects were to continue to receive MMF ≤ 1 g/day. Subjects who were receiving corticosteroids when they entered the LTE were permitted to continue or withdraw their steroids. Corticosteroid tapering and withdrawal was permitted at the discretion of the investigator in accordance with local practice.

CRITERIA FOR EVALUATION:

Safety: Safety endpoints included the frequency of adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs, and laboratory test measures. 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.

Hepatitis C virus 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 ≥ 2 out of 6 on modified staging.

Efficacy: Efficacy endpoints are part of the secondary outcome measures in the LTE phase. The effects of belatacept relative to tacrolimus was assessed through composite and graft survival, triple composite of AR, death and graft loss, incidence of severity, treatment and outcome of AR, change in renal function, and incidence of HCV recurrence. Graft loss was defined as impairment of liver function to such a degree that the subject died or underwent re-transplantation.

Renal function was evaluated via the assessment of calculated glomerular filtration rate (cGFR), which was based on serum creatinine using the Modification of Diet in Renal Disease (MDRD) formula.

Pharmacokinetics: Belatacept trough levels were summarized at specified visits (every 6 months) during the LTE, at the time of suspected AR and HCV recurrence, and 8 weeks post last dose of belatacept.

STATISTICAL CONSIDERATIONS:

Data Sets:

- The ITT population (N = 250) includes all subjects who were randomized to the initial study and also received a transplant. Subjects were grouped according to the treatment to which they were randomized.
- The ITT-LTE population (N = 145) includes all subjects who were randomized to the initial study, received a transplant, completed 12 months of study treatment, and entered into the LTE phase. Subjects were grouped according to the treatment to which they were randomized initially. All efficacy and safety analyses were carried out using this population unless otherwise specified.
- The PK analysis population (N = 145) includes all subjects with available plasma concentration-time data who had received at least 1 dose of belatacept.
- The death cohort (N = 40) includes all randomized and transplanted subjects in the ITT population who died.

Safety: The evaluation of drug safety was based primarily on clinical AEs and laboratory abnormalities reported during the study. There was no statistical testing of group differences with respect to frequencies of AEs or marked (laboratory) abnormalities (MAs). Cumulative safety data are provided in this report for the ITT-LTE population and are presented according to the treatment groups of initial randomization. Kaplan-Meier analyses and the assessment of deaths utilize the overall ITT population.

Any AEs that occurred before randomization or more than 56 days after the last infusion/dose of the LTE were excluded from safety summaries for the ITT-LTE population, but were included on the comprehensive listing. However, deaths, malignancies, and serious infections were summarized up to database lock. Summaries are presented by treatment groups and categorized by System Organ Classes (SOCs) and Preferred Terms (PTs), using Medical Dictionary for Regulatory Activities (MedDRA), Version 14. These AE summaries were based on proportions, which represent the number of subjects experiencing AEs divided by the number of subjects.

Summary information (the number and percent of subjects by treatment) was tabulated for the following:

- All AEs
- Most common AEs (reported in at least 5% of subjects in any treatment group)
- Related events
- Related events categorized by severity
- Serious adverse events (SAE)
- Discontinuations due to AEs

Adverse events of special interest (malignancies and serious infections) were also summarized. Additionally, AEs and SAEs were summarized in terms of incidence rates using person-years of follow-up starting from the first dose after randomization. Incidence rates were calculated to adjust for differences in exposure to drug.

Laboratory MAs using pre-defined abnormality criteria were descriptively summarized.

Efficacy: For efficacy analyses, no statistical testing was performed. Unless otherwise specified, the following efficacy analyses were produced for the ITT-LTE population. The proportion of subjects with the

triple composite endpoint of AR, graft loss and death was summarized within each treatment group using point estimates and corresponding 95% confidence intervals (CIs). The proportion included all subjects who experienced at least one episode of AR, graft loss, or death up to the time of database lock (i.e., end of study). Similarly, subject survival, graft survival, and subject survival with a non-functioning graft was summarized by treatment group for both the ITT-LTE population as well as the ITT population.

For each of the above endpoints, two-sided 95% CIs were also generated for the difference between each of the belatacept treatment groups and each of the tacrolimus treatment groups.

