



Bristol-Myers Squibb Company

Belatacept (BMS-224818)

**FDA's Cardiovascular and Renal Drugs
Advisory Committee**

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EXECUTIVE SUMMARY

Renal transplantation is the preferred treatment for end-stage renal disease because it confers improved survival and quality of life over dialysis.¹ While the calcineurin inhibitors (CNIs), cyclosporine (CsA) and tacrolimus, used for post-transplantation immunosuppression have lowered acute rejection (AR) rates and improved 1-year graft survival, there has not been a commensurate improvement in long-term survival, which remains suboptimal. As the understanding of AR has developed, data show that all rejection episodes do not have the same impact on graft survival, which may explain why the favorable impact of the CNIs on overall AR rates has not improved long-term transplant outcomes. Moreover, the CNIs adversely affect renal function, blood pressure, lipids and the development of new onset diabetes after transplantation (NODAT), and thus contribute directly to the progressive renal dysfunction (manifested histologically as chronic allograft nephropathy or interstitial fibrosis and tubular atrophy) and high rates of cardiovascular (CV) events that are the primary causes of allograft loss and patient mortality.

Belatacept represents a new class of therapeutic agents in transplantation immunosuppression. It is an intravenously (IV) administered biologic that specifically targets key co-stimulatory signals required for full T-cell activation. It has been developed by Bristol-Myers Squibb (BMS) to address renal transplant recipients' need for new immunosuppressive therapies that can provide acceptable control of the alloimmune response and comparable short-term outcomes to the CNIs, while avoiding their renal, CV and metabolic toxicities, in order to support improved long-term patient and graft survival.

Belatacept was studied in a comprehensive development program across a broad range of de novo renal transplant recipients, including recipients of standard kidneys and marginal, extended criteria kidneys. Two (2) belatacept dose regimens were evaluated in order to identify a dose with adequate immunosuppressive efficacy while minimizing the risks of immunosuppression-related toxicities. Subjects in the core clinical studies have been followed for a median of 2 years or more after transplantation, allowing for characterization of the durability of efficacy and longer-term safety. In the core clinical studies, 949 subjects, representing a substantial clinical experience in renal

transplantation, have received belatacept. In these 3 studies (1 Phase 2 and 2 Phase 3), 477 received the more intensive (MI) belatacept dose regimen, 472 received the less intensive (LI) belatacept dose regimen, and 478 received the comparator CsA. All subjects received basiliximab induction, and maintenance immunosuppression with mycophenolate mofetil (MMF) and corticosteroids.

In the 2 Phase 3 studies, belatacept was non-inferior to CsA on the proportion of renal transplant recipients who survived with a functioning graft at 12 months. The proportion of subjects who survived with a functioning graft was numerically higher with belatacept than CsA, and the narrow confidence intervals (CIs) leave little uncertainty as to the non-inferiority of belatacept to CsA. Treatment with belatacept resulted in substantial improvements in post-transplant renal function, which is known to be the strongest determinant of long-term graft survival, CV events, and transplant recipient mortality.^{2,3,4,5} At 12 months, renal function benefits of 13 to 15 and 4 to 7 mL/min/1.73 m², favoring belatacept, were observed in recipients of standard criteria donor and extended criteria donor kidneys, respectively. Moreover, there was less structural damage (chronic allograft nephropathy) in the renal allografts of belatacept treated subjects. These renal function differences appear to be widening over time, particularly in recipients of standard criteria donor kidneys. Belatacept-treated subjects also had lower blood pressure (6 to 9 mm Hg systolic and 3 to 4 mm Hg diastolic), an approximately 50% lower frequency of NODAT, and a more favorable lipid profile relative to CsA. Both the belatacept MI and LI dose regimens resulted in similar efficacy, which was maintained for at least 24 months after transplantation.

Belatacept was associated with an increased frequency of early, treatable AR episodes compared with CsA. Although the rates of AR were higher with belatacept than CsA, the absolute event rates, graft function, and survival data provide substantial evidence that belatacept is an effective immunosuppressant for the prophylaxis of allograft rejection. Furthermore, the impact of these rejection episodes on the subject and graft was limited and was captured in the long-term outcomes and measures of renal function in these studies, both of which favoured belatacept.

Overall, belatacept was well tolerated and its safety profile was consistent with that of a targeted immunosuppressant. In addition to avoiding the renal, CV and metabolic toxicities of CsA as detailed above, there were fewer deaths and serious infections in

subjects treated with belatacept LI than in subjects treated with CsA or belatacept MI. The principal safety concerns with belatacept therapy are post transplant lymphoproliferative disorder (PTLD) with central nervous system (CNS) involvement and progressive multifocal leukoencephalopathy (PML). These immunosuppression-related risks were highest in the belatacept MI-based regimen, which provided double the exposure to belatacept as the LI regimen during Months 2 to 7 after transplantation. PML was only reported in the belatacept MI group, and 6 of the 9 cases of CNS PTLD occurred in the belatacept MI group. In addition, lack of immunity to Epstein-Barr virus (EBV) increased the risk of developing PTLD. Thus, the risks of belatacept can be minimized by use of the belatacept LI dose and also by limiting belatacept use to EBV-positive recipients.

BMS has developed a comprehensive Risk Evaluation and Mitigation Strategy (REMS) that will educate physicians and patients about the risks associated with belatacept-based immunosuppression, and the importance of patient and dose selection to minimizing these risks. These efforts can be expected to be highly effective as they will target the small community of transplant surgeons and transplant nephrologists, who are already familiar with the management of immunosuppressant regimens and their safety consequences, which include the identified risks associated with belatacept. In addition, a thorough pharmacovigilance plan is proposed that includes routine and enhanced safety monitoring, as well as 4 post-marketing observational studies in the United States (US) complemented by 2 planned post-marketing international observational studies, to further characterize these risks and identify any new risks associated with belatacept in the clinical setting. One of these studies is a 6,000 patient prospective cohort study to assess PTLD, serious infections, death, graft loss, and acute rejection. Several of the other studies capitalize on existing transplant databases that capture data on 100% of recipients in the US and over 70% of renal transplant recipients in Europe.

In conclusion, belatacept represents a new treatment option for renal transplant recipients that addresses the unmet medical need that exists today. Belatacept provides short-term outcomes comparable to the CNIs while avoiding their renal, CV and metabolic toxicities which compromise transplant recipient health and outcomes. The key risks associated with belatacept were CNS PTLD and PML. In the clinical studies, the impact of these events on the subject or the graft were captured in the primary survival endpoint, indicating that while medically serious, the detrimental effects of these events did not

outweigh the overall benefits of belatacept to the subject or the allograft. The absolute risk of CNS PTLD was low and will be further reduced via the proposed contraindication of belatacept use in EBV-seronegative recipients and those with unknown serostatus. The recommended dose is the belatacept LI regimen, which was associated with lower rates of death, serious infections, CNS infections, and CNS PTLD than the belatacept MI regimen. A comprehensive risk evaluation and mitigation strategy is proposed to minimize the risks of belatacept and monitor its safety in clinical practice. Thus, based upon its demonstrated efficacy and manageable safety profile, belatacept is recommended for approval for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.

Organization of the Document

This document is divided into 11 major sections. The unmet medical need is summarized in Section 1; Section 2 summarizes the development objectives. Section 3 provides a summary of interactions with health authorities. Background information on the belatacept mechanism of action and a summary of the nonclinical toxicology and clinical pharmacology program is provided in Section 4. The clinical development program, selected methods and subject characteristics are summarized in Section 5. Sections 6 and 7 summarize the key efficacy and safety data, respectively. Belatacept dose recommendation is discussed in Section 8. The risk-management strategies and the continued assessment of belatacept after approval are summarized in Sections 9 and 10, respectively. An overall assessment of the benefits and risks are provided in Section 11.

1 UNMET MEDICAL NEED

Despite improvements in renal transplantation associated with the introduction of calcineurin inhibitors, there remains a significant unmet medical need for new immunosuppressive agents that can provide excellent short term patient and graft survival while avoiding the renal, CV, and metabolic toxicities associated with CNIs to support improved patient and graft survival after renal transplantation. Belatacept has been developed as a new therapeutic option to address this unmet medical need.

Renal transplantation is the preferred treatment for end-stage renal disease because it confers improved survival and quality of life over dialysis.¹ There are approximately

500,000 patients with end-stage renal disease and approximately 17,000 kidney transplant procedures performed each year in the US. The goal of transplantation is to achieve normal renal function and normal life span for patients with end stage renal disease.

After transplantation, transplant recipients require lifelong immunosuppression to suppress the alloimmune response and maintain a functioning graft. Prior to the introduction of the CNIs (CsA and tacrolimus), AR rates were high and graft survival was poor.⁶ Use of CNIs introduced a new era of immunosuppressive therapy with improved short term outcomes. Current immunosuppressive regimens yield 1-year graft survival rates of 90% for recipients of deceased donor grafts and 95% for recipients of living donor grafts⁷ and AR rates are approximately 10% to 20% in the first year after transplantation.

Despite a favorable impact on short-term outcome, the CNIs may contribute to poor long-term outcome due to their renal, CV, and metabolic toxicities.⁸ CNIs are known to increase the risk of new onset diabetes, to raise blood pressure, and to have adverse effects on lipids.⁸ These CNI toxicities may contribute to suboptimal long-term patient and graft survival. Five- and 10-year patient survival rates with a functioning graft are 68% and 39% for recipients of deceased donor transplants, and 80% and 57% for recipients of living donor transplants, respectively.⁹ Over a 10-year period, approximately half of all transplant recipients require a new transplant, return to dialysis or die.

The primary causes of long-term graft loss are death with a functioning graft, most commonly due to CV disease, and progressive renal dysfunction due to chronic allograft nephropathy.^{7,10,11} CNIs can contribute to these causes through effects on CV risk factors and nephrotoxicity. The nephrotoxicity of CNIs is of particular concern because maintaining post-transplantation renal function is an inherent goal of transplantation and has emerged as the strongest determinant of long-term graft survival, CV events and transplant recipient mortality.^{2,3,4,5}

AR, characterized by findings of cellular infiltrates or antibody deposition on allograft biopsy, represents recipient immunologic response to the transplanted kidney. As the understanding of AR has developed, data show that all rejection episodes do not have the

same impact on graft survival, which may explain why reduction in overall AR rates has not improved long term patient and graft survival. With current treatments for AR, few AR episodes lead to graft loss. A subset of AR episodes do impact graft survival, namely those associated with poor renal function after episodes of AR,^{12,13} the presence of antibody mediated rejection¹⁴ higher Banff grade¹⁵ and late, recurrent or chronic rejection.^{16,17}

The concerns about long-term transplant outcomes and the risk associated with CNIs are of growing importance due to the increasing reliance on higher risk extended criteria donor kidneys, now 20% of deceased donors in the US.^{7,18} Extended criteria donor organs are defined as those from older donors or those with certain comorbid conditions that have an increased risk of graft failure over optimal kidneys¹⁹ and their use is intended to satisfy the critical shortage of organs. One and 5-year graft survival for recipients of extended criteria donor kidneys is poorer than that for non-extended criteria donor kidneys.²⁰ Extended criteria donor kidneys and their typically older recipients may be particularly vulnerable to the toxic effects of CNIs.²⁰ Due to limited data, the optimal regimen for recipients of extended criteria donor kidneys is unknown, nevertheless, the need for new immunosuppressants that maintain excellent short term outcomes while improving factors that impact long term outcomes may be particularly beneficial in recipients of extended criteria donor kidneys.

In response to the known toxicities of the CNIs, the transplantation community has focused on developing strategies to avoid or minimize CNIs to improve post-transplantation renal function and longer term outcomes. However, these attempts have not been successful. For example, a CNI-free, sirolimus based immunosuppressive regimen led to increases in rates of AR and mortality compared with CsA that led to early study termination. Additionally, there was no renal function benefit noted in the CNI-free regimen in this study.²¹ Another approach has been to reduce the dose of CNIs; however, the benefits of this approach with regard to renal function improvement are inconsistent.^{22,23,24,25,26}

In summary, despite the advances made in renal transplantation through the use of CNIs, there remains a significant unmet medical need for new therapeutic agents that can provide acceptable control of the alloimmune response, while preserving renal function

and avoiding CV toxicity so as to support improved longer term graft and subject survival after renal transplantation of both standard and extended criteria donor kidneys. In order to improve long term outcomes, new immunosuppressants are needed that have a more targeted mechanism of action than the CNIs, provide effective immunosuppression and avoid the off-target toxicities of CNIs including nephrotoxicity and CV and metabolic effects.

2 DEVELOPMENT OBJECTIVES

The belatacept development program was designed to demonstrate that belatacept provided excellent short-term survival comparable to a CNI based regimen while avoiding the CNI toxicities that contribute to long-term allograft loss and mortality. The primary focus was improving post-transplant renal function, because of its critical importance to long-term transplant outcomes. The program also assessed blood pressure, new onset diabetes, and lipids. A broad range of renal transplant recipients were included to demonstrate consistency of the effectiveness of belatacept. Two belatacept dose regimens were studied in Phase 3 to allow the identification of an effective dose with an acceptable safety profile. Finally, the Phase 3 studies had 1-year primary endpoints but were designed as 3-year studies to capture longer term safety and efficacy data.

3 HEALTH AUTHORITY INTERACTIONS

Although the US Food and Drug Administration (FDA) has not issued formal recommendations on the clinical evaluation of therapeutics for solid organ transplantation, BMS has conducted the belatacept development program based on feedback provided by the FDA regarding design and objectives. Key interactions with the FDA are summarized in [Table 1](#).

Subsequent to the initiation of the belatacept renal Phase 3 studies, Committee for Medicinal Products for Human Use (CHMP) developed guidance on the clinical investigation of immunosuppressant therapies for solid organ transplantation. This came into effect in February 2009; the belatacept development program is generally consistent with that guidance.

Table 1: Summary of FDA Interactions

Date	Interaction
October 2000	Investigational new drug (IND) application for solid organ transplantation.
September 2004	End-of-Phase-2 Meeting. The following were agreed with the FDA: <ul style="list-style-type: none">• Key elements of the Phase 3 studies, including the co-primary endpoints of non-inferiority on the composite of death and graft loss with a 10% margin, and superiority on the composite renal impairment endpoint.• The definition and analyses of AR and other CV and metabolic endpoints of clinical importance.• Clinical pharmacology program.
January 2005	Fast track designation on the basis of the belatacept's potential to address a serious aspect (renal function) of a serious disease (organ transplantation).
August 2005	Special Protocol Assessment for Study IM103008 submitted to the FDA and agreed upon.
December 2007	FDA request for assessment of mycophenolic acid (MPA)/MPAG (the glucuronide metabolite of MPA) levels in belatacept-treated subjects.
February 2008	Orphan designation based on the limited number of renal transplant recipients in US.
April 2008 and May 2009	Pre-Biologics Licensing Application (BLA) meetings where agreements were reached on the format, content, and timing of the BLA.
June 2009	BLA submitted to the FDA.
November 2009	Safety Update Report submitted to the FDA.

4 BACKGROUND

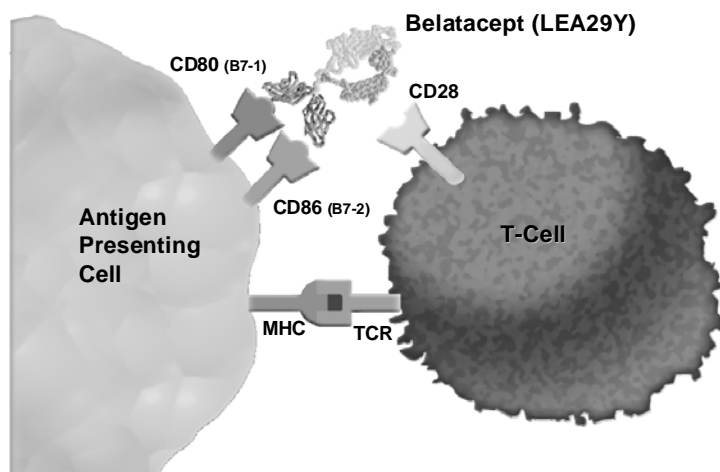
4.1 Mechanism of Action

Belatacept (LEA29Y, BMS-224818) represents a new class of therapeutic agents in transplantation immunosuppression that differs from existing immunosuppressive agents in the restricted distribution of its molecular target and the specificity of its effect. Belatacept is a recombinant soluble fusion protein consisting of the extracellular domain of human CTLA-4 and a fragment (hinge–CH2–CH3 domains) of a modified Fc domain of human IgG1.

Belatacept is a second generation, higher avidity variant of abatacept (Orencia[®]), a marketed compound for reducing signs and symptoms in adult subjects with moderately

to severely active rheumatoid arthritis and in children with moderately to severely active polyarticular juvenile idiopathic arthritis. Belatacept targets the blockade of CD28:CD80/CD86 interactions, key costimulatory signals required for T-cell activation (Figure 1). Activated T cells are the predominant immune mediators of allograft rejection. T cells require at least 2 signals for full activation. The first signal is delivered by the T-cell receptor and the second via costimulatory molecules. The interaction of CD28 with CD80 and CD86 is the most important costimulatory signal for the initial activation of naive T cells.

Figure 1: Belatacept Potently and Selectively Blocks T-cell Activation



4.2 Nonclinical Toxicology

Belatacept was evaluated in a comprehensive drug safety evaluation program, which supports the dose and regimens for belatacept used clinically. Although the 2 amino acid mutations in belatacept increase binding affinity in human and non-human primates for CD80 and CD86 as compared to abatacept, the binding affinity of belatacept for murine CD80 and CD86, as well as in vivo bioactivity in rodents, is lower with belatacept as compared to abatacept. Therefore, abatacept was used for chronic rodent toxicology and carcinogenicity assessments. Other relevant abatacept toxicology studies, which complement the belatacept studies, were also included. Key findings from general

toxicology studies, and findings regarding malignancy, host resistance to infection, autoimmunity and reproductive toxicology are summarized below.

In mice treated for up to 6 months with abatacept (at exposures ≥ 5 times the exposure of belatacept in humans) and in monkeys treated for up to 6 months with belatacept (≥ 6 times the exposure of belatacept in humans) or up to 1 year with abatacept (≥ 9 times the exposure of belatacept in humans), all findings were reversible, related to the pharmacology of the drug, except for renal karyomegaly observed only in mice and not considered relevant to humans. The findings related to pharmacology include minimal decreases in serum IgG and/or minimal to moderate decreases in the size and number of lymphoid germinal centers. There were no clinical manifestations of infections or dose-limiting or significant target-organ toxicities, including in the CNS.

No evidence of lymphomas, solid tumors, or preneoplastic morphologic changes, such as lymphoid hyperplasias, were observed in the chronic monkey studies despite the confirmed presence of viruses known to induce these changes in the abatacept-treated monkeys and presumably in the belatacept monkeys. However, there was an increased incidence of virally mediated tumors in the carcinogenicity study in mice including an increased incidence of mammary tumors at higher doses and lymphoma at all doses, presumably due to decreased control of murine specific viruses in the presence of long-term immunomodulation.

Murine host resistance studies suggest that protective in vivo immune responses to most pathogens are largely preserved in animals treated with CD28 costimulation blockade. However, belatacept may increase the risk of clinical infection by some pathogens (e.g., herpes simplex virus) that require an effective CD4⁺ T cell-mediated immune response for eradication or control. No increases in infections were observed in toxicology studies conducted in monkeys, mice, or adult rats. In contrast, infections leading to moribundity and deaths were observed in juvenile rats given abatacept and pregnant and lactating rats given belatacept, likely a consequence of immature and/or compromised immune function in these animals.

No evidence of autoimmunity was observed following long-term treatment with belatacept or abatacept in mice or monkeys. However, rats treated with abatacept for up to 3 months exhibited histologic findings of autoimmune toxicities affecting the pancreas

and thyroid. Importantly, no evidence of autoimmunity has been observed following long-term treatment with belatacept and/or abatacept in mice, monkeys or humans, indicating that rats may be uniquely sensitive to the effects of CD28 blockade.

No effect on fertility or teratogenicity was observed with belatacept or abatacept. Belatacept was excreted in the milk of lactating rats. It is not known whether belatacept is excreted in human milk or absorbed systemically after ingestion by a nursing infant. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from belatacept in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Treatment of rats with abatacept during early gestation and throughout the lactation period showed limited alterations of immune function in the F₁ generation. An increase in the T cell-dependent antibody response in female pups and an isolated case of inflammation of the thyroid were observed at exposures 11 times the exposure of belatacept in humans.

In humans, belatacept use was associated with an increased number of PTLD cases, particularly PTLD involving the CNS (see Section 7.2.3). In addition there were 2 cases of PML in belatacept MI-treated subjects (1 in a renal transplant recipient and 1 in a liver transplant recipient). Potential mechanisms for the increased incidence of CNS PTLD and the occurrence of PML in human transplant patients treated with belatacept as compared with CsA were investigated in monkeys by evaluating the effect of belatacept on CNS immunity. Belatacept did not penetrate the blood-brain barrier and did not impact the number of immune cells (macrophage, dendritic cells, T cells, and B cells) or CD80 or CD86 expression in the brain of healthy monkeys. In addition, CD86 was not detected on brain endothelial cells of these monkeys. In another study, the effect of belatacept on the chemotaxis of immune cells across human brain microvascular endothelial cells in vitro was evaluated. Although CD86 was demonstrated to be expressed on these cells, belatacept did not inhibit the migration of T cells across the cells in response to a chemokine signal. Thus, belatacept does not appear to have a direct effect on the CNS or impair the ability of cells to traffic into the CNS.