The primary reason for the termination of the LTE phase of the study was due to an observed increase in the number of deaths and graft loss in 2 of the 3 belatacept treatment groups. Therefore, the following summaries are provided in an appendix for the cohort of subjects who died: demographic and disease characteristics, AR (rate, severity, treatment, and outcome), serious infections, malignancies, and HCV recurrence.

Pharmacokinetics: The trough levels of belatacept were summarized at specified visits throughout the study (including every 6 months during the LTE). The PK samples, including those collected at rejection episodes, are also listed.

SUMMARY OF RESULTS:

Cumulative safety data (from randomization through the last subject visit date) for the ITT-LTE cohort is provided. The MA summaries include marked abnormalities for subjects in the ITT-LTE population occurring only during the LTE phase (after Month 12). The assessment of deaths utilizes the overall ITT population. Frequencies of AEs are provided in text and tables.

Baseline/Demographic Characteristics and Disposition:

Baseline demographics of transplant recipients in the ITT-LTE population were generally similar and balanced across treatment groups (Table 1). Baseline pre-transplant and disease characteristics of transplant recipients who entered the LTE were generally similar across treatment groups. The mean Model for End-Stage Liver Disease (MELD) score in each group was between 20 and 24 and the most common cause of end-stage liver disease (ESLD) was non-cholestatic cirrhosis.

Before termination of the study by the sponsor, the most common reasons for discontinuation during the LTE period were due to AEs and withdrawal of consent (Table 2).

Extent of Exposure:

Exposure data in this report are cumulative (from the time of randomization through LTE) and presented for the ITT-LTE population. The mean duration of exposure to belatacept during the study was 714.6, 757.7, and 762.4 days in the basiliximab + belatacept MI, belatacept MI, and belatacept LI groups, respectively. The mean duration of exposure to tacrolimus was 796.4 and 816.1 days in the tacrolimus + MMF and tacrolimus groups, respectively.

Table 1: Baseline Demographic Characteristics of Transplant Recipients: All Randomized and Transplanted Subjects who entered Long-term Extension (ITT-LTE)

Characteristic	BASI+Bela MI+MMF N=30	Bela MI+MMF N=27	Bela LI+MMF N=24	TAC+MMF N=38	TAC N=26
	Number (%) of Subjects				
AGE (YEARS)					
N	30	27	24	38	26
MEAN (SD)	53.1 (8.89)	54.6 (5.89)	54.5 (6.78)	53.9 (9.01)	54.5 (6.11)
MEDIAN	54.5	55.0	54.5	54.0	55.0
Q25 - Q75	49.0 - 58.0	50.0 - 59.0	49.0 - 60.0	49.0 - 59.0	51.0 - 59.0
MIN - MAX	30.0 - 66.0	41.0 - 66.0	44.0 - 66.0	28.0 - 68.0	40.0 - 67.0
AGE CATEGORY, N (%)					
18-45	6 (20.0)	2 (7.4)	2 (8.3)	7 (18.4)	2 (7.7)
46-65	23 (76.7)	24 (88.9)	21 (87.5)	26 (68.4)	23 (88.5)
>65	1 (3.3)	1 (3.7)	1 (4.2)	5 (13.2)	1 (3.8)
GENDER, N (%)					
MALE	24 (80.0)	19 (70.4)	16 (66.7)	33 (86.8)	19 (73.1)
FEMALE	6 (20.0)	8 (29.6)	8 (33.3)	5 (13.2)	7 (26.9)
RACE, N (%)					
WHITE	28 (93.3)	23 (85.2)	23 (95.8)	34 (89.5)	23 (88.5)
BLACK/AFRICAN AMERICAN	1 (3.3)	2 (7.4)	0	3 (7.9)	2 (7.7)
AMERICAN INDIAN/ALASKA NATIVE	0	1 (3.7)	0	0	0
ASIAN	0	0	1 (4.2)	0	0
OTHER	1 (3.3)	1 (3.7)	0	1 (2.6)	1 (3.8)
ETHNICITY*, N (%)					
HISPANIC OR LATINO	4 (13.3)	2 (7.4)	1 (4.2)	2 (5.3)	3 (11.5)
NOT HISPANIC OR LATINO	15 (50.0)	9 (33.3)	4 (16.7)	15 (39.5)	14 (53.8)
MISSING	11 (36.7)	16 (59.3)	19 (79.2)	21 (55.3)	9 (34.6)

* This information is collected for US recipients only. Ethnicity data is available for two non-US subjects and thus included

Table 2: Reasons for Study Discontinuation During LTE- All Randomized and Transplanted Subjects Who Entered LTE (ITT-LTE)

	Number (%) of Subjects				
	BASI+Bela MI+MMF N = 30	Bela MI+MMF N = 27	Bela LI+MMF N = 24	TAC+MMF N = 38	TAC N = 26
NUMBER ENTERED LONG-TERM EXTENSION, N	30	27	24	38	26
NUMBER DISCONTINUED STUDY, N (%)	30 (100)	27 (100)	24 (100)	38 (100)	26 (100)
ADVERSE EVENT	2 (6.7)	5 (18.5)	2 (8.3)	1 (2.6)	0
SUBJECT WITHDREW CONSENT	2 (6.7)	1 (3.7)	2 (8.3)	3 (7.9)	2 (7.7)
ADMINISTRATIVE REASON BY SPONSOR	23 (76.7)	21 (77.8)	18 (75.0)	31 (81.6)	23 (88.5)
DEATH	2 (6.7)	0	0	3 (7.9)	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	0	0	0	1 (3.8)
OTHER	1 (3.3)	0	2 (8.3)	0	0

Note: 1. Subjects who entered Long Term Extension (LTE) are used as denominator.
2. Exposure Duration for Belatacept is defined as last infusion date - first infusion date + 28 days.
Exposure Duration for Tacrolimus is defined as last dose date - first dose date + 10 days.
3. Subjects who answered YES to enter Long Term Extension (LTE) and exposure duration is greater than or equal to 365 days are counted as entering LTE.

Safety Results:

The study was terminated, per recommendation from the DMC, due to an imbalance in deaths in 2 out of the 3 belatacept treatment groups. However, no clear causal relationship between belatacept and the reported deaths could be established. The following are key safety findings from the time of randomization through the last subject visit date:

- Overall (ITT population), more subjects died in the belatacept MI and LI groups than in the other 3 groups; 11 subjects (23%) in the belatacept MI group and 12 subjects (25%) in the belatacept LI group relative to 6 (12%), 4 (8%), and 7 subjects (14%) in the remaining 3 groups (basiliximab + belatacept MI, tacrolimus + MMF, and tacrolimus alone groups, respectively).
- The rate of SAEs was comparable across all 5 treatment groups.
- Among the belatacept groups, there was 1 fatal case of progressive multifocal leukoencephalopathy (PML) (belatacept MI group, prior to Month 12), 1 fatal case of post-transplant lymphoproliferative disorder (PTLD) (belatacept LI group, prior to Month 12), and 1 non-fatal case of PTLD (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 postoperative fluid loss and 3 to 4 g/day MMF dose due to transaminitis. Both cases of PTLD involved the liver and neither involved the central nervous system (CNS).
- The proportion of ITT-LTE subjects with serious infections was generally similar across all 5 treatment groups. As previously reported in the 12-month report (ITT population), higher rates of viral and fungal infections were reported in the belatacept treatment groups; most were non-serious.
- From the time of randomization to the end of the study, the proportion of ITT-LTE subjects who had HCV recurrence was 67% (8 subjects), 50% (6 subjects), and 22% (2 subjects) in the basiliximab + belatacept MI, belatacept MI, and belatacept LI groups compared with 65% (11 subjects) and 73% (8 subjects) in the tacrolimus + MMF and tacrolimus groups, respectively.

Safety results since randomization (12-month plus LTE) are summarized for the ITT-LTE population in Tables 3 and 4.