4.3 Clinical Pharmacology

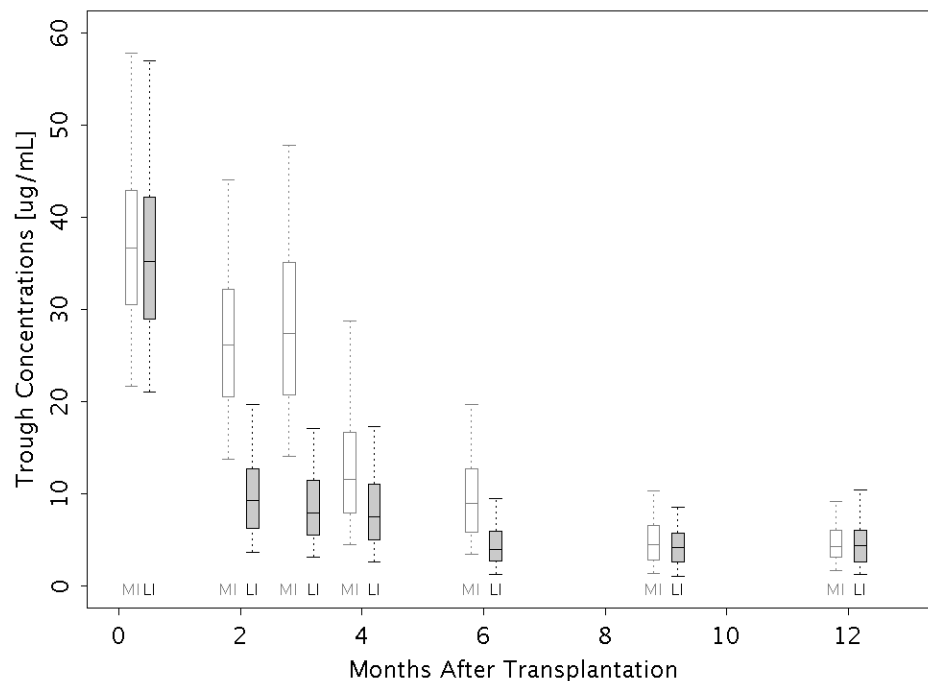
Belatacept has a consistent and predictable pharmacokinetic (PK) profile. It exhibits linear pharmacokinetics, a low volume of distribution consistent with restriction to the extracellular space, and an apparent terminal elimination half-life in serum of approximately 8 to 10 days.

Belatacept clearance and volume of distribution increased with body weight, supporting body weight-based dosing (mg/kg). Age, gender, race, renal function, hepatic function, diabetes, and concomitant dialysis did not affect clearance of belatacept.

The time invariance of belatacept PK, minimal potential for PK drug-drug interaction, and the low mean variability in belatacept exposure indicate that dose is a good predictor of belatacept exposure and support that therapeutic drug monitoring is not necessary for belatacept.^{27,28,29}

Based on an integrated assessment of the in vitro PK-PD relationship for the inhibition of allo-response by belatacept and results from an in vivo primate transplant model, target trough concentrations of 20, 5, and 2 µg/mL during Month 1, Month 2 to 3, and Month 4 to 6 after transplantation, respectively, were identified to design the dose regimens in renal transplantation subjects. Overall, > 80% of the renal transplant recipients treated with the recommended dosing regimen (LI regimen) achieved the intended target trough concentrations in Phase 3 studies. Data from the Phase 3 studies also demonstrated that the observed trough concentration of belatacept during Month 2 to 7 was approximately 2 to 3-fold higher for the MI regimen compared to the LI regimen (Figure 2), consistent with the 2-fold higher cumulative dose for the MI regimen during Month 2 to 6. Trough concentrations of belatacept were then tapered to similar values during the maintenance phase (beyond Month 7), when the dose and frequency of administration were identical for the 2 regimens.

Figure 2: Belatacept Serum Trough Concentrations for LI and MI Regimens in Phase 3 Studies - Observed Data Pooled from IM103008 and IM103027



Distribution of belatacept trough concentration in subjects treated with belatacept in Phase 3 Studies IM103008 and IM103027; the horizontal line in the middle of the box is the median, the box is the inter-quartile range 25th percentile to 75th percentile, the whiskers are the 5th and 95th percentiles.

Mycophenolic Acid Exposure

CsA lowers MPA exposure by inhibiting the entero-hepatic recirculation of MPA; MPA is the active form of MMF. When similar doses of MMF were administered together with belatacept or CsA, approximately 40% higher MPA exposures were observed in subjects receiving the belatacept-based regimen compared with the CsA-based regimen.

The clinical relevance of the increased exposure to MPA in belatacept-treated subjects is unknown. Despite increased exposure to MPA, there was not a greater frequency of MMF-related toxicities, such as gastrointestinal adverse events (AEs) or leukopenia, in belatacept- versus CsA-treated subjects.

Regarding immunosuppressive efficacy, earlier clinical trials have demonstrated that 3 g versus 2 g per day of MMF results in approximately 40% higher MPA exposure. This is similar to the increase in exposure seen in belatacept compared with CsA treated subjects. These earlier trials showed that an increase in MPA exposure of this degree may not result in reductions in AR.^{30,31} Increased exposure to MPA has been associated with reductions in AR in several recent studies.^{27,32,33} However, a 53% rate of AR was seen in a study of basiliximab, MMF and corticosteroids, a regimen that would, due to the absence of CsA, result in MPA exposure similar to the belatacept studies. Thus, an increase in MPA exposure alone does not explain the much lower AR rates of 17% to 22% (see Section 6.3.1) seen in the belatacept Phase 3 studies.

5 CLINICAL DEVELOPMENT PROGRAM

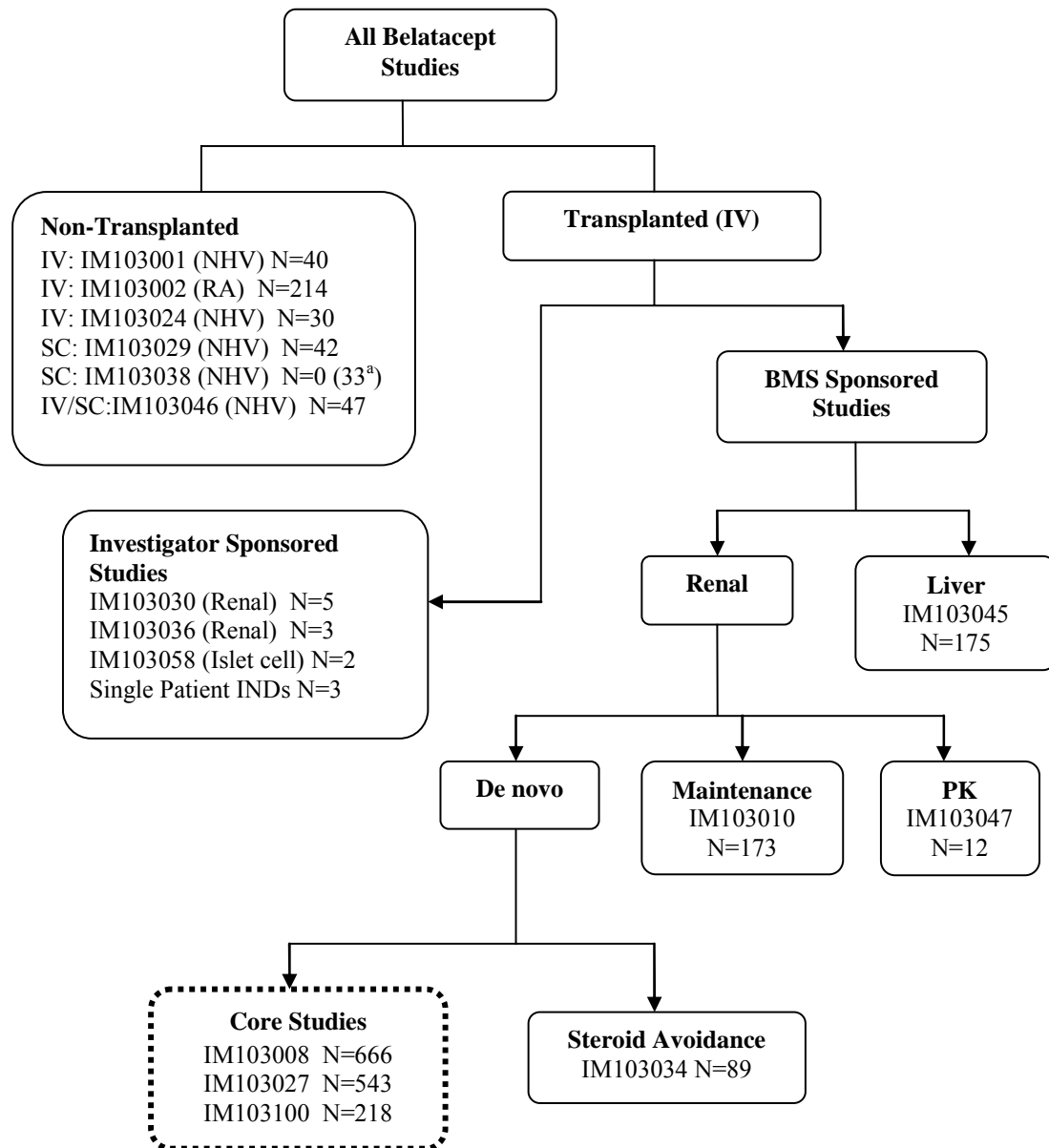
5.1 Overview of the Clinical Development Program

The efficacy and safety profile of belatacept was characterized in a comprehensive development program that included studies in healthy volunteers, in transplant recipients, in subjects with rheumatoid arthritis, and in investigator-sponsored studies (Figure 3). Overall, 2249 subjects have been enrolled in belatacept clinical studies as of January 2009, of whom 1436 have received belatacept.

The primary efficacy and safety data in support of belatacept comes from 3 similarly designed studies in de novo renal transplant recipients, hereafter referred to as the core studies: a Phase 2 study (IM103100) and 2 Phase 3 studies (IM103008 and IM103027). All 3 studies are ongoing (Table 2).

Belatacept is also being evaluated in 4 additional ongoing Phase 2 studies, which evaluate belatacept in combination with different immunosuppressive agents or in different populations: IM103034 (a steroid avoidance study in renal transplant subjects), IM103010 (a calcineurin inhibitor [CNI] switch study in subjects who had received a renal transplant prior to enrollment), IM103045 (a study in liver transplant subjects), and IM103047 (a PK study in renal transplant subjects).

Figure 3: Belatacept Clinical Development Program



^a Follow-up immunogenicity study: N = 33 subjects who were treated in IM103029
IV = intravenous, NHV = normal healthy volunteer, RA = rheumatoid arthritis

Table 2: Core Phase 2 and 3 Clinical Studies with Belatacept in Transplant Recipients

Study Number	Objectives	Study Design	Type of Subjects	Dosage Regimen Background Therapy	Study Duration	No. of Subjects (ITT)
IM103008	Efficacy, safety, immunogenicity, PK	Phase 3, randomized, partially-blinded, active-controlled	De novo renal transplant, SCD	IV belatacept (MI and LI) or CsA ^a Basiliximab induction, and maintenance with MMF + corticosteroids	3 years	Bela MI: 219 Bela LI: 226 CsA: 221
IM103027	Efficacy, safety, immunogenicity, PK	Phase 3, randomized, partially-blinded, active-controlled	De novo renal transplant, ECD	IV belatacept (MI and LI) or CsA ^a Basiliximab induction, and maintenance with MMF + corticosteroids	3 years	Bela MI: 184 Bela LI: 175 CsA: 184
IM103100	Efficacy, safety, immunogenicity, PK Efficacy, safety	Phase 2, randomized, partially-blinded, active-controlled Long-term extension	De novo renal transplant	IV belatacept (MI and LI) or CsA ^b Basiliximab induction, and maintenance with MMF + corticosteroids Belatacept: 5 mg/kg every 4 or 8 wks; IV or CsA: target trough level 150-300 ng/mL Maintenance with MMF or another approved IMPDH + corticosteroids (weaning/withdrawal permitted)	12 months Through Study Year 11 (Month 131) ^c	Bela MI: 74 Bela LI: 71 CsA: 73 No. entered Year 2 Bela MI: 52 Bela LI: 50 CsA: 26

ECD - extended criteria donors, IMPDH - inosine monophosphate dehydrogenase, ITT - intent-to-treat population, IV - intravenous, MMF - mycophenolate mofetil, PK - pharmacokinetics, SCD - standard criteria donors

^a **Belatacept MI** = 10 mg/kg Days 1 and 5 then every 2 wks through Month 3, then every 4 wks through Month 6, then 5 mg/kg every 4 wks; **Belatacept LI**: 10 mg/kg Days 1 and 5, then every 2 wks through Month 1, then every 4 wks through Month 3, then 5 mg/kg every 4 wks; **CsA** = twice daily for trough serum 150-300 ng/mL during Month 1 and 100-250 g/mL thereafter

^b **Belatacept MI** = 10 mg/kg Days 1, 5, 15 then every 2 wks through Month 3, then every 4 wks through Month 6, then 5 mg/kg every 4 or 8 wks; **Belatacept LI** = 10 mg/kg Days 1, 15, 29, 57, 85, then 5 mg/kg every 4 or 8 wks; **CsA** = 7 ± 3 mg/kg then dose for target serum levels (Month 1, 150-400 ng/mL; thereafter, 150-300 ng/mL)

^c If belatacept is not approved by Study Year 11 (Month 131) in the individual countries where the subjects are enrolled, it will be extended for another year.

5.2 Study Design and Methods of the Core Studies

5.2.1 Phase 2 Study (IM103100)

Study Design

The IM103100 study was a Phase 2 trial in de novo renal transplant recipients designed to assess the efficacy of belatacept versus CsA at 6 months, when used in combination with MMF, corticosteroids, and basiliximab, using a non-inferiority design.

Dose Selection

Two (2) dosing regimens, a less intensive (LI) and a more intensive (MI) regimen, were tested in Phase 2. The regimens were designed based on a stepwise approach and an integrated assessment of in vitro, nonclinical, and clinical data. In order to maximally inhibit allo-response and provide transplant efficacy, the target concentrations (see below) for the LI and MI regimens were selected from a PK-PD relationship for the inhibition of allo-response in vitro. These target concentrations were first tested in a primate renal transplant study and shown to have transplant immunosuppressive efficacy.

Both regimens employed a 10 mg/kg dose during the initial post-transplant phase, but varied with regard to the rapidity of the taper. The LI dosing regimen was targeted to achieve C_{min} of 20 µg/mL through Day 29 after transplantation and 5 µg/mL through Month 3, while the MI dosing regimen was targeted to achieve C_{min} of 20 µg/mL through Month 3 and 5 µg/mL through Month 6. During the maintenance phase, a once-every-8-week and a once-every-4-week dosing schedule (dose 5 mg/kg) were evaluated to target maintenance C_{min} of 0.25 and 2 µg/mL, respectively.

Results

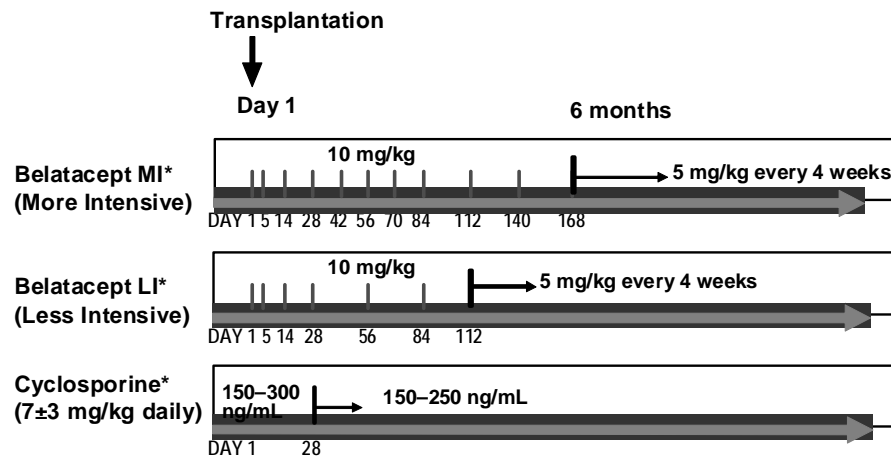
In this Phase 2 study, a total of 74, 71, and 73 subjects were randomized to the belatacept MI, belatacept LI, and CsA groups, respectively. Belatacept was as effective as CsA in the prevention of death, graft loss, and AR. Rates of subclinical rejection were higher in the LI group, and in those randomized to the every 8 week maintenance schedule. Assessments of renal function and chronic allograft nephropathy favored belatacept compared with CsA. Evaluations of blood pressure, cholesterol, and hemoglobin A1c

modestly favored belatacept. The overall safety profile of belatacept and CsA was similar. AEs commonly associated with treatment with CNIs were less common with belatacept than with CsA in this study. Three (3) cases of PTLD occurred in the belatacept MI treatment group. A total of 128 subjects entered the long-term extension phase (102 in the belatacept group and 26 in the CsA group) and data are available for over 70 subjects treated with belatacept for at least 5 years in this study. GFR in this cohort has been maintained over time (mean GFR was 74 mL/min/1.73m² at Month 84) and no new safety findings have emerged.

5.2.2 Dose Selection for Phase 3

In the Phase 2 study, the belatacept MI regimen demonstrated acceptable efficacy, but 3 cases of PTLD were reported in MI-treated subjects, while the LI regimen was associated with an elevated rate of subclinical rejection and no cases of PTLD. As a result, the MI regimen studied in Phase 2 was taken forward into the Phase 3 trials to further characterize its efficacy and safety. A Day 5 dose was added to the Phase 2 LI regimen (i.e., there were 4 belatacept doses of 10 mg/kg during Month 1 post-transplant in the Phase 3 LI regimen while there were 3 belatacept doses of 10 mg/kg during Month 1 post-transplant in the Phase 2 LI regimen) to ensure that target drug concentrations were achieved in the early period after transplantation and to reduce the rates of subclinical rejection. This updated LI regimen was then studied in Phase 3 to determine if it would provide comparable efficacy to the MI regimen, but reduce the overall burden of immunosuppression and offer an improved safety profile. In addition, maintenance dosing was established at 5 mg/kg every 4 weeks based upon the higher rates of subclinical rejection noted with the every 8 week schedule in the Phase 2 study.

Figure 4: Belatacept Treatment Regimens in the Phase 3 Studies



* All subjects received basiliximab induction, mycophenolate mofetil, and corticosteroid-taper.

5.2.3 Study Design of the Phase 3 Studies (IM103008 and IM103027)

The 2 Phase 3 studies enrolled complementary de novo renal transplantation populations covering the breadth of donor types from deceased, non-heart beating to living donors.

- IM103027 enrolled recipients of organs from deceased donors who met the higher risk, extended donor criteria.
 - Donor age ≥ 60 years, or
 - Donor age 50 to 59 years and ≥ 2 of the following: cerebrovascular accident, hypertension, and serum creatinine >1.5 mg/dL, or
 - Anticipated cold ischemia time ≥ 24 hours, or
 - Donor with cardiac death (non-heart beating donor)
- IM103008 enrolled recipients of organs from living donors and deceased donors who did not meet specified extended donor criteria (standard criteria donor).

The core studies were randomized, global, active-controlled clinical trials. The studies were blinded with respect to assignment of belatacept dose regimen (MI or LI regimen) and open-label with respect to allocation to treatment (belatacept or CsA). Full blinding (belatacept versus CsA) was precluded because of practical and medical reasons,

including needs for periodic dose-level monitoring and dose adjustment needed in CsA-treated subjects.

CsA was selected as the comparator as it had been demonstrated to provide superior graft survival to azathioprine, thereby supporting the establishment of a non-inferiority margin for the primary endpoint of subject and graft survival (see Section 5.2.5). When the belatacept program was designed, a CsA- based regimen in combination with MMF was selected as a comparator because it was the most familiar regimen in renal transplantation and one which was reviewed and approved by the FDA. In 2009, FDA assessed the safety and efficacy of a tacrolimus regimen with MMF and approved labeling for this regimen. Although tacrolimus is the predominant cornerstone CNI used in the United States today, CsA continues to be used as well.

In the core belatacept clinical studies, background medications, including basiliximab, MMF, and corticosteroids, were required by the protocol in all treatment groups. MMF, corticosteroids, and basiliximab were used as concomitant medications with belatacept in non-human primate de novo renal transplant studies where this quadruple drug regimen was successful in prolonging graft survival in this non-human primate model.³⁴ CNI-based immunosuppressive regimens commonly include this same background maintenance regimen with an IL-2 blocker as an induction agent.⁷ Thus, this background regimen allows a direct comparison of belatacept and CsA and facilitates interpretation of the study findings.

Both Phase 3 studies included an evaluation of the primary endpoints at 1 year, but were designed as 3-year studies to characterize long-term efficacy and safety. Thus, while the primary evaluation of efficacy is based on assessments at 12 months; longer term data (follow-up of at least 2 years for all subjects) are available and provided in this document.

5.2.4 Phase 3 Study Endpoints

Co-primary endpoints for the belatacept Phase 3 studies were:

- The composite of subject and graft survival
- A composite renal impairment endpoint to assess preservation of renal function
- Frequency of AR (IM103008 only)

Key secondary endpoints for both studies were measured GFR and biopsy proven chronic allograft nephropathy at Month 12. Established CV risk factors, including NODAT, hypertension, and dyslipidemia were also assessed.

Subject and Graft Survival

Subject and graft survival are the most important clinical endpoints for renal transplant recipients, as the ultimate goal of renal transplantation is to provide patients a functioning kidney that will enhance overall health and longevity.

Death and graft loss are objective endpoints and are relatively immune to the potential bias that can occur in open-label studies such as those in the belatacept program. To minimize any potential bias in reporting of the critical events of subject and graft survival in belatacept trials, independent event adjudication committees assessed death, graft loss and CV events of myocardial infarction and stroke.

In order to provide as complete a data set as possible, a rigorous approach to collection of subject and graft survival status was incorporated into the conduct of these trials. All randomized subjects were asked to participate in milestone visits to monitor survival status and to receive follow-up phone calls if they were unable to attend visits, even after discontinuation of study medication.

Preservation of Renal Function

Optimizing renal function is essential to successful transplantation due to the strong association between renal function and transplant recipient health. Studies in transplanted and non-transplanted populations indicate that subjects with improved renal function experience better quality of life and fewer end-stage renal disease related comorbidities, including hypertension, anemia, malnutrition, and bone disease.^{35,36,37} As renal function is the strongest determinant of long-term graft survival, CV events, and transplant recipient mortality,^{2,3,4,5} the observed benefit in renal function can be expected to have a favorable impact on the long-term outcomes in renal transplant recipients.

The primary renal endpoint in the Phase 3 studies was the proportion of subjects with absolute GFR < 60 mL/min/1.73 m² at Month 12 or with a decline ≥ 10 mL/min/1.73 m² from Month 3 to 12. These were selected to approximate the thresholds of absolute renal

function using serum creatinine (SCr) > 1.5 mg/dL) and renal function decline (> 0.3 mg/dL) that have been shown to predict long-term graft failure. To augment interpretation of the pre-specified composite endpoint of renal function, additional measures of renal function were assessed. Mean GFR values based on measured and calculated (estimated) GFR assessments provide an alternate presentation to facilitate interpretation of the effect of belatacept versus CsA on renal function.