Table 3: Summary of Subjects with AEs Reported After Randomization - All Randomized and Transplanted Subjects Who Entered Long-Term Extension (ITT-LTE)

	BASI+Bela MI+MMF N = 30	Bela MI+MMF N = 27	Bela LI+MMF N = 24	TAC+MMF N = 38	TAC N = 26
DEATHS *	2 (6.7)	3 (11.1)	1 (4.2)	3 (7.9)	0
SAES	18 (60.0)	22 (81.5)	17 (70.8)	29 (76.3)	21 (80.8)
RELATED SAES	5 (16.7)	9 (33.3)	9 (37.5)	12 (31.6)	9 (34.6)
DISCONTINUED DUE TO SAES	2 (6.7)	4 (14.8)	1 (4.2)	1 (2.6)	0
AES	30 (100)	27 (100)	23 (95.8)	38 (100)	26 (100)
RELATED AES	27 (90.0)	21 (77.8)	20 (83.3)	33 (86.8)	23 (88.5)
DISCONTINUED DUE TO AES	2 (6.7)	5 (18.5)	1 (4.2)	1 (2.6)	0

Note: Related AE or SAE is defined as certain, probable, possible or missing.
Death information is from ADAE dataset.

* Deaths presented in this table (N=9) are those reported as an outcome of an adverse event and do not represent all deaths reported in the ITT-LTE population.

Table 4: Summary of Deaths, ITT-LTE

	Basi + bela MI + MMF	Bela MI + MMF	Bela LI + MMF	Tac + MMF	Tac
ITT-LTE (N)	**30**	**27**	**24**	**38**	**26**
Deaths post Month 12; No. of Subjects (%)	2 (6.7%)	4 (14.8%)	1 (4.2%)	3 (7.9%)	0

Abbreviations: Basi = basiliximab; Bela = belatacept; ITT = intent-to-treat (randomized and transplanted); LI = less intensive; LTE = long-term extension; MI = more intensive; MMF = mycophenolate mofetil; Tac = tacrolimus

Other Results:

Efficacy:

Cumulative efficacy data (from the time of randomization to the end of the study) for the ITT-LTE cohort is provided in this section.

The following findings were identified for the ITT-LTE population:

- The frequency of the composite endpoint of AR, graft loss, and death from randomization in the belatacept treatment groups was higher (25% to 37%; 6 to 11 subjects) compared to that in the tacrolimus treatment groups (21% [8 subjects] and 23% [6 subjects] in tacrolimus + MMF and tacrolimus, respectively).
- At the end of the study, the proportion of ITT-LTE subjects surviving with a functioning graft was 93% (28 subjects), 85% (23 subjects), and 96% (23 subjects) in the basiliximab + belatacept MI, belatacept MI, and belatacept LI groups and 92% (35 subjects) and 96% (25 subjects) in the tacrolimus + MMF and tacrolimus groups, respectively.
- For all groups during the LTE, AR drove the composite endpoint. The cumulative frequency of AR was highest (30%, 9 subjects) in the basiliximab + belatacept MI group and lowest (16%, 6 subjects) in the tacrolimus + MMF group; most AR were Banff grade I or II. Clinically suspected and central biopsy proven AR findings in the ITT-LTE population are the same after Month 12 as during the first 12 months of the study. Most ITT-LTE subjects had 1 episode of clinically suspected and biopsy proven AR.
- The mean cGFR was higher in the belatacept treatment groups up to Month 30 compared to the tacrolimus treatment groups.

A summary of efficacy measures is provided in Table 5.

Table 5: Summary of Efficacy Results - All Randomized and Transplanted Subjects who Entered the LTE (ITT-LTE)

Parameter	Basi + Bela MI + MMF (N=30)	Bela MI + MMF (N=27)	Bela LI + MMF (N=24)	Tac + MMF (N=38)	Tac (N=26)
Composite AR/Death/Graft loss by study end, n (%)	11 (36.7)	10 (37.0)	6 (25.0)	8 (21.1)	6 (23.1)
Difference from Tac + MMF	15.6	16.0	3.9	NA	NA
(95% CI for the diff)	(-5.8, 36.8)	(-6.0, 38.0)	(-16.6, 26.8)		
Difference from Tac	13.6	14.0	1.9	NA	NA
(95% CI for the diff)	(-10.8, 36.1)	(-10.9, 37.3)	(-21.8, 26.0)		
Subject and Graft survival by study end, n (%)	28 (93.3)	23 (85.2)	23 (95.8)	35 (92.1)	25 (96.2)
Difference from Tac + MMF	1.2	-6.9	3.7	NA	NA
(95% CI for the diff)	(-14.5, 15.3)	(-25.7, 8.8)	(-13.2, 17.5)		
Difference from Tac	-2.8	-11.0	-0.3	NA	NA
(95% CI for the diff)	(-18.1, 13.1)	(-29.4, 6.2)	(-16.9, 15.3)		
Death or graft loss, n[a]	2	4	1	3	1
Death, n	2	4	1	3	0
Graft loss, n	0	1	0	0	1
Acute Rejection by study end, n (%)	9 (30.0)	6 (22.2)	6 (25.0)	6 (15.8)	6 (23.1)
Banff Grade:					
I	8 (26.7)	5 (18.5)	2 (8.3)	5 (13.2)	3 (11.5)
II	1 (3.3)	1 (3.7)	4 (16.7)	1 (2.6)	1 (3.8)
III	0	0	0	0	2 (7.7)