Renal function differences were categorized using the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative stages of chronic kidney disease (CKD)³⁵ classification, which has been developed to associate the level of kidney function with the complications of CKD and to stratify the risk of loss of kidney function and the development of CV disease.

Clearance of an iothalamate, a true glomerular filtration marker and "gold standard" method for assessing renal function, was used to assess the primary endpoint of renal function in these studies (i.e., measured GFR). To further standardize assessment of GFR in the belatacept Phase 3 trials, samples were analyzed at a blinded, experienced central laboratory using a validated assay and extensive quality control measures.

The Modification of Diet in Renal Disease (MDRD) formula, proposed by Levey et al., using isotope-dilution mass spectrometry-traceable assays was used for calculating GFR in the belatacept Phase 3 studies. This formula has been shown to predict GFR more accurately in the transplant population, and has the best correlation between predicted and measured value compared with other formulae, such as Nankivell.^{38,39}

Chronic allograft nephropathy was selected as a key secondary endpoint in the Phase 3 studies at Month 12 as it is a permanent, structural measure that reflects renal function and has important clinical implications. Chronic allograft nephropathy is a final common pathway of many pathologic processes such as chronic rejection or drug nephrotoxicity that can impact long term graft survival¹⁰ and is the leading cause of graft loss after the first year.¹¹ The current Banff Classification of Renal Allograft Pathology uses the term "interstitial fibrosis and tubular atrophy" rather than chronic allograft nephropathy, the term in use at the time the protocols were developed.⁴⁰ The histologic criteria for the definition of interstitial fibrosis and tubular atrophy are analogous to those used to define

chronic allograft nephropathy. Chronic allograft nephropathy provides the structural correlate of renal function assessed by measured and calculated GFR.

Acute Rejection

While the occurrence of AR has historically been associated with inferior graft outcomes, data support that all AR episodes do not have the same impact on patient and graft survival. The impact of early, cellular, and treatable AR on long-term patient and graft outcomes may be less than episodes lacking these characteristics.⁴¹ The belatacept Phase 3 program specified that AR rates must be considered in the context of the totality of the data, and that features of AR beyond incidence rates would be assessed. These measures include an analysis of the timing, characteristics (including the presence of anti-donor HLA antibodies) and outcomes of AR.

While accepted as a secondary endpoint by the FDA, AR was made the third co-primary endpoint in Study IM103008 due to a recommendation by the CHMP. In IM103027, AR was a secondary endpoint because it was expected that the accentuated bias against belatacept, due to the expected high frequency of delayed graft function and the use of lymphocyte depleting therapy for anticipated delayed graft function in CsA-treated patients in the extended criteria donor population, would confound comparison of AR rates.

AR was defined as biopsy-proven rejection (read by the central pathologist) that was either clinically suspected according to protocol-defined reasons or clinically suspected for any reason and treated. Histologic assessment adhered to the Banff 97 criteria⁴² which are based upon the location and extent of lymphocytic infiltrates in the graft. The protocol defined reasons for clinical suspicion of AR were: an unexplained rise of serum creatinine $\geq 25\%$ from baseline; unexplained decreased urine output; fever and graft tenderness; or, serum creatinine that remained elevated within 14 days post-transplantation.

Cardiovascular and Metabolic Endpoints

Cardiovascular disease is the most common cause of death in renal transplant recipients with a functioning graft.⁷ Renal transplant recipients have a 50-fold higher risk of CV

death than the general population. CNI-related side effects, including diabetes mellitus, lipid abnormalities, and hypertension may exacerbate underlying disease and further increase CV risk for renal transplant recipients. Diabetes onset after renal transplantation is associated with increased CV events and reduced allograft and subject survival.^{43,44,45}

The goals of the belatacept development program focus on improving factors that impact long-term outcome of renal transplant recipients. Therefore, measures of diabetes, lipid abnormalities, and hypertension, which are associated with long-term renal transplant outcome, were included as efficacy measures in the belatacept Phase 3 studies.

5.2.5 Design Considerations in the Belatacept Phase 3 Program

The co-primary objectives in both Phase 3 studies were to demonstrate that belatacept, as compared to CsA, was:

- Non-inferior in the composite endpoint of subject and graft survival at 12 months with a pre-specified margin of 10%.
 - A 10% non-inferiority margin for the co-primary endpoint of subject and graft survival was selected based on regulatory precedent with the primary endpoints employed in pivotal studies in similar registrational studies (tacrolimus, sirolimus).
 - Consistent with the ICH guidance, 10% is also lower than the estimated smallest effect size of CsA, 11.1%, which was obtained from the CsA registrational studies. These were the only available studies that had demonstrated the superiority of CsA with respect to subject and graft survival at 1 year. The comparison group in these studies was treated with azothioprine plus steroids rather than placebo.
 - Given the sample size assumptions regarding patient and graft survival, the 10% non-inferiority margin would ensure that the observed rate of subject and graft survival in a given belatacept group could not differ from that observed in the CsA group by more than 3% in IM103008 and 0.5% in IM103027, while still satisfying the 10% margin.
 - This margin established the minimal threshold for further evaluation of the totality of the study results, consistent with regulatory precedent. This includes the assessment of superiority in renal function required for both of the belatacept studies as the second co-primary endpoint. This margin was not intended to establish a bound for clinical indifference in this endpoint. To exclude such a narrow margin would render the trials infeasible in renal transplantation.

- While the prespecified non-inferiority margin was used for estimation of sample size of the studies, the observed results of this non-inferiority endpoint demonstrated that subject and graft survival favored belatacept, and the lower limits of the difference in subject and graft survival between belatacept and CsA were well within the limits of the 10% non-inferiority margin (see Section 6.1).
- The following imputation method was used to address any missing data for the primary survival analysis at Month 12: a subject with unknown status at Month 12 was considered as having met the endpoint if the subject had AR, chronic allograft nephropathy, PTLN, malignancy, discontinuation of study medication due to lack of efficacy or due to pre-specified AEs, a last measured or calculated $\text{GFR} < 40 \text{ mL/min/1.73 m}^2$, or delayed graft function during 12 months after transplantation. Otherwise, a subject with unknown status at Month 12 was considered as having not met the endpoint.
- Superior in the composite endpoint of measured $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$ at Month 12 or a decrease of $\geq 10 \text{ mL/min/1.73 m}^2$ from 3 to 12 months.
 - Imputation method used for the primary analysis at Month 12: a subject with missing measured GFR was considered as meeting the composite endpoint if a subject had a graft loss or death during the 12-month post-transplant period. Linear regression and quartile methods were used to impute other missing GFR values using available iothalamate and MDRD GFR values. Subjects with missing GFR values after the imputation methods were applied were excluded from the analysis.
- Non-inferior in the frequency of AR by 12 months (a third co-primary objective in IM103008 and a secondary objective in IM103027), with a pre-specified margin of 20%.
 - This margin was not intended to define a criterion for establishing clinically comparable rates of AR between belatacept and CsA. Rather, it established a framework for the statistical evaluation of the frequency of rejection, anticipating that the full evaluation of this endpoint would require detailed characterization of the episodes that extended beyond the number observed.
 - Based on limited clinical experience with CsA-free regimens, the smallest effect size of CsA on this endpoint was estimated to be 38% absolute reduction in rejection rate. Selection of a 20% non-inferiority margin therefore preserves ~ 50% of this estimated CsA effect and is not greater than the estimated smallest effect size of CsA used with similar background therapy.
 - The margin was considered clinically justified in conjunction with superiority in renal function and non-inferiority in subject and graft survival, as clinically important rejection episodes were expected to be reflected in these endpoints as well.

- Finally, given the emerging understanding of AR features that impact outcome, belatacept studies were designed to assess the totality of the AR data, including clinical and histologic characteristics of AR episodes and outcomes of subjects who had AR. This allowed interpretation of the rejection rate in the overall clinical benefit-risk assessment of belatacept.
- There was no imputation of missing values for this endpoint.

A sequential testing procedure was employed in the Phase 3 studies for testing the co-primary and key secondary hypotheses (not including measured GFR at Month 12) according to the pre-specified hierarchy order. The nominal type I error rate was set at 2.7% using Dunnett adjustment, preserving the overall experiment-wise type I error rate at 2.7% for each belatacept treatment group versus the CsA group and at 5% overall for the entire study. The treatment differences between each belatacept treatment group and CsA group were tested at the 0.027 significance level. All tests for treatment comparison were 2-sided.

There was no statistical testing of group differences with respect to frequencies of AEs; comparative statements were based on clinical interpretation of the data.

5.2.6 Key Endpoint Data Collection

Rates of collection of key assessments in the Phase 3 studies were high, strengthening the interpretation of the study results (Table 3). Rates of collection of measured GFRs and protocol biopsies for chronic allograft nephropathy were better than what has been previously reported in multicenter trials in transplantation.^{26,46,47}

Table 3: Availability of Key Data in Belatacept Phase 3 Studies (% of Subjects with Data)

Parameter	IM103008	IM103027
Subject and Graft Status at Month 12	99.5	98
Measured GFRs		
Month 3	91	90
Month 12	88	84
Calculated GFRs		
Month 3	93	95
Month 12	90	87
Centrally-read Biopsies		
Baseline	89	85
Month 12	79	73
Acute Rejection	94	94

Data from Year 1 database lock.

5.3 Subject Characteristics

The 3 core studies enrolled a broad range of renal transplant recipients and donor types, reflecting the diversity of patients in the renal transplant population. Baseline characteristics were similar across treatment groups within each of the core studies and baseline disease characteristics were consistent with the inclusion criteria for each study.

The baseline characteristics in the Phase 3 studies are shown in [Table 4](#). Most notably, recipients and donors of extended criteria donor kidneys (IM103027) were older compared with recipients and donors of standard criteria donor kidneys (IM103008).

Table 4: Selected Baseline Characteristics for Transplant Recipients in Phase 3 Studies

	IM103008			IM103027		
	Belatacept			Belatacept		
	MI N=219	LI N=226	CsA N=221	MI N=184	LI N=175	CsA N=184
Mean Age (years)	43.6	42.6	43.5	56.7	56.1	55.7
Gender (n, %)						
Male	151 (68.9)	146 (64.6)	165 (74.7)	119 (64.7)	129 (73.7)	116 (63.0)
Race (n, %)						
White	132 (60.3)	133 (58.8)	139 (62.9)	137 (74.5)	134 (76.6)	137 (74.5)
Black	15 (6.8)	23 (10.2)	17 (7.7)	25 (13.6)	24 (13.7)	22 (12.0)
Asian	27 (12.3)	29 (12.8)	27 (12.2)	7 (3.8)	3 (1.7)	4 (2.2)
Geographic Region (n, %)						
North America	95 (43.4)	92 (40.7)	94 (42.5)	49 (26.6)	40 (22.9)	45 (24.5)
South America	35 (16.0)	36 (15.9)	33 (14.9)	45 (24.5)	47 (26.9)	50 (27.2)
Europe	55 (25.1)	64 (28.3)	58 (26.2)	89 (48.4)	86 (49.1)	89 (48.4)
PRA (most recent) ≥ 20% (n, %)	23 (10.5)	30 (13.3)	18 (8.1)	0 (0.0)	1 (0.6)	6 (3.3)
Recipient EBV serology						
Positive	194 (88.6)	199 (88.1)	184 (83.3)	169 (91.8)	156 (89.1)	168 (91.3)
Negative	25 (11.4)	27 (11.9)	37 (16.7)	14 (7.6)	19 (10.9)	16 (8.7)
Unknown	0	0	0	1 (0.5)	0	0
Reported Cause of End-stage Renal Disease (n, %)						
Glomerulonephritis	48 (21.9)	73 (32.3)	55 (24.9)	41 (22.3)	46 (26.3)	33 (17.9)
Diabetes	31 (14.2)	22 (9.7)	26 (11.8)	26 (14.1)	19 (10.9)	36 (19.6)
Polycystic Kidneys	31 (14.2)	31 (13.7)	30 (13.6)	31 (16.8)	34 (19.4)	32 (17.4)
Dialysis Prior to Transplant, n (%)	177 (80.8)	192 (85.0)	186 (84.2)	172 (93.5)	165 (94.3)	170 (92.4)
Disease History, n (%)						
History of Diabetes	38 (17.4)	33 (14.6)	37 (16.7)	38 (20.7)	28 (16.0)	53 (28.8)
History of Hypertension	198 (90.4)	208 (92.0)	208 (94.1)	169 (91.8)	165 (94.3)	171 (92.9)
History of Dyslipidemia	97 (44.3)	91 (40.3)	91 (41.2)	90 (48.9)	97 (55.4)	103 (56.0)

PRA - panel reactive antibodies

Recipient EBV serology from BLA database lock; all other data from Year 1 database lock.

Baseline characteristics of transplant donors in the Phase 3 studies were consistent with each study's inclusion and exclusion criteria. In IM103008, 56% to 60% were living donors, 40% to 44% were deceased, and the mean cold ischemia time of the deceased donor kidneys ranged from 15 to 17 hours. In IM103027, all organs were from deceased donors (see Section 5.2.3 for definition of extended criteria donor).

In these studies, the distribution of human leukocyte antigen (HLA) mismatches in donor-recipient pairs was comparable; 47% to 55% of donor-recipient pairs had 3 to 4 mismatches, with approximately 20% with 1 to 2 mismatches and approximately 20% with 5 to 6 mismatches.

In the Phase 3 studies, 26% of subjects enrolled in Study IM103008 and 23% of those in Study IM103027 came from the US, with large proportions of subjects coming from Europe, and South America. Despite the fact that approximately 75% of the Phase 3 population were enrolled outside of the US, the trial data are applicable to the US population and practice due to similarities in the patient populations resulting from standardization of patient entry criteria and similarities in medical care provided across the global investigational sites as a result of the study protocols. Furthermore, the use of concomitant immunosuppressive medications, anti-microbial prophylaxis, procedures for the suspicion and treatment of AR, and assessment of renal function were standardized to be consistent with US medical practice. Finally, there were few differences in the efficacy and safety results across geographic regions, indicating that the results are generalizable to the US population.

5.4 Exposure and Follow-up

A total of 949 subjects have received belatacept in the core studies, with a median exposure of 5.7 years in IM103100, and 2 years in IM103008 and IM103027. At the time of database lock for the BLA, all subjects in these studies had passed the Month 12 milestone, and approximately 50% had passed the Month 24 milestone. A total of 77 subjects had received belatacept for 5 years and 27 had been treated for more than 7 years. In the pooled safety population, the median exposure to belatacept LI, belatacept MI, and CsA was 751, 754, and 724 days, respectively (see [Table 15](#)).

The median exposure at the time of the database lock for the Safety Update Report (SUR) had increased by approximately 100 days in each treatment group, with all subjects in the Phase 3 trials having passed the Month 24 milestone.

Subjects who discontinued study drug were asked to remain in the study to enable collection of key safety data. Therefore, the duration of follow-up is longer than the duration of exposure among subjects who have discontinued study therapy. Among subjects who discontinued study therapy for a reason other than death, the median additional follow-up after the date of treatment discontinuation was 334, 366, and 296 days in the belatacept MI and LI, and CsA groups, respectively.

In the Phase 2 and 3 studies, background immunosuppressive medication (basiliximab, MMF, and corticosteroids) use was balanced across the treatment groups, similar across studies, and administered in doses consistent with the protocol. CsA trough concentrations were also in the range specified in the protocol.

6 CLINICAL EFFICACY

Efficacy endpoints from the Phase 3 IM103008 and IM103027 studies are presented in this section. The primary evaluation of efficacy is based on assessments at 12 months using the Year 1 database lock (June/July 2008) or the BLA database lock (March 2009). Longer term data (with complete follow-up of 2 years) using the SUR database locks are available and also provided in this document.

6.1 Subject and Graft Survival

Both belatacept dose groups were non-inferior to CsA in the first co-primary endpoint of subject and graft survival in both studies, based on the pre-specified 10% non-inferiority margin (Table 5). Subject and graft survival was 95%, 97%, and 93% in the belatacept MI, LI and CsA groups, respectively in IM103008; 86%, 89%, and 85%, respectively, in IM103027. The observed lower bound of the 97.3% CIs for the difference between belatacept and CsA excluded a 1.5% to 4.3% difference from CsA for the LI regimen and a 2.9% to 6.6% difference from CsA for the MI treatment regimen across both Phase 3 studies. See Section 7.2.2 for causes of death.

In IM103008, there was no single predominant adjudicated cause of graft loss. In IM103027, primary graft thrombosis was the adjudicated cause of graft loss by Month 12 in 7/17 (41%) and 8/16 (50%) of the cases of graft loss in the belatacept MI and LI groups, respectively versus 2/20 (10%) of the cases of graft loss in the CsA group. While these rates of thrombotic graft loss in belatacept subjects differ from CsA, they are consistent with published data.⁴⁸ A thorough examination of thrombotic and embolic AEs did not identify an overall risk of thrombosis with belatacept (see Section 7.2.5.4).

Table 5: Subject and Graft Survival at Month 12: Primary Analysis

Endpoint	Number (%) of Subjects					
	IM103008			IM103027		
	Belatacept MI N = 219	Belatacept LI N = 226	CsA N = 221	Belatacept MI N = 184	Belatacept LI N = 175	CsA N=184
Sub/Graft Surv	209 (95.4)	218 (96.5)	206 (93.2)	159 (86.4)	155 (88.6)	156 (84.8)
Diff from CsA (CI) ^a	2.2 (-2.9, 7.5)	3.2 (-1.5, 8.4)	--	1.6 (-6.6, 9.9)	3.8 (-4.3, 11.9)	--
Death or GL ^b	10 (4.6)	8 (3.5)	15 (6.8)	25 (13.6)	20 (11.4)	28 (15.2)
Death	6 (2.7)	4 (1.8)	7 (3.2)	8 (4.3)	4 (2.3)	8 (4.3)
Graft Loss	4 (1.8)	5 (2.2)	8 (3.6)	17 (9.2)	16 (9.1)	20 (10.9)
Imputed as GL or Death	0	0	1 (0.5)	2 (1.1)	1 (0.6)	3 (1.6)

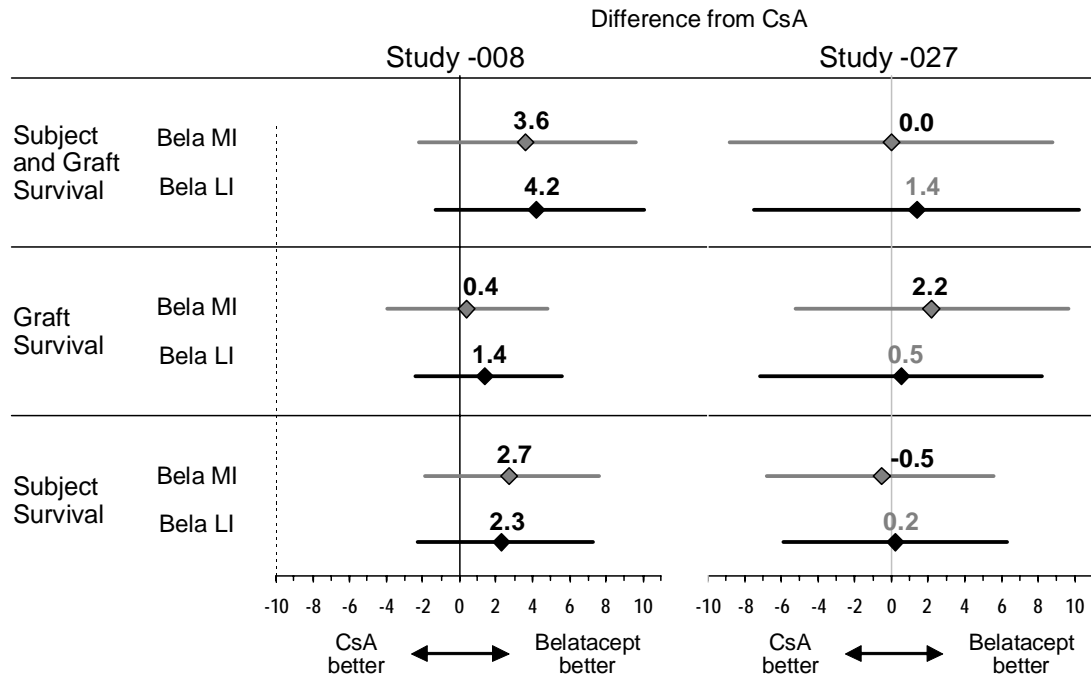
Data from the BLA database lock

^a 97.3% CI

^b A subject that had graft loss and then died by Month 12 was counted once in this row.

The similarity between the belatacept and CsA groups in subject and graft survival at 12 months was maintained at Month 24. Based on the SUR database lock, when all subjects had passed the 24 Month time point in the study, subject and graft survival was 94%, 95%, and 91% in the belatacept MI, LI, and CsA groups, respectively, in IM103008 and 83%, 84%, and 83%, respectively, in IM103027 (Table 6). The difference from CsA for each belatacept regimen on the composite of subject and graft survival and the individual components, with 97.3% CIs is presented in Figure 5.

Figure 5: Summary of Difference in Subject and Graft Survival up to Month 24



Difference (%) = Difference from CsA (97.3% CIs)

Composite endpoint of subject and graft survival is based on data with imputation.

Data from the SUR database lock.

Table 6: Summary of Difference in Subject and Graft Survival up to Month 24

	IM103008			IM103027		
	Belatacept MI N = 219	Belatacept LI N = 226	CsA N = 221	Belatacept MI N = 184	Belatacept LI N = 175	CsA N = 184
Subject and graft survival						
N (%)	206 (94.1)	214 (94.7)	200 (90.5)	152 (82.6)	147 (84.0)	152 (82.6)
Difference from CsA	3.6	4.2		0.0	1.4	
(97.3% CI)	(-2.2, 9.6)	(-1.3, 10.1)		(-8.8, 8.8)	(-7.5, 10.2)	
Graft survival						
N (%)	212 (96.8)	221 (97.8)	213 (96.4)	166 (90.2)	155 (88.6)	162 (88.0)
Difference from CsA	0.4	1.4		2.2	0.5	
(97.3% CI)	(-3.9, 4.8)	(-2.4, 5.6)		(-5.2, 9.6)	(-7.2, 8.2)	
Subject survival						
N (%)	212 (96.8)	218 (96.5)	208 (94.1)	171 (92.9)	164 (93.7)	172 (93.5)
Difference from CsA	2.7	2.3		-0.5	0.2	
(97.3% CI)	(-1.9, 7.6)	(-2.3, 7.3)		(-6.8, 5.6)	(-5.9, 6.3)	

Data from the SUR database lock.

Composite endpoint of subject and graft survival is based on data with imputation.

6.1.1 Summary of Subject and Graft Survival

In summary, all 4 belatacept groups were non-inferior to CsA for the primary endpoint of subject and graft survival at Month 12 and up to the SUR database lock across the 2 Phase 3 studies. Confidence intervals of the difference between belatacept and CsA show that a 1.5% and 4.3% difference was excluded for the recommended LI regimen at 12 months. Both the primary analysis and a pre-specified Month 24 analysis show a trend toward lower rates of death and graft loss for the LI regimen compared with CsA, leaving little uncertainty as to the non-inferiority of belatacept LI compared with CsA with respect to subject and graft survival.

6.2 Renal Function and Structure

Belatacept treatment resulted in clinically important improvements in renal function over CsA as assessed by both measured and calculated GFR. The differences between belatacept and CsA were seen as early as 4 weeks after transplantation, and maintained for a median of 2 years after transplantation in recipients of both standard criteria donor and extended criteria donor kidneys. The slopes of the calculated GFR curves over time were more favorable for the belatacept groups than for CsA. In addition, the difference in GFR between belatacept and CsA widened over time, particularly in recipients of standard criteria donor kidneys. The differences in GFR were accompanied by less chronic allograft nephropathy in belatacept-treated subjects than in CsA-treated subjects. The renal function improvements with belatacept treatment demonstrate better overall transplantation effectiveness, improved allograft health compared to treatment with a CsA-based regimen, and may have a favorable impact on long-term outcomes in renal transplant recipients.

6.2.1 Effects at 12 Months

In both Phase 3 studies, a smaller proportion of subjects in each belatacept group met the composite renal impairment endpoint (co-primary endpoint; $< 60 \text{ mL/min/1.73 m}^2$ or decrease of $\geq 10 \text{ mL/min/1.73 m}^2$ from Month 3 to Month 12, based on measured GFR). The difference for belatacept versus CsA was statistically significant for all but the LI group in IM103027, where differences trended favorably but did not reach statistical significance (Table 7). A lower proportion of subjects in each belatacept group met the composite renal impairment endpoint of in both Phase 3 studies based on calculated GFR.

Table 7: Composite Renal Impairment Endpoint at Month 12 Based on Measured GFR

	IM103008			IM103027		
	Belatacept MI N = 219	Belatacept LI N = 226	CsA N = 221	Belatacept MI N = 184	Belatacept LI N = 175	CsA N = 184
N in analysis	209	214	213	176	170	178
Met Endpoint, N (%)	115 (55.0)	116 (54.2)	166 (77.9)	124 (70.5)	130 (76.5)	151 (84.8)
GFR < 60	91 (43.5)	92 (43.0)	144 (67.6)	98 (55.7)	105 (61.8)	120 (67.4)
Decrease ≥ 10 M3 to M12	48 (23.0)	50 (23.4)	60 (28.2)	31 (17.6)	47 (27.6)	44 (24.7)
95% CI (%)	48.3, 61.8	47.5, 60.9	72.4, 83.5	63.7, 77.2	70.1, 82.8	79.6, 90.1
Diff from CsA (97.3% CI)	-22.9 (-32.6,-12.9)	-23.7 (-33.3,-13.7)	--	-14.4 (-24.0,-4.7)	-8.4 (-17.8, 1.0)	--
p-value	<0.0001	<0.0001	--	0.0018	0.0656	--

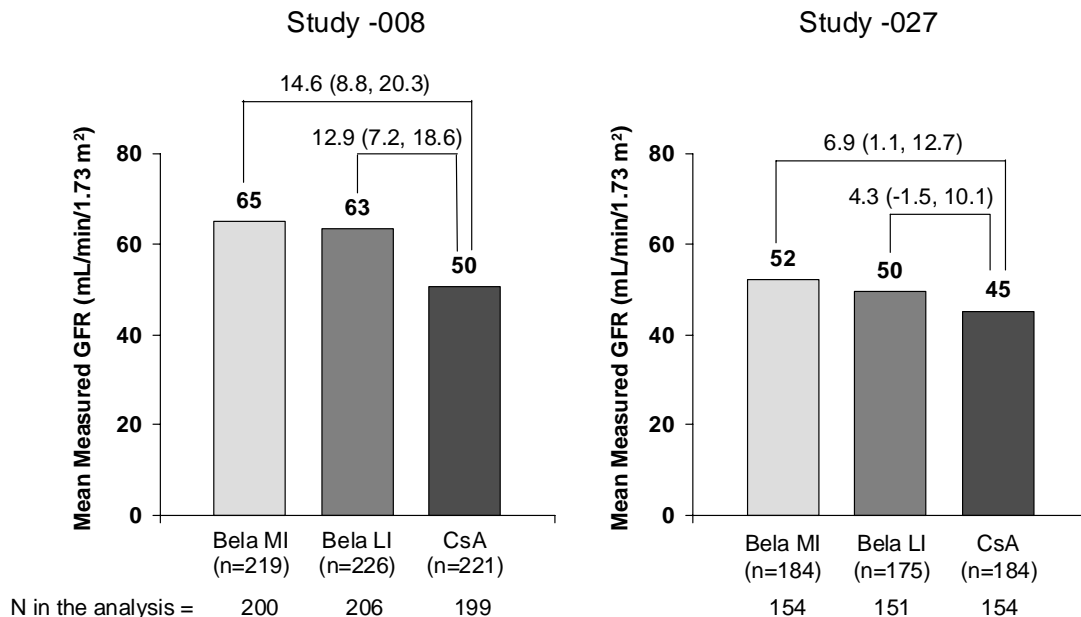
Data from the BLA database lock

Composite renal impairment endpoint: measured GFR < 60 mL/min/1.73 m² at Month 12 or decrease ≥ 10 mL/min/1.73 m² from Month 3 to Month 12

Compared with CsA, improvements in renal function with belatacept, as assessed by mean measured GFR at Month 12, were (Figure 6):

- 13 to 15 mL/min/1.73m² higher (25% - 30% over CsA) in recipients of standard criteria donor kidneys
- 4 to 7 mL/min/1.73 m² higher (10% - 15% over CsA) in recipients of extended criteria donor kidneys

Figure 6: Mean Measured GFR at Month 12



CI = 97.3% CI of the difference from CsA
Data from Year 1 database lock

The observed renal function differences were not explained by differential use of non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers across the treatment groups, and were consistent when compared to subjects with high or low CsA trough levels.

Structural changes consistent with the observed renal function improvement were also seen. Chronic allograft nephropathy (a histologic measure of allograft damage and a major contributor to late allograft loss) was assessed on protocol specified Month 12 allograft biopsies. Compared with CsA, subjects treated with belatacept had a 8% to 11% reduction in the prevalence of chronic allograft nephropathy (data pooled across both studies) at 12 months (Table 8). The prevalence of chronic allograft nephropathy at Month 12 was higher in IM103027 (45% - 52%) than in IM103008 (18% - 32%, Table 9). The presence of chronic allograft nephropathy was associated with greater impairment in renal function in all 3 treatment groups.

Table 8: Prevalence of Chronic Allograft Nephropathy at Month 12, Subjects Pooled by Randomized Treatment Group Across Studies IM103008 and IM103027

	Belatacept MI N = 403	Belatacept LI N = 401	Cyclosporine N = 405
Number of Subjects in the Analysis	402	400	403
Prevalence (n, %)	122 (30.3)	134 (33.5)	166 (41.2)
95% CI	25.9 - 34.8	28.9 - 38.1	36.4 - 46.0
Difference from CsA	-10.8	-7.69	--
Weighted Diff from CsA (97.3% CI)	-11.2 (-18.2, -4.1)	-7.4 (-13.9, -0.9)	-
p-Value	0.002	0.025	-

Data from Year 1 database lock

Table 9: Prevalence of Chronic Allograft Nephropathy at Month 12 in Each Phase 3 Study

	Belatacept MI N=219	Belatacept LI N=226	Cyclosporine N=221
IM103008			
Number of Subjects in the Analysis	219	226	219
Prevalence (n, %)	40 (18.3)	54 (23.9)	71 (32.4)
95% CI	13.1, 23.4	18.3, 29.5	26.2, 38.6
Difference from CsA (97.3% CI)	-14.2 (-23.2, -5.0)	-8.5 (-17.9, 0.9)	-
IM103027	N=184	N=175	N=184
Number of Subjects in the Analysis	183	174	184
Prevalence (n, %)	82 (44.8)	80 (46.0)	95 (51.6)
95% CI	37.6, 52.0	38.6, 53.4	44.4, 58.9
Difference from CsA (97.3% CI)	-6.8 (-18.2, 4.7)	-5.7 (-17.2, 6.0)	-

Data from Year 1 database lock

6.2.2 Temporal Trends

Improvements in renal function were apparent in the first month after transplantation. The differences observed at Month 12 were maintained in both studies up to Month 24. There was a consistently greater absolute difference seen in recipients of standard criteria

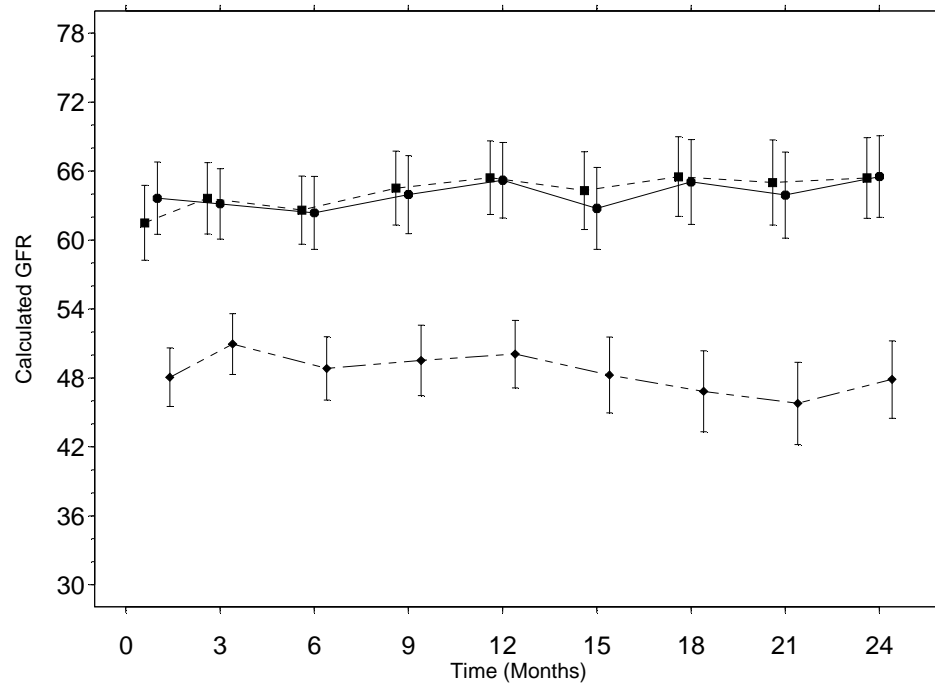
donor kidneys than in recipients of extended criteria donor kidneys ([Figure 7](#) and [Figure 8](#)).

Renal function with belatacept, as assessed by the difference from CsA in mean calculated GFR (97.3% CI), was:

- In recipients of standard criteria donor kidneys
 - 15 (10, 20) mL/min/1.73m² higher at Month 12 for both belatacept MI and LI
 - 18 (12, 23) mL/min/1.73m² higher at Month 24 for both belatacept MI and LI
- In recipients of extended criteria donor kidneys
 - 8 (2, 13) mL/min/1.73 m² higher at Month 12 for belatacept MI
 - 8 (3, 13) mL/min/1.73 m² higher at Month 12 for belatacept LI
 - 10 (3, 16) mL/min/1.73 m² higher at Month 24 for belatacept MI
 - 8 (2, 14) mL/min/1.73m² higher at Month 24 for belatacept LI

Data from the Phase 2, IM103100 study suggest that renal function (determined by calculated GFR) in belatacept-treated subjects is maintained up to 7 years after transplantation.

Figure 7: Mean Calculated GFR (in mL/min/1.73 m², with Imputation) in IM103008



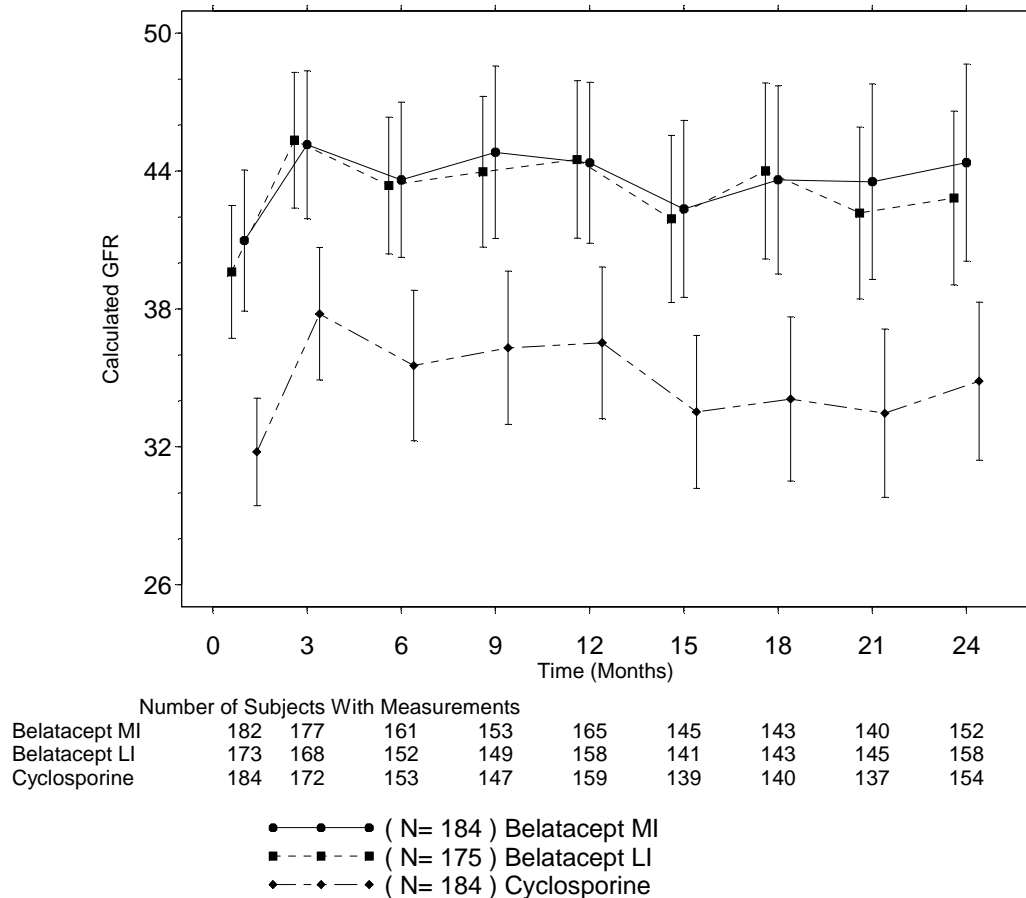
	Number of Subjects With Measurements								
Belatacept MI	214	207	170	180	201	174	167	167	191
Belatacept LI	220	211	185	176	200	178	181	174	201
Cyclosporine	214	201	189	174	199	171	160	160	182

●—●—● (N= 219) Belatacept MI
 ■--■--■ (N= 226) Belatacept LI
 ◆-◆-◆ (N= 221) Cyclosporine

Based on imputed calculated GFR values.
Error bars represent 95% CI for the mean.

Data from SUR database lock

Figure 8: Mean Calculated GFR (in mL/min/1.73 m², with Imputation) in IM103027



Based on imputed calculated GFR values.
Error bars represent 95% CI for the mean.

Data from SUR database lock

For the CsA group, the slope of the GFR curve over time (representing annual rate of decline) was approximately -2 mL/min/1.73m²/year from Month 3 (the time when post-transplant GFR appeared to stabilize) onward, which is consistent with the rates for CsA in epidemiologic studies (Table 10 and Table 11).^{49,50,51,52} For belatacept-treated subjects the slope was positive for recipients of standard criteria donor kidneys and -0.6

to -0.8 mL/min/1.73m²/year for recipients of extended criteria donor kidneys. Slope analyses based on GFR assessments obtained at milestone visits only (Months 3, 6, 12 and 24 or Months 3, 12 and 24) show differences between belatacept and CsA consistent with these findings.

**Table 10: Slope for Calculated GFR from Month 3 to Month 24:
IM103008**

Slope (mL/min/1.73 m ² /year)	Belatacept MI N = 219	Belatacept LI N = 226	Cyclosporine N = 221
Point estimate (SD)	1.32 (0.64)	1.22 (0.63)	-1.96 (0.64)
95% CI	0.07, 2.58	-0.01, 2.44	-3.22, -0.70

CI - confidence interval, SD - standard deviation

Data from SUR database lock

Note: Based on calculated GFR with imputation

**Table 11: Slope for Calculated GFR from Month 3 to Month 24:
IM103027**

Slope (mL/min/1.73 m ² /year)	Belatacept MI N = 184	Belatacept LI N = 175	Cyclosporine N = 184
Point estimate (SD)	-0.59 (0.76)	-0.85 (0.75)	-2.01 (0.76)
95% CI	-2.07, 0.90	-2.32, 0.62	-3.49, -0.53

CI - confidence interval, SD - standard deviation

Data from SUR database lock

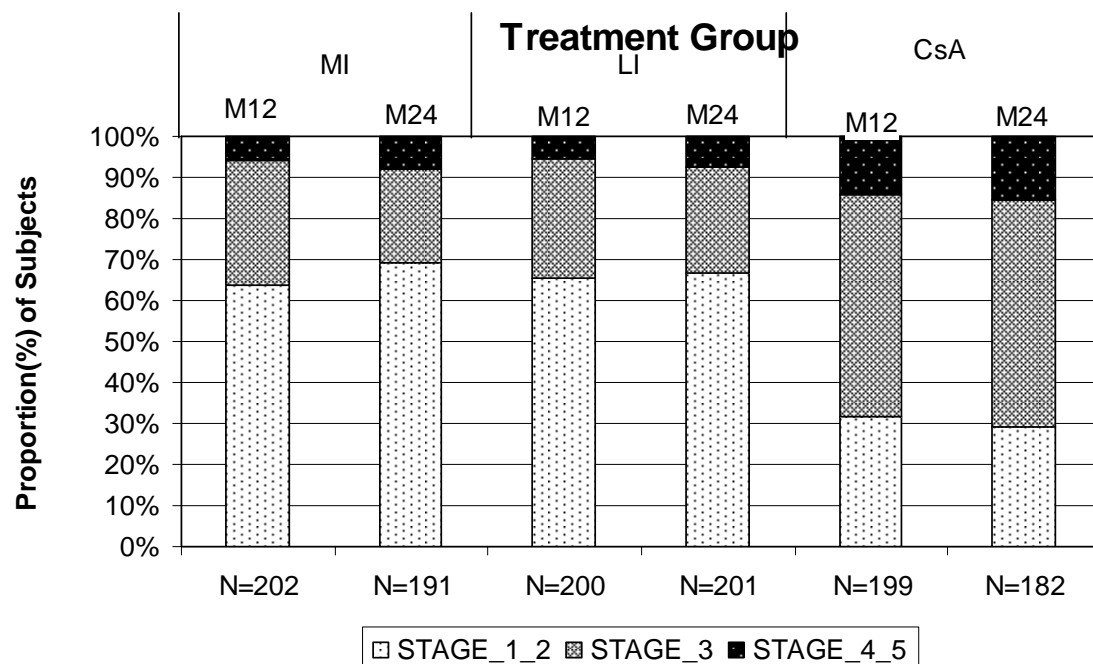
Note: Based on calculated GFR with imputation

Categorical assessment of renal function using National Kidney Foundation's Kidney Disease Outcomes Quality Initiative stages of CKD³⁵ allows further characterization of the renal function impact of belatacept versus CsA. This classification of kidney disease has been developed to associate the level of kidney function with the complications of CKD and to stratify the risk of loss of kidney function and the development of CV disease.

At Months 12 and 24, the distribution of CKD (according to calculated GFR) across the treatment groups in both Phase 3 studies was as follows (Figure 9 and Figure 10):

- Stage 1 or 2: higher proportions of belatacept-treated subjects than CsA-treated subjects.
- Stage 3: lower proportions of belatacept-treated subjects than CsA treated subjects in recipients of standard criteria donor kidneys; generally similar across the treatment groups in recipients of extended criteria donor kidneys.
- Stage 4 or 5: lower proportions of belatacept-treated subjects than CsA-treated subjects.