Table 5: Summary of Efficacy Results - All Randomized and Transplanted Subjects who Entered the LTE (ITT-LTE)

Parameter	Basi + Bela MI + MMF (N=30)	Bela MI + MMF (N=27)	Bela LI + MMF (N=24)	Tac + MMF (N=38)	Tac (N=26)
cGFR (mL/min/1.73 m^2):					
Baseline (Day 1)					
n	27	24	20	33	23
Mean (SD)	64.4 (32.98)	85.6 (34.74)	78.0 (31.65)	77.9 (32.13)	83.0 (35.80)
Month 12					
n	29	25	24	36	24
Mean (SD)	88.1 (21.45)	101.3 (25.01)	94.8 (27.89)	67.8 (22.07)	61.7 (20.49)
Month 24					
n	13	15	15	22	15
Mean (SD)	84.8 (26.18)	87.6 (21.43)	96.3 (26.02)	73.3 (22.82)	66.3 (21.63)

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

Abbreviations: AR = acute rejection; Basi = basiliximab; Bela = belatacept; cGFR = calculated glomerular filtration rate; CI = confidence interval; ITT = intent-to-treat (population); LI = less intensive; LTE = long-term extension; mGFR = measured glomerular filtration rate; MI = more intensive; NA = not applicable; SD = standard deviation; Tac = tacrolimus

Pharmacokinetic Results: Belatacept trough levels were summarized at specified visits (every 6 months) during the LTE. In the first 12 months of the study, steady state trough serum concentrations of belatacept during maintenance phase (post Month 6) were similar in both the LI and the MI regimens. Belatacept trough levels in the long-term portion of the study were maintained at steady state levels. The geometric mean trough serum concentration of belatacept at Year 2, post-transplant, ranged from 4.20 to 4.75 μg/mL across the LI and the MI regimens.

CONCLUSIONS:

- Long-term follow-up beyond Month 12 revealed an imbalance in death in 2 of the 3 belatacept-based immunosuppressive regimens (MI and LI) in OLT recipients. No clear causal relationship between belatacept treatment and the reported deaths could be established.
- The proportion of subjects surviving with a functioning graft from the time of randomization (ITT-LTE) was comparable between the basiliximab + belatacept + MMF, tacrolimus + MMF, and tacrolimus alone groups.
- The cumulative frequencies (from the time of initial randomization) of the composite endpoint of AR, graft loss, and death in the belatacept treatment groups was higher, particularly for the belatacept MI groups, than that observed in the tacrolimus treatment groups (ITT-LTE population).
- Across treatment groups, few subjects experienced AR after Month 12.
- Consistent with the findings in the 12-month IM103045 report (ITT population), renal function (based on cGFR) remained higher in belatacept-treated subjects (ITT-LTE population).
- Steady state Cmin of belatacept achieved during the maintenance phase was maintained in the LTE phase for both the MI and LI regimens.
- The frequency of HCV recurrence in the ITT-LTE population was similar across treatment groups, except in the belatacept LI group where it was lower than in the other belatacept and control treatment groups. Interpretation is limited by the small number of HCV positive subjects in each group.
- Before termination of the study by the sponsor, the most common reasons for discontinuation during the LTE phase were due to AEs and withdrawal of consent. Frequencies of subjects discontinuing due to these reasons were low and generally similar across treatment groups; however, numerically more subjects in the belatacept treatment groups discontinued the study due to AEs.
- The limited number of subjects enrolled in this exploratory study which was further reduced in the LTE phase, is an important limitation in the interpretation of study findings.

DATE OF REPORT: 08-Sep-2011