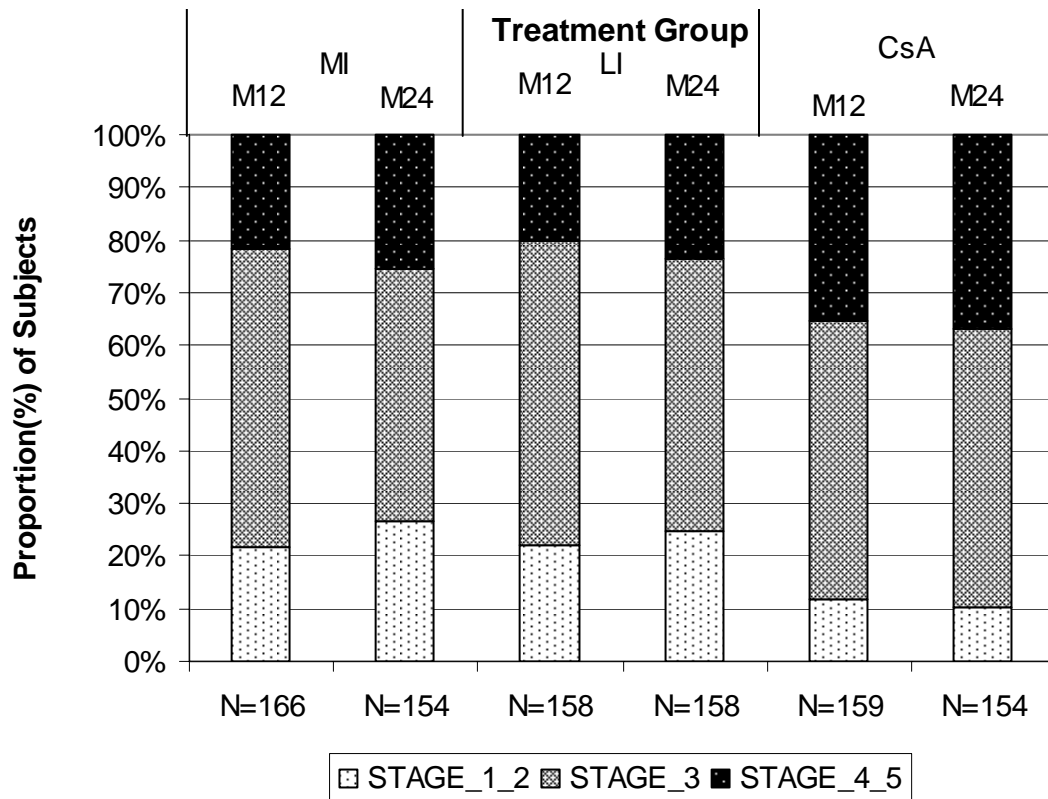
Figure 9: Chronic Kidney Disease Based on Calculated GFR with Imputation at Months 12 and 24 in IM103008



Data from the SUR database lock

GFR in mL/min/1.73 m²: Stage 1 - GFR ≥ 90; Stage 2 - GFR < 90 to ≥ 60; Stage 3 - GFR < 60 to ≥ 30; Stage 4 - GFR < 30 to ≥ 15; Stage 5 - GFR < 15 or dialysis

Figure 10: Chronic Kidney Disease Based on Calculated GFR with Imputation at Months 12 and 24 in IM103027



Data from the SUR database lock

GFR in mL/min/1.73 m²: Stage 1 - GFR ≥ 90; Stage 2 GFR < 90 to ≥ 60; Stage 3 - GFR < 60 to ≥ 30; Stage 4 - GFR < 30 to ≥ 15; Stage 5 - GFR < 15 or dialysis

The cumulative impact of the differential effects of belatacept and CsA on renal transplant recipients is apparent in a post hoc analysis of progression to Stage 4 or 5 CKD. In this analysis, subjects with death or graft loss, in addition to those with GFR < 15 mL/min/1.73 m², were considered to have stage 5 CKD. Stage 4 CKD, which corresponds to a GFR threshold of less than 30 mL/min/1.73 m², was selected as it is associated with a high prevalence of complications and symptoms of CKD and poor survival, and approximates the level at which preparations for a return to dialysis and/or re-transplantation are initiated.^{36,53} By 2 years after transplantation, approximately 20% of CsA-treated subjects in IM103008, versus approximately 10% of belatacept-treated

subjects, had developed a GFR of less than 30 mL/min/1.73 m², experienced graft loss or died (Figure 11). In IM103027, approximately 45% of CsA-treated subjects versus approximately 30% of belatacept-treated subjects experienced this level of progression (Figure 12). Together, these data demonstrate that in recipients of both standard criteria and extended criteria donor kidneys, belatacept may alter the natural history of the transplanted kidney, and delay the time to GFR decline and graft loss relative to CsA.

Figure 11: Time Stage 4/5 CKD, Graft Loss or Death in IM103008: All Randomized and Transplanted Subjects

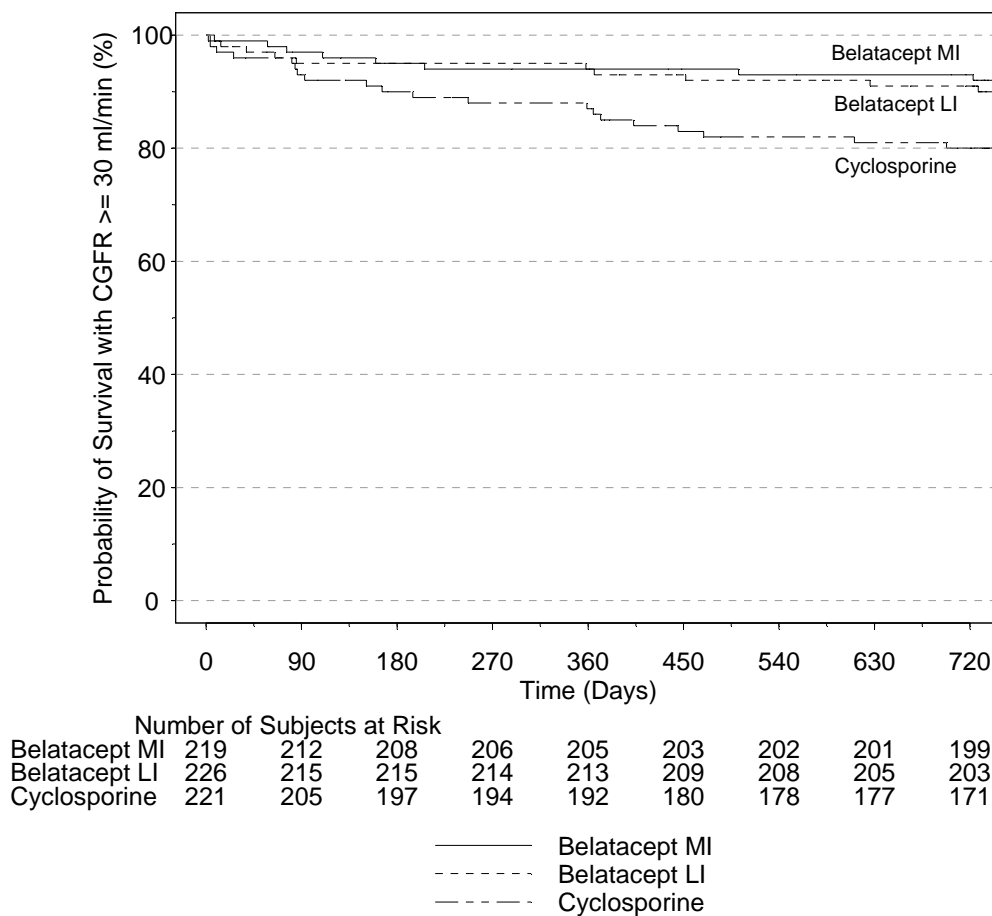
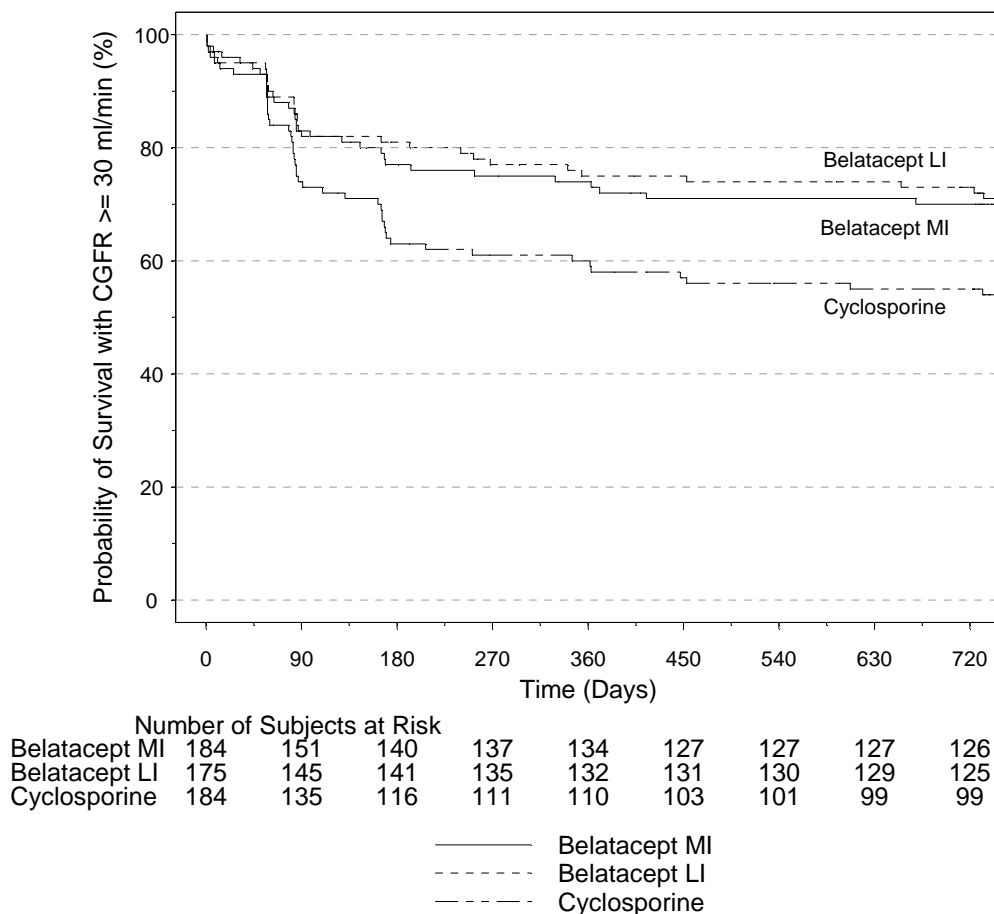


Figure 12: Time to Stage 4/5 CKD, Graft Loss or Death in IM103027: All Randomized and Transplanted Subjects



6.2.3 Summary of Renal Function and Structure

Belatacept demonstrated consistent, clinically relevant improvements in renal function compared with CsA. Improvements in GFR were seen as early as 1 month after transplantation and persisted or improved beyond Month 24. Divergent slopes of calculated GFR suggest continued widening of the renal function difference between belatacept and CsA. Reductions in the prevalence of chronic allograft nephropathy in

belatacept-treated subjects were consistent with GFR evidence of improved allograft health.

The clinical importance of the renal function differences observed in the belatacept trials is evident based on comparisons to published epidemiologic data. The thresholds for the composite renal impairment endpoint were selected to approximate the thresholds of renal function ($\text{SCr} > 1.5 \text{ mg/dL}$ or change $\geq 0.3 \text{ mg/dL}$) that have been shown to predict poor long-term allograft survival.³ CKD stages were defined in non-transplanted populations based on their correlation with comorbidities and ability to predict patient prognosis. They have also been applied to transplanted populations, in whom they are associated with increasing numbers and severity of comorbidities,^{36,54,55} and worsening transplant outcomes.^{54,56} Thus, by this measure, the greater proportions of belatacept-treated subjects with lower stages of CKD at Months 12 and 24 suggest a long-term subject and graft survival advantage over CsA.

6.3 Acute Rejection

This section contains a comprehensive assessment of AR, the impact on subject and graft outcomes, and the clinical significance. The frequency, distribution of Banff histologic grades, and treatment of AR episodes are presented first. As the belatacept program is primarily focused on long-term preservation of renal function and allograft and subject outcomes, features of AR beyond incidence rates are also presented, including the effect of AR on the key endpoints of composite subject and graft survival and renal function. Finally, the clinical significance of AR is discussed. While AR occurred more frequently and at higher histologic grades in belatacept-treated compared with CsA-treated subjects, AR in belatacept treated subjects was early, treatable and had limited impact on overall subject and graft survival as well as on renal structure and function due to the restricted clinical consequences of the episodes.

6.3.1 Incidence, Grade, and Timing

AR rates were higher in the belatacept groups compared with CsA, particularly in recipients of standard criteria donor kidneys (IM103008) (Table 12). The AR rates for each belatacept group (except the belatacept MI group in IM103008) met the protocol-

specified margin for non-inferiority (upper bound of the 2-sided 97.3% CI < 20%) compared with CsA.

The rates of AR were similar for belatacept-treated subjects across treatment groups and across studies (17% - 22%), but varied considerably (7% - 14%) in the CsA groups of the 2 Phase 3 studies. The AR rate observed with CsA in the recipients of standard criteria donor kidneys (7%) was less than the rates (10% - 28%) reported from recent studies of similar, 4-drug, CsA-based regimens.^{22,57,58}

AR in belatacept-treated subjects generally occurred early; nearly all episodes occurred by 6 months and most occurred by 3 months. Few subjects (< 3%) had more than 1 episode of AR. The proportion of subjects with subclinical rejection at the Month 12 biopsy was 4% to 6% across all treatment groups, demonstrating a low frequency of chronic and/or recurrent AR. After Year 1 (up to SUR database lock), 23 episodes of AR (10 belatacept MI, 1 belatacept LI, 12 CsA) were reported in the Phase 3 studies.

6.3.2 Acute Rejection Characterization

In recipients of standard criteria donor kidneys (IM103008), Banff grade II or III AR (characterized by vascular lymphocytic infiltration) occurred in 18%, 12%, and 4% of subjects in the belatacept MI, belatacept LI, and CsA groups, respectively. In recipients of extended criteria donor kidneys (IM103027), Banff grade II or III AR was observed in 14%, 14%, and 12% of subjects in the belatacept MI, belatacept LI and CsA groups, respectively (Table 12).

Table 12: Summary of Acute Rejection by Banff Grade by Month 12 in Phase 3 Studies

Banff Grade	Belatacept MI	Belatacept LI	Cyclosporine
IM103008			
N in the Analysis	219	226	221
Acute Rejection, N (%)	49 (22.4)	39 (17.3)	16 (7.2)
Diff. from CsA (97.3% CI)	15.1 (7.9, 22.7)	10.0 (3.3, 17.1)*	
Banff Grade, N (%)			
Mild Acute (IA)	7 (3.2)	4 (1.8)	3 (1.4)
Mild Acute (IB)	3 (1.4)	8 (3.5)	5 (2.3)
Moderate Acute (IIA)	17 (7.8)	16 (7.1)	6 (2.7)
Moderate Acute (IIB)	20 (9.1)	10 (4.4)	2 (0.9)
Severe Acute (III)	2 (0.9)	1 (0.4)	0
IM103027			
N in the Analysis	184	175	184
Acute Rejection, N (%)	33 (17.9)	31 (17.7)	26 (14.1)
Diff. from CsA (97.3% CI)	3.8 (-4.7, 12.4)*	3.6 (-5.0, 12.3)*	
Banff Grade, N (%)			
Mild Acute (IA)	0	4 (2.3)	2 (1.1)
Mild Acute (IB)	7 (3.8)	2 (1.1)	2 (1.1)
Moderate Acute (IIA)	10 (5.4)	17 (9.7)	17 (9.2)
Moderate Acute (IIB)	16 (8.7)	8 (4.6)	5 (2.7)
Severe Acute (III)	0	0	0

Data from BLA database lock

* Met the protocol-specified margin for non-inferiority (upper bound of the 2-sided 97.3% CI < 20%) compared with CsA

Banff grade II and III rejections are characterized by lymphocytic infiltrates in the arteries or arterioles on renal biopsy, and may be associated with the presence of anti-donor HLA antibodies and/or antibody-mediated rejection, both of which are predictors of poor graft function and survival after rejection.^{15,42,59,60,61,62} The available data did not permit a full characterization of the frequency of antibody-mediated rejection; however, the presence of anti-donor HLA antibodies was assessed centrally in all subjects. Overall, anti-donor HLA antibodies were present in 4 belatacept MI, 1 belatacept LI, and 6 CsA-treated subjects with rejection.

- Recipients of standard criteria donor kidneys (IM103008): 2/44, 0/37 and 1/14 subjects with AR assessed for antibodies had anti-donor HLA antibodies by Month 12 in the belatacept MI, LI and CsA groups respectively.
- Recipients of extended criteria donor kidneys (IM103027): 2/32, 1/31 and 5/25 subjects with AR assessed for antibodies had anti-donor HLA antibodies by Month 12 in the belatacept MI, LI and CsA groups respectively.

Thus, despite the higher frequency of Banff grade II rejections in belatacept-treated subjects, few were associated with anti-donor HLA antibodies, which is consistent with their limited impact on graft outcomes.

6.3.3 Treatment and Disposition

Episodes of AR are treated with a short course of additional immunosuppression, typically corticosteroids or lymphocyte-depleting therapy for more refractory episodes. More belatacept-treated than CsA-treated subjects with rejection were given lymphocyte-depleting therapy either as initial therapy or for corticosteroid-resistant rejection:

- Recipients of standard criteria donor kidneys (IM103008): 26/48, 20/39, and 2/16 subjects in the belatacept MI, LI, and CsA groups, respectively.
- Recipients of extended criteria donor kidneys (IM103027): 15/32, 7/31, and 6/26 subjects in the belatacept MI, LI and CsA groups, respectively.

Despite knowledge of treatment assignment, there was no greater tendency by investigators to discontinue subjects from belatacept than CsA after an episode of AR. Approximately half of the subjects with AR in each treatment group remained on assigned study therapy at Month 12, irrespective of Banff grade. Most subjects who discontinued therapy after AR switched to tacrolimus.

6.3.4 Impact of Acute Rejection on Subject and Graft Outcomes

The impact of AR on the subject and graft was evaluated by assessing SCr recovery after the AR episode, renal function indicated by Month 12 GFR, and subject and graft survival.

In the Phase 3 studies, serum creatinine recovery to baseline was similar in belatacept-treated and CsA-treated subjects. Rates of creatinine recovery to within 110% of pre-AR values were 56% to 72% in belatacept-treated subjects and 54% to 79% in CsA-treated subjects.

Of those with AR, 4/49, 6/39 and 3/16 in the MI, LI and CsA groups in IM103008 and 13/33, 7/31 and 17/26 in the MI, LI and CsA groups in IM103027 had a Month 12 GFR < 30 mL/min/1.73 m² (Stage 4 - 5 CKD). Table 13 presents CKD stages at Month 12 for subjects with AR. A small proportion of the overall study population had AR and Month 12 GFR < 30 mL/min/1.73 m² (Stage 4 - 5 CKD) with similar rates across treatment arms within each study.

Table 13: Chronic Kidney Disease Stage at Month 12 in Subjects with AR

Number (%) of Subjects						
	IM103008			IM103027		
	Belatacept MI (N=219)	Belatacept LI (N=226)	CsA (N=221)	Belatacept MI (N=184)	Belatacept LI (N=175)	CsA (N=184)
AR n (%)	49 (22.4)	39 (17.3)	16 (7.2)	33 (17.9)	31 (17.7)	26 (14.1)
CKD Stage 1 or 2	23 (10.5)	11 (4.9)	3 (1.4)	1 (0.5)	5 (2.9)	1 (0.5)
CKD Stage 3	22 (10.0)	22 (9.7)	10 (4.5)	19 (10.3)	19 (10.9)	8 (4.3)
CKD Stage 4 or 5	4 (1.8)	6 (2.7)	3 (1.4)	13 (7.1)	7 (4.0)	17 (9.2)

Data from BLA database lock

GFR in mL/min/1.73 m²: Stage 1 - GFR ≥ 90; Stage 2 GFR < 90 to ≥ 60; Stage 3 - GFR < 60 to ≥ 30; Stage 4 - GFR < 30 to ≥ 15; Stage 5 - GFR < 15

Death and graft loss are imputed as CKD Stage 5

When death and graft loss are assessed separately, AR episodes in belatacept-treated subjects had a limited effect on overall subject and graft survival in the Phase 3 studies. Among subjects with AR there were few cases of death or graft loss (for any cause) by Month 12 ([Table 14](#)).

Table 14: Graft Loss and Death by Month 12 by Acute Rejection Status

	IM103008			IM103027		
	Belatacept MI N = 219	Belatacept LI N = 226	CsA N = 221	Belatacept MI N = 184	Belatacept LI N = 175	CsA N = 184
Subjects with protocol-defined AR	49	39	16	32	31	26
Graft Loss	1	2	0	2	3	5
Death	2	1	0	0	1	2

Data from Year 1 database lock

6.3.5 Safety Outcomes of AR

To examine the impact of AR and the additional immunosuppression used to treat AR on safety, we examined the rates of infection and neoplasia in the overall studies, and across sub-groups of subjects who did and did not experience AR in the Phase 3 studies. Since AR in belatacept-treated subjects occurred early, 12 months or more of follow-up from the time of AR treatment are available on nearly all subjects who experienced AR.

In the overall study population, infections and malignancies occurred with similar frequency in all treatment groups (Sections 7.2.3, 7.2.4). Similarly, there was no appreciable impact of AR on rates of serious infections, viral infections, or neoplasms. Use of lymphocyte-depleting therapies for the treatment of AR was found to be a risk factor for development of PTLD in belatacept-treated subjects (in the core studies), as reported in the literature.^{63,64} A thorough discussion of PTLD is provided in Section 7.2.3.2.

6.3.6 Summary of Acute Rejection

AR occurred more frequently and at a higher histologic grade in belatacept-treated subjects compared with CsA-treated subjects. The AR rates for the belatacept LI group in IM103008 and both belatacept groups in IM103027 met the protocol-specified margin of 20% for non-inferiority compared with CsA. Most AR episodes occurred by Month 3 and were treatable; recovery of SCr was similar in all treatment groups and there were few cases of AR associated with the presence of anti-donor HLA antibodies. A small proportion of the overall study population had AR and severe renal dysfunction,

indicating the limited overall impact of these events. Lymphocyte-depleting therapy for treatment of AR, a risk factor for PTLD in belatacept-treated subjects, was used more often in the belatacept groups than in the CsA groups.

AR has historically been associated with inferior graft outcomes, though current data support that all AR episodes do not have the same impact on patient and graft survival.⁴¹ Higher histologic grade, late AR, rate of recurrence, antibody-mediated rejection, presence of anti-donor HLA antibodies, and poor renal function after AR, have been associated with adverse long-term outcomes.^{14,65,66} In contrast to these features, AR in the belatacept Phase 3 studies occurred early, was not recurrent, not associated with high rates of anti-donor HLA antibody production, and had limited impact on renal function. Phase 3 data suggest that AR episodes had limited impact on overall subject and graft survival, and on renal function due to the restricted clinical consequences of the episodes. In addition, the composition of the inflammatory infiltrate during episodes of AR may correlate with outcomes.^{67,68} The results from a small sub-study show that in belatacept-treated subjects experiencing AR, there was an increased proportion of regulatory T cells observed in the allografts that may have attenuated the impact of AR.⁶⁹

The use of lymphocyte-depleting therapy is a risk factor for PTLD and may contribute to the morbidity of AR. The data on AR from the Phase 3 studies suggest that it may be possible to refine the treatment algorithm for AR episodes in belatacept-treated subjects to reduce the need for lymphocyte-depleting therapy, as recommended in the recent Kidney Disease Improving Global Outcomes guidelines.⁷⁰ The guidance for the treatment of AR episodes in the belatacept protocols was based upon clinical experience developed in patients receiving CNI based immunosuppression regimens. With CNI regimens, higher histologic grades of AR have been less responsive to treatment and had a poorer prognosis than AR with lower grades.⁷¹ The finding that most AR in belatacept-treated subjects occurred early and were not associated with the presence of anti-donor HLA antibodies, suggests that the AR may respond to corticosteroids and/or a switch to CNIs alone. This possibility is supported by the generally favorable response to therapy in belatacept-treated subjects with AR, the observation that approximately half of the belatacept subjects with AR remained on belatacept, and isolated instances in which belatacept-treated subjects with higher grade AR were successfully treated without the need for lymphocyte-depleting therapy.

Interestingly, there may be a paradoxical effect of belatacept dose on AR, based on a higher observed rate of AR in the MI than the LI group in the IM103008 study, and a higher observed rate of Banff grade IIb AR in the MI group than the LI group in the IM103027 study.

Studies are ongoing to further characterize the AR episodes in belatacept-treated subjects to enhance our understanding of the effects of belatacept on immune responses. An initial study aims to use immunohistochemistry to characterize the inflammatory cells seen on allograft biopsies of subjects in the belatacept studies. This will lead to a better understanding of the relative roles of regulatory and effector T cells in subjects receiving belatacept, and may inform refinement of treatment algorithms for management of AR in belatacept-treated subjects.

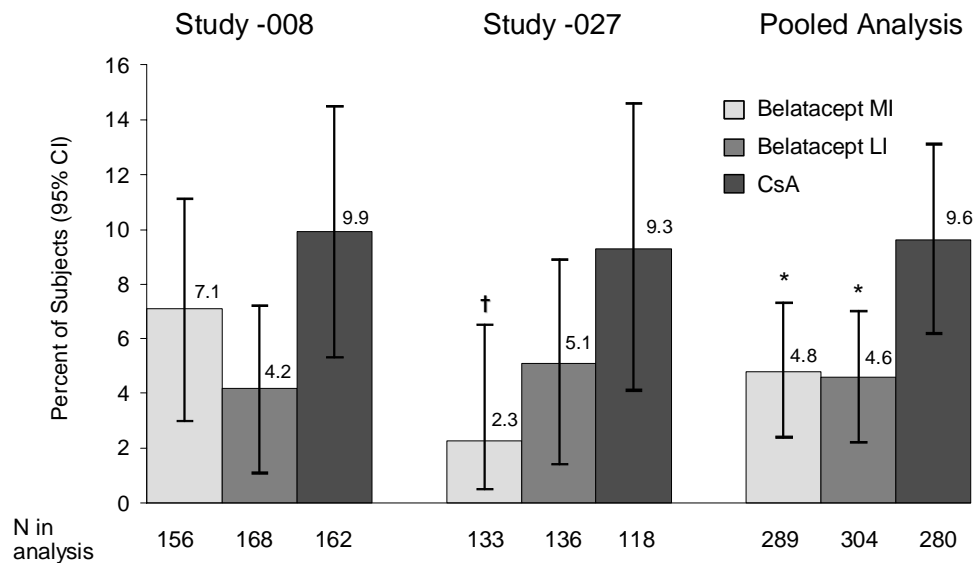
6.4 Cardiovascular and Metabolic Endpoints

Cardiovascular and metabolic endpoints were prospectively assessed to supplement the measured benefits on renal function. Belatacept (at Month 12) was associated with an approximately 50% reduction in the risk of NODAT, a 6 to 9 mmHg reduction in systolic blood pressure and 3 to 4 mmHg reduction in diastolic blood pressure, and a shift towards a less atherogenic lipid profile, relative to CsA-based therapy.

6.4.1 New Onset Diabetes Mellitus After Transplantation

The incidence of NODAT, defined as use of an antidiabetic agent for > 30 days or ≥ 2 fasting plasma glucose values > 126 mg/dL (as determined by a central laboratory) in a subject not diabetic at baseline, was reduced by approximately 50% in subjects treated with belatacept versus CsA in a pooled analysis, with consistent results across studies ([Figure 13](#)).

Figure 13: Summary of New Onset Diabetes Mellitus After Transplantation (NODAT) by Month 12



NODAT was defined as treatment with anti-diabetic medication for a duration of ≥ 30 days or at least 2 fasting plasma glucose tests indicating fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L). NODAT was assessed only after Week 4.

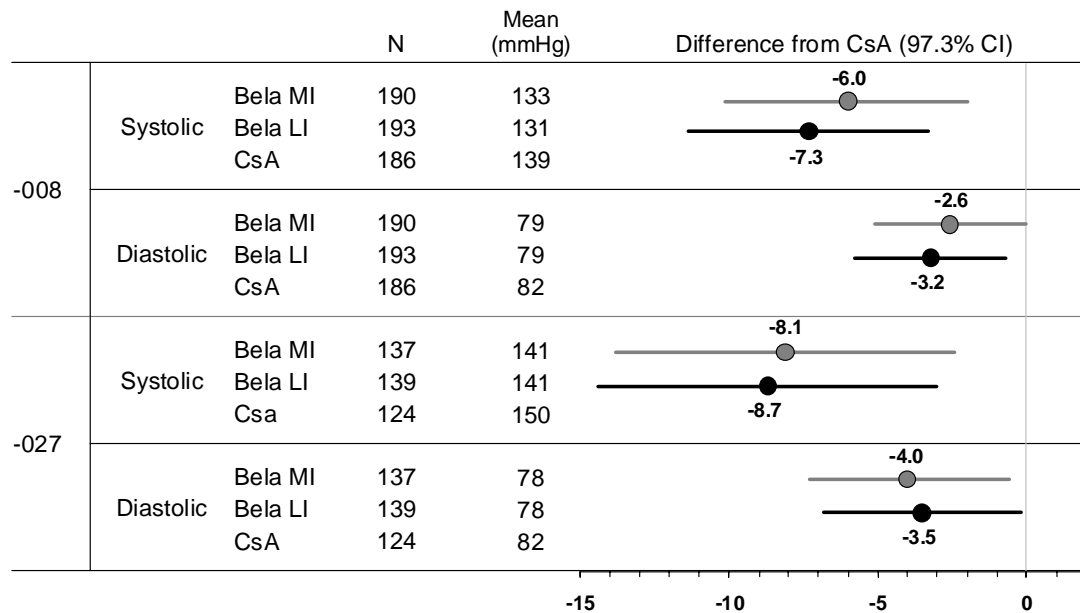
† $P = 0.03$ versus CsA; * $P < 0.02$ versus CsA.

Data from Year 1 database lock.

6.4.2 Hypertension

Mean blood pressure at Month 12 was lower in the belatacept groups compared with CsA by approximately 6 to 7 mmHg systolic and 3 mmHg diastolic in recipients of standard criteria donor kidneys, and 8 to 9 mmHg systolic and 4 mmHg diastolic in recipients of extended criteria donor kidneys (Figure 14). These improvements in blood pressure were not a result of greater use of antihypertensive therapies in belatacept-treated subjects, but in fact, were associated with less intense use of such medications.

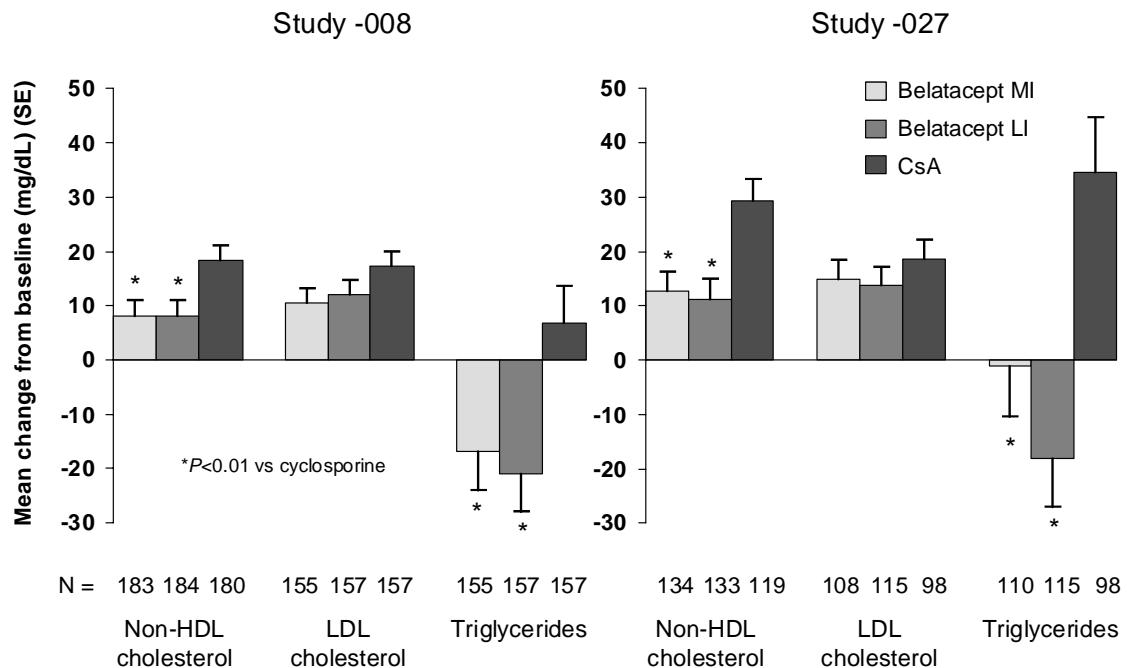
Figure 14: Blood Pressure at Month 12 - Difference from Cyclosporine



Data from Year 1 database lock.

6.4.3 Dyslipidemia

Compared with CsA, belatacept treatment had a favorable impact on non-high density lipoprotein (non-HDL) cholesterol and triglycerides (Figure 15).

Figure 15: Change from Baseline in Serum Lipids at Month 12

Data from Year 1 database lock.

Mean non-HDL cholesterol levels increased from baseline to Month 12 in all treatment groups. In a pooled analysis of non-HDL cholesterol, change from baseline to Month 12 was significantly lower in the pooled belatacept group compared with CsA ($p < 0.001$). The difference resulted from relative reductions in triglycerides ($p \leq 0.0165$ mg/dL for MI and LI versus CsA in each study) and smaller relative increases in LDL cholesterol ($p > 0.05$ for MI and LI versus CsA in each study). HDL cholesterol levels were similar in belatacept- and CsA-treated subjects. These effects on dyslipidemia were seen despite a trend toward less antihyperlipidemic medication use in belatacept treated subjects.

6.4.4 Summary of Cardiovascular and Metabolic Endpoints

Belatacept was associated with an approximately 50% reduction in the risk of NODAT, reduction in systolic and diastolic blood pressure and a shift towards a less atherogenic lipid profile, relative to CsA-based therapy.

Renal transplant recipients have a 50-fold higher risk of CV death than the general population and CV disease is the most common cause of death in renal transplant recipients with a functioning graft.⁷ Diabetes after transplantation is associated with increased CV events, and reduced allograft and subject survival.^{43,44,45} Elevated blood pressure in renal transplant recipients is an important predictor of CV death and graft loss⁷² and non-HDL cholesterol levels are an important predictor of CV risk.^{70,73}

The magnitude of blood pressure reduction observed with belatacept treatment relative to CsA is clinically significant,^{74,75,76} and improvements in NODAT, hypertension, and dyslipidemia have been associated with improved long-term outcomes in this high CV risk population.

7 CLINICAL SAFETY

Overall, belatacept was well tolerated in recipients of living and deceased donor renal transplants when studied for a median of 2 years in Phase 3 trials and median of 5.7 years in a Phase 2 trial.

Section 7.1 provides information on the immunosuppressive agents that were co-administered with belatacept in the core studies. Section 7.2 describes the methods used to evaluate safety in the belatacept program. Section 7.2 presents the results of the safety evaluation.

7.1 Methods

7.1.1 Safety Monitoring

At the start of the Phase 3 clinical development program, an independent Data Monitoring Committee (DMC) was established. The DMC regularly reviewed accumulating safety data and allowed the Phase 3 studies to continue without modification.

All serious adverse events (SAEs) were captured according to ICH guidelines. An SAE is any untoward medical occurrence that 1) results in death, 2) is life-threatening, 3) requires hospitalization or causes prolongation of hospitalization, 4) results in persistent

or significant disability/incapacity or 5) is an important medical event. A serious infection is an infection that is reported as a serious adverse event.

To complement standard safety monitoring practices, an extensive program to monitor and collect information on events of clinical interest was implemented. Events were identified as being of clinical interest due to an increased number of AEs in the belatacept treatment groups in IM103100 (i.e., congestive heart failure, pulmonary edema, proteinuria), belatacept's mechanism of action and its immunosuppressive properties (i.e., malignancies, PTLT, infections, and autoimmune disorders) or its pharmaceutical properties (i.e., infusion reactions). Thrombosis was added during Phase 3 based on an increased number of graft losses attributed to graft thrombosis in belatacept-treated subjects in IM103027. Monitoring activities included ongoing identification of events of clinical interest and deployment of supplemental case report forms (CRFs) to gather additional information on AEs of infections and malignancies. This approach was implemented to ensure that no safety signals would be missed or given inadequate review.

7.1.2 Data Analyses for Safety

Safety data from the 3 core studies were evaluated across treatment groups (belatacept MI, belatacept LI, and CsA) within each study, and pooled by treatment group across the 3 core studies. Pooling provides added sensitivity for detecting differences across treatment groups and aids in the detection of safety signals for rare events.

While there were small differences between the Phase 2 and the Phase 3 LI dosing regimen (an additional dose of belatacept was given on Day 5 in the Phase 3 studies; for full description of doses, see Sections 5.2.1 and 5.2.2), a review of the data indicated that the safety findings were generally consistent across studies. These findings, together with the overall similarities in study design, dosing, comparator regimen and background immunosuppressants, supported pooling the safety data from the 3 core studies (IM103008, IM103027, and IM103100) as the primary method of describing the safety profile of belatacept. Individual study data are described selectively to support the consistency of the findings across each study, and to indicate any clinically meaningful differences between study populations.

The data were analyzed using 4 timepoints:

1. All events occurring by 12 months after transplant, a timepoint that coincides with the primary efficacy endpoints and that all subjects have reached (using the BLA database lock: March 2009).
2. All events occurring cumulatively up to 26-Jan-2009 (using the BLA database lock: March 2009), which permits characterization of the complete safety experience with belatacept.
3. Events of death and CNS infections using the cut-off for the Safety Update Report (SUR database lock: June/July 2009), in order to provide 4 to 6 months of additional information.
4. All events of PTLD (and deaths due to PTLD) and PML occurring up to 14-Dec-2009.

In the pooled safety population, the median exposure to belatacept LI, belatacept MI, and CsA was 751, 754, and 724 days, respectively (Table 15). A total of 77 subjects had received belatacept for 5 years and 27 had been treated for more than 7 years. Of the subjects (belatacept MI, LI, and CsA) who were treated for at least 2 years at the time of the BLA database lock, 15% were from the Phase 2 study and 85% were from the Phase 3 studies. At the time of the BLA database lock, 62% of subjects (belatacept MI, LI, and CsA) who were treated for at least 3 years were from the Phase 2 study and 38% were from the Phase 3 studies.

Table 15: Extent of Exposure in the Pooled Core Studies up to BLA Database Lock

	Number (%) of Subjects		
	Belatacept MI N=476	Belatacept LI N=471	CsA N=465
Mean, days (SD)	782 (607)	801 (604)	680 (469)
Median, days (Range)	751 (28–2829)	754 (28–2883)	724 (10–2703)
≥ 6 Months	386 (81)	392 (83)	384 (83)
≥ 12 Months	366 (77)	369 (78)	350 (75)
≥ 24 Months	256 (54)	256 (54)	229 (49)
≥ 36 Months	67 (14)	69 (15)	42 (9)
≥ 48 Months	41 (9)	40 (8)	18 (4)
≥ 60 Months	38 (8)	39 (8)	16 (3)

Data from the BLA database lock.

Of the subjects (belatacept MI, LI, and CsA) who were treated for at least 2 years at the time of the SUR database lock, 88% were from the Phase 3 studies and 12% were from the Phase 2 study. At the time of the SUR database lock, 40% of subjects who were treated for at least 3 years were from the Phase 2 study and 60% were from the Phase 3 studies.

The SUR (supporting the BLA submitted on 30-Jun-2009), was submitted on 03-Nov-2009. This SUR contained 4 to 6 months of additional safety information on the 7 ongoing belatacept studies. With the exception of deaths, PTLTD, CNS infections, and PML (mentioned above), data from the SUR are not provided in this document. However, no change was seen in the safety profile of belatacept in the SUR.

Review of the safety data indicated that the belatacept LI regimen had a better safety profile than the belatacept MI regimen. Thus, descriptions of the safety findings focus on comparing the LI regimen to CsA, and the LI regimen to the MI regimen.

7.2 Safety Results

7.2.1 Adverse Events

Nearly all subjects in the core studies experienced one or more AEs. The majority of subjects experienced an AE within the first 3 months after transplantation and at similar frequencies across treatment groups, suggesting these events may be associated with peri-surgical morbidity of the transplant operation rather than an adverse reaction to study drug.

The most common ($\geq 10\%$) AEs reported were similarly distributed across the 3 treatment groups. The most common AEs reported with a 2% increase in the belatacept LI group compared with the CsA group up to the BLA database lock included hypophosphatemia, diarrhea, and cough. AEs occurring more frequently with CsA than with belatacept LI included dyslipidemia, graft dysfunction and leukopenia. CsA-associated AEs, such as hirsutism and tremor, were reported more frequently with CsA than with belatacept.

7.2.2 Deaths, Serious Adverse Events, and Adverse Events Leading to Discontinuation

The frequency of deaths at Month 12 and at SUR database lock is presented in Table 16. Across all 3 treatment groups, infections (including sepsis, pneumonia, septic shock) and cardiac disorders (including cardiac arrest, cardio-respiratory arrest, myocardial infarction, and sudden death) were the leading cause of death (up to the SUR database lock). There was no predominant cause of death among study subjects in any individual treatment group.

Table 16: Deaths (Pooled Core Studies: IM103008, IM103027, IM103100)

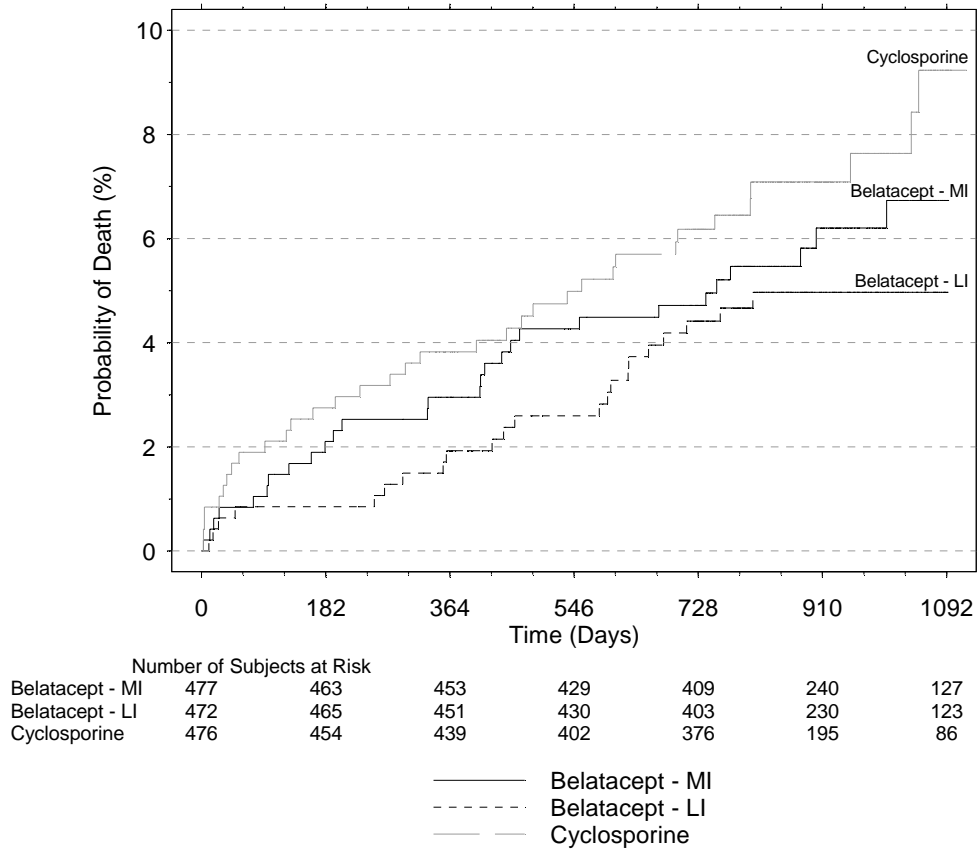
	Belatacept MI N = 477	Belatacept LI N = 472	CsA N = 476
Up to Month 12	14 (2.9)	9 (1.9)	18 (3.8) ^a
Up to SUR database lock	31 (6.5)	23 (4.9)	35 (7.4) ^a

Data from the SUR database lock.

^a An additional subject in the IM103100 CsA group died but is not included in this table because this subject was not treated. The cause of death was unknown.

The time to onset of all deaths pooled across all 3 studies reported up to year 3 is illustrated in the Kaplan-Meier plot in [Figure 16](#). As shown, there was a separation of the CsA group from the belatacept LI group, with more subjects in the CsA group dying earlier in the study. This separation was sustained throughout the 3-year time period. This analysis was also performed pooling only the Phase 3 studies (excluding the Phase 2 study), and the results were consistent with the Pooled Core Studies.

Figure 16: Kaplan-Meier Estimates of Time to Onset of Death up to Year 3 (Pooled Core Studies)



MedDRA Version: 12.0

All randomized and transplanted subjects from Studies -008 and -027

All randomized, transplanted and treated subjects from Study -100

The frequency of SAEs up to Month 12 was lower in the belatacept LI group (56%) than in the belatacept MI and CsA groups (61% and 63%, respectively) ([Table 17](#)). Up to the BLA database lock, the frequency of SAEs was generally similar in the belatacept MI, belatacept LI, and CsA groups (69%, 66%, and 68%, respectively).

Infections were the most common SAEs and were reported with a lower frequency in the belatacept LI group (23%) than in the belatacept MI and CsA groups (27% each) up to Month 12. Up to the BLA database lock, the frequency of serious infections was 30% in the belatacept LI group and 35% in each of the belatacept MI and CsA groups. Additional details on infections are provided in Section 7.2.4. CMV infection, upper respiratory tract infection, pyrexia, and blood creatinine increased were the most common SAEs and were reported with similar frequencies in the belatacept MI, belatacept LI, and CsA groups.

Note that events of transplant rejection in Table 17 reflect cases from the IM103100 study where sites were instructed to report suspected or confirmed episodes of acute rejection as SAEs. In the Phase 3 studies, sites reported rejection episodes and their details on specially designed case report forms and they were captured as efficacy events.

Table 17: Serious Adverse Events for at Least 2% of Subjects in Any Group Up to Month 12 (Pooled Core Studies)

System Organ Class (%) Preferred Term (%)	Belatacept - MI N = 477	Belatacept - LI N = 472	Cyclosporine N = 476	Total N = 1425
TOTAL SUBJECTS WITH AN EVENT	289 (60.6)	263 (55.7)	298 (62.6)	850 (59.6)
INFECTIONS AND INFESTATIONS	128 (26.8)	108 (22.9)	129 (27.1)	365 (25.6)
CYTOMEGALOVIRUS INFECTION	26 (5.5)	28 (5.9)	25 (5.3)	79 (5.5)
URINARY TRACT INFECTION	25 (5.2)	24 (5.1)	30 (6.3)	79 (5.5)
PNEUMONIA	9 (1.9)	6 (1.3)	10 (2.1)	25 (1.8)
PYELONEPHRITIS	10 (2.1)	6 (1.3)	6 (1.3)	22 (1.5)
RENAL AND URINARY DISORDERS	68 (14.3)	64 (13.6)	83 (17.4)	215 (15.1)
RENAL FAILURE ACUTE	6 (1.3)	7 (1.5)	13 (2.7)	26 (1.8)
URETERIC STENOSIS	5 (1.0)	7 (1.5)	10 (2.1)	22 (1.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	59 (12.4)	59 (12.5)	80 (16.8)	198 (13.9)
GRAFT DYSFUNCTION	15 (3.1)	13 (2.8)	21 (4.4)	49 (3.4)
THERAPEUTIC AGENT TOXICITY	0	0	10 (2.1)	10 (0.7)
VASCULAR DISORDERS	24 (5.0)	35 (7.4)	47 (9.9)	106 (7.4)
LYMPHOCELE	5 (1.0)	9 (1.9)	17 (3.6)	31 (2.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	35 (7.3)	27 (5.7)	34 (7.1)	96 (6.7)
PYREXIA	24 (5.0)	22 (4.7)	22 (4.6)	68 (4.8)
INVESTIGATIONS	28 (5.9)	24 (5.1)	36 (7.6)	88 (6.2)
BLOOD CREATININE INCREASED	19 (4.0)	19 (4.0)	28 (5.9)	66 (4.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	28 (5.9)	18 (3.8)	24 (5.0)	70 (4.9)
LEUKOPENIA	12 (2.5)	3 (0.6)	10 (2.1)	25 (1.8)
IMMUNE SYSTEM DISORDERS	19 (4.0)	21 (4.4)	10 (2.1)	50 (3.5)
TRANSPLANT REJECTION	16 (3.4)	18 (3.8)	8 (1.7)	42 (2.9)

Data from the BLA database lock

The proportion of subjects with AEs leading to discontinuation up to Month 12 was lower in the belatacept LI group (11%) than in the CsA group (14%), and similar in the belatacept MI group (10%). Up to BLA database lock, the proportion of subjects with AEs leading to discontinuation was lower in the belatacept LI group (14%) than in the CsA group (17%), and similar in the belatacept MI group (14%).

7.2.3 Malignancies and PTLD

7.2.3.1 Overall Malignancies

In the pooled analysis up to the BLA database lock, the frequency of malignant neoplasms excluding non-melanoma skin cancer was similar in the belatacept LI (4.9%) and CsA (4.8%) groups, and higher in the belatacept MI group (6.7%) (Table 18). Non-melanoma skin cancer was reported with lower frequency in the belatacept LI group (1.3%) than in the CsA (2.3%) and belatacept MI (3.1%) groups. PTLD was reported more frequently in both belatacept treatment groups than in the CsA group, with the CNS being the predominant site of presentation (see Section 7.2.3.2). Malignancy excluding non-melanoma skin cancer and PTLD was similar across treatment arms.

Table 18: Malignant Neoplasms (Pooled Core Studies)

	Number of Subjects (%)					
	Up to Month 12			Up to BLA Database Lock		
	Belatacept			Belatacept		
	MI N =477	LI N =472	CsA N =476	MI N =477	LI N =472	CsA N =476
Any malignant neoplasms	17 (3.6)	10 (2.1)	16 (3.4)	43 (9.0)	26 (5.5)	31 (6.5)
Non-melanoma skin cancer	5 (1.0)	1 (0.2)	5 (1.1)	15 (3.1)	6 (1.3)	11 (2.3)
Malignant neoplasms excluding non-melanoma skin cancers	12 (2.5)	9 (1.9)	11 (2.3)	32 (6.7)	23 (4.9)	23 (4.8)
PTLD	4 (0.8)	4 (0.8)	1 (0.2)	8 (1.7)	6 (1.3) ^a	2 (0.4)
Malignant neoplasms excluding non-melanoma skin cancers and PTLD	8 (1.7)	5 (1.1)	10 (2.1)	24 (5.0)	18 (3.8)	21 (4.4)

Data from the BLA database lock.

^a One additional case of PTLD, which occurred after Safety Update DBL, is counted in this group but is not included in the overall malignancy count. Subjects counted once in the any malignant neoplasm row could be counted in more than 1 row appearing below it.

Other than CNS PTLD, there were no primary CNS neoplasms. There was no excess of other known virally mediated tumors, such as cervical cancer or Kaposi's sarcoma. The frequency of breast cancer was similar in the belatacept LI (0.2%, 1/472) and CsA (0.2%, 1/476) groups, and higher in the belatacept MI group (0.8%, 4/477). Three (3) of the 4 subjects in the belatacept MI group had abnormal mammograms at baseline, and 2 of these 3 cases presented within 3 months of starting belatacept; thus, these data do not appear to indicate an increased risk of breast cancer with the belatacept MI regimen.

7.2.3.2 PTLD Incidence and Presentation

PTLD consists of a spectrum of diseases ranging from benign plasma cell hyperplasia to frank malignant lymphoma. In renal transplantation, the highest incidence of PTLD is usually observed within the first 18 months after transplantation.^{77,78,79} The reported rates of PTLD in the literature for renal transplant recipients range from 0.4% to 2.3%.^{77,78,79} The site and extent of PTLD presentation in renal transplant recipients impacts prognosis and survival. Allograft and lymph node PTLD (which comprise approximately 20% of all PTLD cases) have a 60% to 65% 5 year survival rate, whereas extrarenal presentations of lung, liver, CNS, gastrointestinal, and disseminated PTLD (which comprise approximately 60% of all PTLD cases) have a 22% to 43% 5 year survival rate.⁸⁴ Renal transplant recipients with PTLD localized to a single site also have improved 5 year survival compared to those with diffuse multiple site PTLD (74% versus 49%).⁸⁰

The development of PTLD has been associated with the overall intensity of immunosuppression and specific risk factors including (1) EBV-seronegative recipient status, (2) use of lymphocyte-depleting therapies, (3) cytomegalovirus (CMV) disease, and (4) age greater than 60 years.^{64,77,78,81,82} Of these risk factors, EBV-negative status, typically comprising approximately 10% to 20% of adult populations, has the strongest association with PTLD. Mild forms of PTLD can be treated by withdrawal of immunosuppression while more advanced forms may require treatment with chemotherapy and radiation therapy.

In the core studies, up to 14-Dec-2009, there were 8 cases (1.7%) of PTLD in the belatacept MI group, 6 cases (1.3%) in the belatacept LI group, and 2 cases (0.4%) in the CsA group ([Table 19](#)). The distribution of PTLD cases across the studies were as follows.

- Study IM103008: 3 belatacept MI, 2 belatacept LI, and 1 CsA
- Study IM103027: 2 belatacept MI, 4 belatacept LI, and 0 CsA
- Study IM103100: 3 belatacept MI, 0 belatacept LI, and 1 CsA

Of note, there were no PTLD cases reported in the Phase 2 belatacept LI dose group. The predominant histological PTLD phenotype was of B-cell origin, with the exception of 1 subject in the belatacept LI group who had a T cell PTLD. For belatacept subjects, all but 1 case of PTLD developed within the first 18 months. The risk of developing PTLD appears to be highest in this time period, and declines thereafter, consistent with the temporal trends reported in the literature.^{63,83}

All reported cases of PTLD in belatacept subjects presented either in the renal allograft or in the CNS, and there was no involvement of other sites or disseminated PTLD. The 2 cases of PTLD in CsA subjects also presented in the renal allograft, but had other sites of involvement. While PTLD affecting the renal allograft occurred at similar rates in belatacept- and CsA-treated subjects, PTLD affecting the CNS only occurred in belatacept-treated subjects. The overall proportions of subjects who had PTLD with CNS presentation were 75% (6/8) and 50% (3/6) in the belatacept MI and LI groups, respectively. All renal PTLD cases in subjects treated with belatacept occurred by Month 6 after transplantation, whereas CNS PTLD most often occurred between Month 6 and Month 18 after transplantation. There was 1 CNS PTLD case in an EBV-positive subject in the belatacept LI group that occurred 46 months after transplantation. The 2 cases of renal PTLD in the CsA group occurred at 5 and 47 months after transplantation. Of the subjects with PTLD, 4/8 (3 CNS, 1 renal), 3/6 (2 CNS, 1 renal), and 2/2 (2 renal) subjects in the belatacept MI, LI, and CsA groups, respectively, died.

Table 19: Post-transplant Lymphoproliferative Disorder by Recipient EBV Status and Site of Presentation (Pooled Core Studies)

	Belatacept MI N=477	Belatacept LI N=472	CsA N=476
Number of cases	8	6	2
Site of presentation			
Renal	2	3	2
EBV-negative	1	1	1
EBV-positive	0	2	0
EBV-unknown	1	0	1
CNS	6	3	0
EBV-negative	4	1	0
EBV-positive	2	2	0
Fatal	4	3 ^a	2
Renal	1	1	2
CNS	3	2	0

Data as of 14-Dec-09.

^a Of the 3 deaths reported in the LI group, 2 were reported after the SUR database lock.

While EBV-negative subjects made up 12% of the trial population across the belatacept treatment groups, half of the cases of PTLD in belatacept-treated subjects occurred in this EBV-negative subgroup. The rate of PTLD and CNS PTLD in belatacept-treated subjects was 10-fold higher in EBV-negative recipients (7.3%, 7 of 96 for any PTLD; 5.2% for CNS PTLD) compared with EBV-positive recipients (0.7%, 6 of 805 for any PTLD; 0.5% for CNS PTLD). CNS PTLD represented approximately 70% of the cases for both EBV-negative (5 of 7 cases) and EBV-positive (4 of 6 cases) transplant recipients.

External Review of PTLD Histology

The previously mentioned analyses of PTLD in the belatacept clinical studies were based upon cases as diagnosed by local clinical and pathologic assessment. To supplement the local findings and standardize the pathologic assessment, a post-hoc central evaluation was conducted by a blinded pathologist. The central assessment was performed for 13 of the 16 PTLD cases (6, 5 and 2 in the belatacept MI, LI and CsA groups, respectively) that had available biopsy material. The most recent case reported on 14-Dec-2009 is still

pending central pathology assessment. Central and local pathology assessment was comparable for 11 of the 13 cases. There were 2 centrally assessed cases that were classified as not compatible with the diagnosis of PTLD. Both cases were in EBV-positive subjects in the belatacept LI group and had been diagnosed as PTLD involving the renal allograft by the local pathologist. The central pathologist assessed one of the cases as acute rejection and the other as reactive T-cell proliferation. Both subjects received treatment for PTLD based on local assessment and as of 01-Dec-2009, the subjects are alive with a functioning graft.

PTLD in the Liver Transplantation Study IM103045

In addition to the 16 subjects with PTLD in the renal transplantation program, 2 of the 146 belatacept-treated subjects in the liver transplantation study (IM103045) developed PTLD in the hepatic allograft 10 to 15 months after transplantation. These 2 belatacept-treated subjects (regimen currently blinded) were EBV-positive. One subject has died and one subject is alive with a functioning graft. Belatacept dosing regimens in this study were similar to the MI and LI regimens in the Phase 3 renal transplant studies, but included an additional Day 3 dose of 10 mg/kg. All subjects received MMF and corticosteroids.

Based on published data, liver transplant recipients have a higher risk for developing PTLD than renal transplant recipients.⁸⁴ In addition, recipient EBV serostatus does not appear to be a risk factor for PTLD in liver transplant recipients, whereas it is the strongest risk factor for renal transplant recipients.⁸⁵ Since disease characteristics and PTLD risk in liver transplant recipients are different than renal transplant recipients and the study is ongoing, these 2 cases of PTLD were not integrated into the analyses of PTLD in the renal program.

7.2.3.3 Risk Factors for PTLD

To identify independent risk factors for the development of PTLD and CNS PTLD in belatacept-treated subjects, a multivariate risk factor analysis was performed on belatacept only subjects for the following variables: age, gender, belatacept dose, EBV and CMV recipient status at the time of transplantation, CMV infection, and use of lymphocyte-depleting therapy. CsA subjects were excluded from the analysis due to the

limited number of cases (n=2). Consistent with the known risks in the literature,^{63,81,86} EBV serostatus was confirmed as the most important risk factor for the development of any PTLD and CNS PTLD. In addition, exposure to lymphocyte-depleting therapy was identified as an important risk factor for any PTLD and CNS PTLD, and CMV infection was identified as a risk factor for CNS PTLD (Table 20). Although baseline CMV negative serostatus was a predictive factor when examined individually, it appears to have less independent association for an increased risk when CMV infection and other variables are taken into account.

Table 20: Key Risk Factors for Post-transplant Lymphoproliferative Disorder (Pooled Core Studies)

Risk Factors	Any PTLD		CNS PTLD	
	Hazard Ratio	(95% CI)	Hazard Ratio	(95% CI)
Recipient EBV Serostatus (Negative versus Positive)	10.35	(3.26, 32.89)	13.04	(3.26, 52.15)
Lymphocyte Depleting Therapy (Yes versus No)	3.58	(1.06, 12.05)	4.62	(1.07, 19.94)
CMV infection post transplant (Yes versus No)	2.74	(0.83, 9.10)	5.63	(1.41, 22.49)
Recipient CMV Serostatus (Negative versus Positive)	1.80	(0.59, 5.51)	1.71	(0.43, 6.76)

Data from the SUR database lock. One additional case of PTLD occurred after the SUR database lock; that patient's information is included in these models.

Results based on Cox proportional hazards model. Select factors from analysis extracted and reported in this table.

7.2.3.4 Comparison of PTLD Rates to Epidemiologic Data

The most direct estimate of the risk of PTLD associated with belatacept therapy is obtained from the belatacept controlled clinical trial experience. To further provide context for the risks of PTLD in EBV-positive and negative subjects treated with belatacept, the incidence rates of PTLD observed in the clinical trials were compared to rates derived from existing large, external transplant databases, including the United States Renal Data System (USRDS) and the United Network for Organ Sharing (UNOS). The USRDS database combines UNOS data for transplant information with CMS claims data for outcomes; hence it is referred to as the CMS data. These analyses of PTLD data

from UNOS and CMS were commissioned by BMS and conducted by an external research group.

Incidence rates were calculated for the 2-year period after transplantation, capturing the period of highest PTLD risk and most complete follow-up for belatacept subjects. Overall rates by EBV serostatus are presented along with rates for transplant recipients receiving CNI-based maintenance regimens, but not receiving lymphocyte-depleting therapy induction. Lymphocyte-depleting therapy induction is reported to increase the risk of PTLD, potentially confounding comparisons of overall rates to the belatacept rates; however, minimal differences in the overall and no-lymphocyte-depleting therapy rates from the external databases were observed (Table 21).

Table 21: Post-transplant Lymphoproliferative Disorder 2-year Incidence Rates by Recipient EBV Serostatus

Database	Incidence Rates per 100 Patient Years of Follow-up	
	EBV-Positive Recipients (95% CI)	EBV-Negative Recipients (95% CI)
CMS ^a	0.28 (0.22, 0.34)	1.03 (0.78, 1.36)
UNOS ^b	0.11 (0.08, 0.13)	0.70 (0.55, 0.87)
CMS excluding LDT induction ^c	0.24 (0.18, 0.33)	0.95 (0.67, 1.36)
UNOS excluding LDT induction ^d	0.09 (0.06, 0.12)	0.54 (0.39, 0.73)
Belatacept core studies ^e	0.33 (0.11, 0.77)	4.09 (1.64, 8.42)

^a Adult kidney-only transplant recipients, 2000-2006, Medicare primary payer, unpublished data.

^b Adult kidney-only transplant recipients, 2000-2006, unpublished data.

^c Adult kidney-only transplant recipients, 2000-2006, Medicare primary payer, CNI maintenance regimen, no lymphocyte-depleting therapy induction, unpublished data.

^d Adult kidney-only transplant recipients, 2000-2006, CNI maintenance regimen, no lymphocyte-depleting therapy induction, unpublished data

^e Belatacept 3 core studies IM103008, IM103027, IM103100

The 2-year EBV-negative incidence rate for belatacept was estimated to be 4.09 cases per 100 years of follow-up. The belatacept rate was significantly higher than both the UNOS

and CMS rates. For EBV-positive subjects, the belatacept incidence rate was estimated as 0.33 cases per 100 years of follow-up, reflecting a lower absolute risk. This rate exceeds the upper boundary of the 95% CI for the UNOS data (0.13 cases per 100 patient-years) and is similar to the upper bound estimated for the CMS data (0.34 cases per 100 patient-years).

In addition, [Table 21](#) highlights the differences in PTLT risk between EBV-positive and EBV-negative transplant recipients. The observed 2-year PTLT rates in EBV-negative recipients in the CMS and UNOS data were (3.5 to 6 times) higher than the rates in EBV-positive recipients. The magnitude of difference is consistent with a recent publication of CTS data (HR 6.5 [95% CI 4.1-10.4]).⁸⁵ In contrast, the relationship of the observed PTLT rate with belatacept in EBV-negative subjects in the belatacept trials to that in EBV-positive subjects (approximately 12 times higher) suggests that the risk of PTLT with belatacept is concentrated in EBV-negative subjects.

These analyses complement the direct estimation of risk through clinical trial data and provide context for the belatacept clinical trial experience. The differences in the data capture as well as the clinical characteristics of the population contribute to the differences in rates seen between UNOS and CMS datasets, and limit their applicability to the clinical trial experience. Thus the robustness of the reference data from the transplant databases lies in the range of estimates provided.

The interpretation of the incidence rates must consider the difference in the distribution of the anatomic site of presentation between the references databases and the belatacept experience. Data from the UNOS database indicate that PTLT with currently available therapies in renal transplant recipients primarily involve the following sites: allograft 11%, stomach 12%, lung 15%, bone marrow 10%, gastrointestinal 27%, liver 16%, and CNS 8% (US adult renal transplant recipients 1995-2006, UNOS database, 18-months follow-up, unpublished data). These estimates are consistent with the literature and demonstrate that CNS involvement with currently available therapies is significantly less frequent than observed in the belatacept trials (approximately 70%). The anatomic site of PTLT is not available in the CMS database.

In summary, comparisons to the external databases provide context to the clinical trial findings regarding PTLT. CNS PTLT occurred at a higher frequency in both

EBV-positive and EBV-negative belatacept-treated subjects than observed with currently available therapies. In EBV-positive subjects, the overall risk of PTLD with belatacept may be higher than that reported in reference databases, but a definitive conclusion cannot be made. However, it can be concluded that the distribution of anatomical site of presentation is different, and that the overall absolute risk of developing PTLD in the EBV-positive population is low. The data reported here demonstrate that in the belatacept clinical trials and the external databases, the greatest risk of developing PTLD was found to be in the EBV-negative population.

7.2.3.5 Summary of PTLD Data and Risk Management Strategy

An important risk observed with belatacept was PTLD involving the CNS. While the frequency of renal PTLD was similar across the 3 treatment groups, the extra-renal presentation of PTLD with belatacept was atypical in that aside from CNS presentation there were no cases of disseminated PTLD or PTLD that involved non-CNS sites. CNS PTLD occurred at a higher frequency in the belatacept treatment groups compared with CsA, and more cases were reported with the MI regimen than the LI regimen. Only 1 case of PTLD has occurred in a belatacept-treated subject after the known high risk period with substantial follow-up of subjects after the first year, consistent with a declining risk over time as reported in the literature.^{80,84} The greatest risk for developing PTLD and CNS PTLD was in the EBV-negative population, representing both an increased relative risk to currently available therapies and a greater than 10 to 13-fold higher risk than in the EBV-positive population (see Section 7.2.3.3).

To reduce the risk of PTLD and CNS PTLD, BMS has proposed a comprehensive risk management strategy (see Section 9), which includes a contraindication to the use of belatacept in patients who are EBV-seronegative or have unknown serostatus, and additional warnings for PTLD in the US Package Insert (USPI).

7.2.4 Infections

In a pooled analysis by treatment group of all events up to database lock, the frequency of infections was similar in the belatacept MI, belatacept LI and CsA groups (79%, 80% and 80%, respectively; [Table 22](#)). The most common infections ($\geq 10\%$) in all 3 treatment

groups were urinary tract infection, upper respiratory tract infection, nasopharyngitis, and CMV infection.

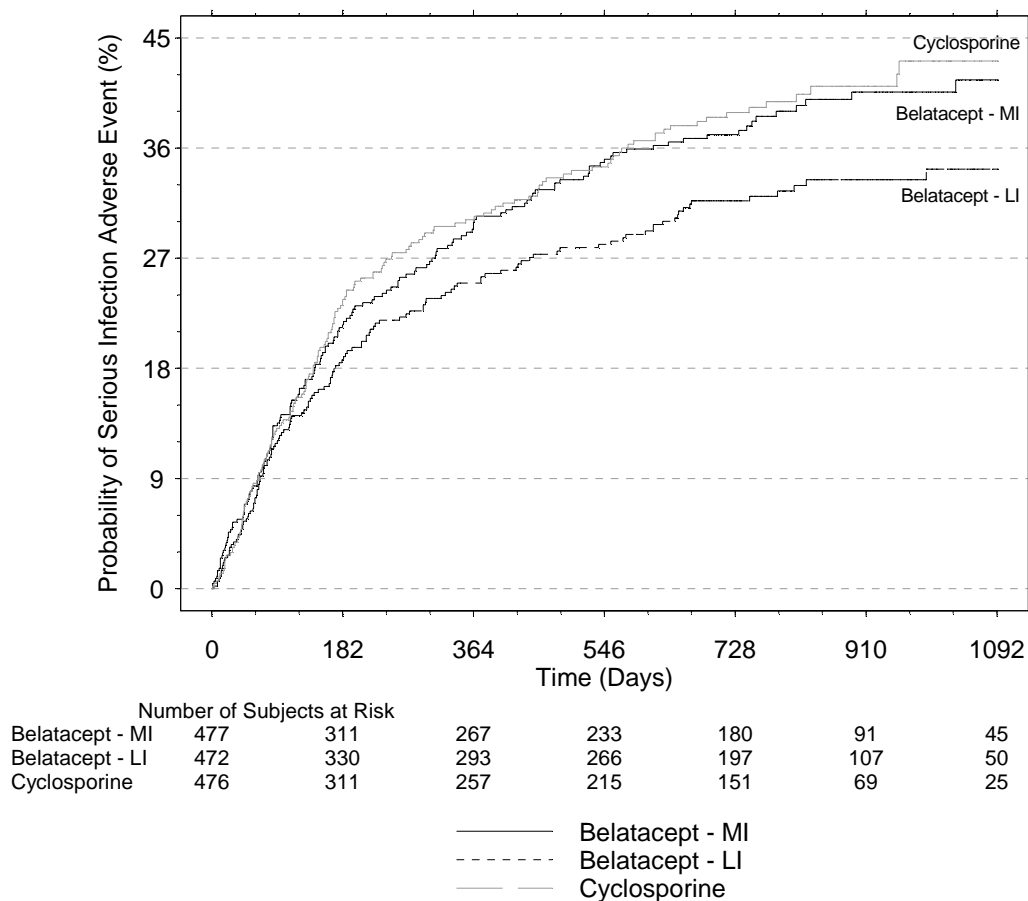
Table 22: Infections Up to Database Lock (Pooled Data) from Core Studies

	Number of Subjects (%)					
	Up to Month 12			Up to Database Lock		
	MI N =477	LI N =472	CsA N =476	MI N =477	LI N =472	CsA N =476
Infections and Infestations	337 (70.7)	339 (71.8)	351 (73.7)	378 (79.2)	376 (79.7)	381 (80.0)
Serious Infections	128 (26.8)	109 (23.1)	130 (27.3)	169 (35.4)	142 (30.1)	166 (34.9)
Viral infections	126 (26.4)	118 (25.0)	132 (27.7)	183 (38.4)	168 (35.6)	160 (33.6)
CMV	53 (11.1)	56 (11.9)	65 (13.7)	65 (13.6)	62 (13.1)	69 (14.5)
Polyoma virus	23 (4.8)	11 (2.3)	23 (4.8)	30 (6.3)	16 (3.4)	26 (5.5)
Herpes	38 (8.0)	31 (6.6)	29 (6.1)	67 (14.0)	57 (12.1)	41 (8.6)
Fungal infections	66 (13.8)	52 (11.0)	72 (15.1)	99 (20.8)	78 (16.5)	95 (20.0)
Tuberculosis	2 (0.4)	2 (0.4)	1 (0.2)	5 (1.0)	3 (0.6)	1 (0.2)

Data from the BLA database lock.

The frequency of serious infections through database lock was lower in the belatacept LI (30%) than in the belatacept MI and CsA groups (35% for both). The most common ($\geq 2\%$) serious infections in all 3 treatment groups were urinary tract infection, CMV, pneumonia, and pyelonephritis.

The time to first serious infection pooled across the 3 core studies reported up to Year 3 is illustrated in the Kaplan-Meier plot in [Figure 17](#). The curves were similar in all three treatment arms until approximately Day 120 when there was a separation of both CsA and belatacept MI from the LI regimen. The difference between the belatacept MI and LI groups began during the period of increased exposure of the belatacept MI regimen. The separation between groups was sustained throughout the remaining 3-year period. This analysis was also performed pooling only the Phase 3 studies (excluding the Phase 2 study), and the results were consistent with the Pooled Core Studies.

Figure 17: Kaplan-Meier Estimates of Time to First Serious Infection up to Year 3 (Pooled Core Studies)

MedDRA Version: 11.1

All randomized and transplanted subjects from Studies -008 and -027

All randomized, transplanted and treated subjects from Study -100

The overall rates of viral infections through database lock were similar across groups (38%, 36%, and 34% in the belatacept MI, LI, and CsA groups, respectively), with somewhat lower rates of overall and specific viral infections in the belatacept LI group versus the MI group. The frequency and severity of CMV infections were not notably different between belatacept- and CsA-treated subjects. The overall incidence of polyoma virus infection was lower in belatacept LI (3.4%) versus CsA (5.5%) and belatacept MI

(6.3%), as was the frequency of polyoma associated nephropathy (0.6% for belatacept LI versus 1.3% for belatacept MI and CsA).

Two cases of PML have been reported in belatacept-treated subjects: 1 renal transplant recipient and 1 liver transplant recipient.

- The case of PML in the renal transplant recipient (63-year-old white female) occurred in study IM103027 and was confirmed by the identification of JC virus in cerebrospinal fluid and resulted in death. This subject was treated with belatacept MI, MMF and corticosteroids, for approximately 2 years.
- The case of PML in a liver transplant recipient (study IM103045) (52-year-old white male) was confirmed by the identification of JC virus in cerebrospinal fluid. The subject was treated with belatacept MI (the MI regimen in the liver transplantation study had one additional 10 mg/kg, dose on Day 3) and MMF (increased to 3 to 4 g/day for first 3 months due to transaminitis, later reduced to 2 g/day) and corticosteroids for approximately 6 months. Belatacept and MMF were discontinued and the subject was maintained on low dose prednisone.

In the pooled analysis up to database lock, herpes virus infections were more frequent in both belatacept groups (12% in LI, 14% in MI) compared with the CsA group (9%). Review of the events indicated that the excess of cases in the belatacept LI group was limited to herpes simplex rather than herpes zoster infections, while in the belatacept MI group the excess was due to both herpes simplex and herpes zoster infections. Very few herpes infections ($\leq 2\%$) in all 3 treatment groups were serious.

The cumulative frequency of fungal infections was lower in the belatacept LI group (17%) compared with the CsA (20%) and MI (21%) groups. Fungal infections with the outcome of death were reported for 3 subjects (1 in each group): belatacept MI group (bronchopulmonary aspergillosis), belatacept LI group (cryptococcosis), and CsA group (severe mucormycosis infection). *Pneumocystis jirovecii* was reported in a small number of subjects: 3, 1, and 2 in the belatacept MI, LI and CsA groups, respectively.

Tuberculosis (TB) was reported more frequently in belatacept- than CsA-treated subjects: 5 cases in the belatacept MI group, 1 case in the CsA group, and 3 cases in the belatacept LI group ([Table 23](#)).

Table 23: Tuberculosis (Pooled Core Studies)

	Belatacept MI N=476	Belatacept LI N=471	CsA N=465
Number of cases	5 (1.0)	3 (0.6)	1 (0.2)
Extrapulmonary involvement	3	3	1
Discontinued study treatment	1	2	0
Status			
Resolved	3	2	1
TB treatment ongoing	1	0	0
Fatal	0	1	0
Resided in an endemic area	4	3	1

Data from the BLA database lock.

The frequency of extrapulmonary TB was consistent with that seen in published reports in transplant populations.⁸⁷ Eight of the 9 subjects with TB lived or had lived in endemic areas (i.e., Brazil, India, or Mali), where the frequency of TB in transplant recipients ranges from 2.4% to 11%.^{88,89}

Study subjects were screened for TB pre-transplant according to local guidelines and none had a history of TB. History of prior Bacillus Calmette Guerin vaccination was positive for 4, negative for 2 and unknown for 3 subjects.

An examination of infections involving the CNS (up to the SUR database lock) indicated a higher risk in belatacept MI-treated subjects (7 cases) compared with belatacept LI (1 case) and CsA (1 case). Two belatacept-treated subjects died due to CNS infections, both in the MI group: 1 subject with PML (mentioned earlier) and 1 subject with West Nile virus.

The following is a summary of infections in the belatacept core studies:

- The overall frequency of infections was similar in the belatacept and CsA groups.
- The frequencies of serious infections, polyoma virus infections and fungal infections were lower in the belatacept LI group, and higher in the CsA and belatacept MI groups.

- Two (2) cases of PML have been reported with belatacept (1 in a renal transplant recipient, 1 in a liver transplant recipient), both in subjects receiving a belatacept MI regimen.
- Belatacept may be associated with increased rates of non-serious herpes infections.
- Belatacept may increase the risk of tuberculosis in subjects already at high risk for contracting the illness; thus, individuals considered to be at high risk of contracting TB should be carefully assessed and monitored via existing guidelines.⁹⁰
- The risk of CNS infections was not elevated in belatacept LI versus CsA-treated subjects, but was increased in subjects treated with belatacept MI.

7.2.5 Other Adverse Events of Clinical Interest

7.2.5.1 *Hypersensitivity and Infusional Events*

There were no reports of anaphylaxis or hypersensitivity to belatacept in the clinical program. The proportion of belatacept-treated subjects with acute infusional events (pre-identified AEs occurring within 1 hour of infusion) up to the BLA database lock was 4% to 5%. The most frequently reported acute infusion-related reactions in both belatacept regimens were hypotension, hypertension, flushing and headache. Most events were non-serious, mild to moderate in intensity, did not recur despite ongoing treatment, and resolved within minutes to days.

7.2.5.2 *Autoimmunity*

The frequency of autoimmune events was approximately 2% in all 3 treatment groups. The most common autoimmune disorder reported in belatacept-treated subjects was psoriasis (3 subjects each in the belatacept MI and LI regimen). The most common autoimmune disorder in CsA subjects was hyperthyroidism (3 subjects).

One subject in IM103027 who received belatacept MI developed Guillain-Barré Syndrome after a urinary tract infection, which later resolved. The clinical significance of this isolated case is not known.

7.2.5.3 Immunogenicity

A comprehensive assessment of immunogenicity in the belatacept program was performed. Among renal transplant recipients, anti-belatacept antibodies were detected in 4% of subjects receiving belatacept and 5.6% of subjects after discontinuation of belatacept. Antibodies were of low titer, and usually diminished or cleared with ongoing exposure to belatacept. Antibodies were more frequently detected with chronic administration at an every-8-week rather than every-4-week interval. Neutralizing antibodies were detected in few subjects. There was no evidence that antibody development was associated with altered clearance of belatacept, AR, graft loss, or safety events such as infusion reactions or autoimmune events. Thus, in the context of immunosuppression for renal allograft transplantation, belatacept does not appear to be highly immunogenic.

7.2.5.4 Thrombotic Events

A detailed evaluation of thrombosis, prompted by a greater number of graft losses attributed to graft thrombosis in belatacept- versus CsA-treated subjects in IM103027 per the independent adjudication committee, did not reveal any increased risk of thrombosis with belatacept. In pooled analyses, there was no excess of adjudicated graft loss due to thrombosis, thrombotic events associated with allograft thrombosis, or overall thrombotic events associated with belatacept LI or belatacept MI versus CsA. Renal vein thrombosis was reported more frequently in the belatacept MI group than the belatacept LI and CsA groups in IM103027 (3.3% versus 1.1% for belatacept LI and 0 for CsA), but the rate of renal vein thrombosis in the belatacept MI group was lower than that reported for recipients of extended criteria donor kidneys in the USRDS database (7.3%).⁷

7.2.5.5 Laboratory Findings

Belatacept was not associated with clinically significant adverse effects on hematology and chemistry laboratory parameters.

Hypophosphatemia was more frequently reported in belatacept-treated subjects by Month 12: 17%, 21%, and 13% in belatacept MI, LI and CsA groups, respectively. The majority of these AEs occurred between 0 - 3 months, none were serious and none

resulted in treatment discontinuations. Upon evaluation of the central laboratory values, the mean and median blood phosphorus levels were similar in the belatacept MI, LI and CsA treatment groups at each specified time point up to Month 12. The etiology of this frequent post-transplant phenomenon is unclear, but may involve early improved renal function with belatacept, phosphaturic effects of parathyroid hormone or more likely fibroblast growth factor-23 and possibly other long-lived serum phosphatonins that clear slowly following successful transplantation.⁹¹

Proteinuria was defined in the protocols as 2+ on a urine dipstick assessment on 2 consecutive visits. Proteinuria up to Month 12 was reported in 0.3% (LI) to 2.3% (MI) more belatacept-treated subjects than CsA-treated subjects (3.7%) in IM103008 and 3.3% (LI) to 4.1% (MI) more belatacept-treated subjects than CsA-treated subjects (6.8%) in IM103027. Review of urine protein by visit indicates an excess of subjects with urine protein 2+ or greater at Month 1, but the urine protein profile at Month 12 was similar in belatacept- and CsA-treated subjects. The increased proteinuria noted in the belatacept subjects in the immediate post-transplant period may be a result of the absence of the constrictive effects of CsA on the renal vasculature.⁸

Belatacept treatment was associated with reductions in serum immunoglobulin levels, but levels returned to the normal range after discontinuation. There was no association between low immunoglobulin levels and the incidence of serious infections.

7.2.6 Safety Summary

The key safety findings included the following:

- Belatacept was generally well tolerated and had a general AE profile similar to that of CsA, with avoidance of some CsA-specific toxicities such as hirsutism and tremor.
- Overall rates of deaths, serious infections and discontinuations due to AEs were lower with belatacept LI, the recommended clinical dose, than with CsA.
- Belatacept use was associated with an increased number of PTLD cases, particularly in the CNS.
 - All but one case of PTLD occurred during the first 18 months post transplant.
 - The risk of PTLD was highest in subjects who were EBV-negative at the time of transplant.

- The risk of developing CNS PTLD may be higher with the belatacept MI regimen than with the belatacept LI regimen, taking into account the increased frequency of CNS infections also observed with the MI regimen
- The frequency of overall infections including CMV infection was similar in the belatacept LI, MI, and CsA groups.
- Two (2) cases of PML have been reported with belatacept, both cases in subjects receiving the belatacept MI regimen, 1 in the renal transplant study IM103027 and 1 in the liver transplant study IM103045.
- Rates of deaths, malignancies, serious infections and CNS infections were lower in subjects receiving the LI regimen than the MI regimen.

Based upon the safety findings in the clinical program, the use of belatacept is proposed to be contraindicated in EBV-seronegative recipients and those with unknown serostatus, and warnings are proposed to communicate the risks of PTLD, infections, and PML. In addition to the product label, key components of the plan include a REMS to communicate PTLD and other risks to physicians and patients, an ongoing safety evaluation through clinical trials, and post-marketing pharmacovigilance and epidemiologic studies. A detailed discussion of the risk management strategies is included in Section 9 of this document.

8 DOSE RECOMMENDATION

Based upon the results of the Phase 3 program, the LI regimen of belatacept has the most favorable benefit-risk profile and is the recommended dose for clinical use.

Subject and graft survival were similar across the 2 belatacept groups in both studies. A comprehensive review of all the renal function data indicates that the 2 belatacept regimens offered similar benefits with regard to renal function and chronic allograft nephropathy. The GFR differences were similar with both belatacept regimens in Study IM103008, and although there were differences between the MI and LI regimens with regard to the measured GFR results in Study IM103027, the calculated GFR data in that study also indicated no difference between the 2 regimens. Likewise, the magnitude of effect on CV and metabolic endpoints such as diabetes, hypertension, and lipids were generally similar across the 2 belatacept groups. Furthermore, the incidence and grade of AR appeared to be higher with the belatacept MI regimen compared with the LI regimen,

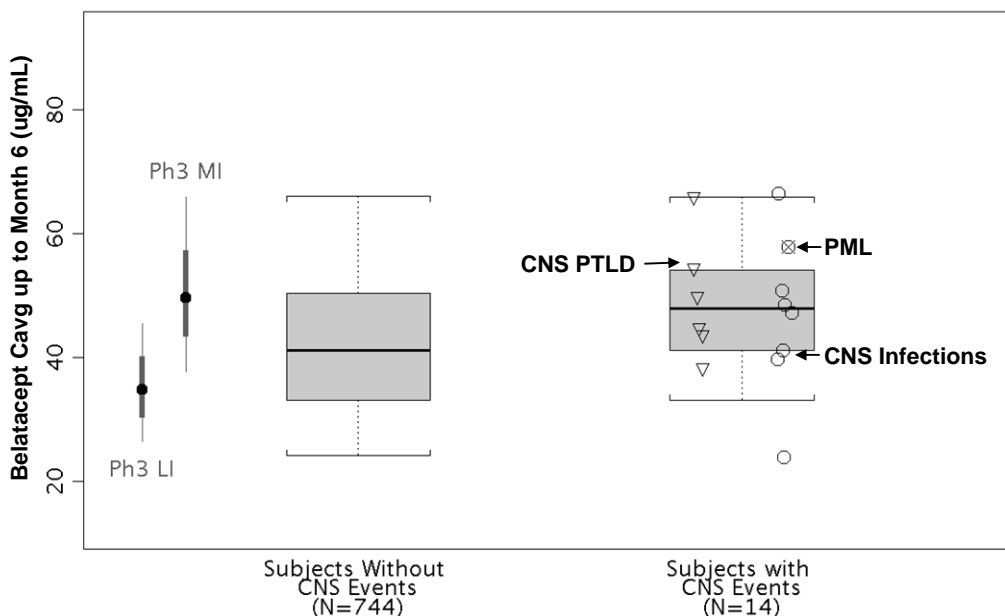
particularly in the IM103008 study. Thus, the results of the Phase 3 studies indicate that the MI regimen offers no demonstrable efficacy advantage over the LI regimen.

The belatacept LI regimen tended to demonstrate a better AE profile than the belatacept MI regimen across several important safety parameters. Rates of deaths, malignancies, serious infections, and CNS infections were lower in subjects receiving the belatacept LI regimen than in subjects receiving the belatacept MI regimen. Further, the cases of PML observed in the program occurred in the MI regimen. The frequency of CNS PTLD also was lower in subjects who received the LI rather than the MI regimen, as was the use of lymphocyte-depleting therapy for treatment of AR, which was a risk factor for PTLD.

Consistent with the different safety event rates between the LI and MI dosing regimens, exposure response analysis supports a more favorable safety profile for the LI regimen than the MI regimen. Subjects in the renal program with CNS events (CNS PTLD and CNS infections, including the 1 renal transplant recipient with PML) tended to have higher cumulative exposure in the peri-transplant period compared with subjects who did not have these events up to the BLA database lock ([Figure 18](#)). There was also a suggestion of an exposure-response relationship for serious infections; the risk of infections increased with higher exposure. Although definitive relationships could not be established because of limited data, the exposure response data, when viewed in totality, showed an association between higher belatacept exposure and increased numbers of some safety events, further supporting the recommendation for the LI dosing regimen.

Based upon these findings, the LI regimen is the recommended dose for clinical use, which would reduce the overall burden of immunosuppression and is expected to reduce the risks associated with belatacept.

Figure 18: Cumulative Average Concentration of Belatacept up to 6 Months After Transplantation in Subjects With and Without CNS Events



Box and whiskers plots are the distribution of belatacept average concentrations (Cavg) up to 6 months after transplantation (Cavg = total cumulative AUC divided by time) in subjects treated with belatacept with and without CNS events in Phase 2 and 3 Studies IM103100, IM103008, and IM103027. For the purpose of calculating Cavg up to 6 months after transplantation, only subjects who were still receiving belatacept administration at 6 months after transplantation were included in the plot. The horizontal line in the middle of the box is the median, the box is the inter-quartile range 25th percentile to 75th percentile, the whiskers are the 5th and 95th percentiles, respectively.

Triangles in the box and whiskers plot on the right represent the individual Cavg of subjects who had CNS PTLD. Open circles represent the individual Cavg of subjects who had CNS infections. The open circle with cross represents the individual Cavg of the 1 renal transplant subject who had PML.

Phase 3 LI and Phase 3 MI thin vertical lines are the 10th percentile to 90th percentile of Cavg up to 6 months post transplantation for LI and MI regimes, respectively. Phase 3 LI and Phase 3 MI thick vertical lines are the 25th percentile to 75th percentile of Cavg, respectively. Dark circles in the middle of Phase 3 LI and Phase 3 MI lines are the median of Cavg, respectively.

Data from the BLA database lock

9 RISK MANAGEMENT STRATEGIES

The primary safety concerns observed with a belatacept immunosuppressive regimen are PTLD, particularly involving the CNS, and serious infections, including PML. Several

risk minimization activities are proposed to minimize the occurrence and mitigate these risks. The goals can be achieved through selection of appropriate patients for belatacept (i.e., those who have EBV-positive serostatus), appropriate selection of the belatacept LI dose, and cautious use of concomitant immunosuppressive treatment, including for episodes of acute rejection and careful monitoring, early diagnosis, and treatment of identified risks.

The established characteristics of the transplant community and intravenous administration of belatacept enhance the ability to achieve success of the proposed risk management strategy. The transplant community is comprised of a limited number of highly specialized centers staffed by health care providers including transplant surgeons, transplant nephrologists, transplant coordinators, and pharmacists who are familiar with the risks of immunosuppression including PTLD, serious infections, and PML. There are approximately 200 adult renal transplant centers in the US, with approximately half performing 80% of all kidney transplantations. Over 50 of these centers, representing about 1/3 of the adult renal transplant volume, have participated in the belatacept clinical trial programs and are familiar with the profile of belatacept. Transplant centers adopt new agents based on their experience with the new agent and institution of immunosuppressive protocols for that agent based on multidisciplinary input. These factors will contribute to an anticipated slow market uptake of belatacept and facilitate implementation of the proposed risk management plan. The projected use of belatacept in the first year after approval is estimated to be 1 to 2 times those exposed in clinical trials.

EBV-negative serostatus is present in approximately 15% of adults and has a known association with the risk of developing PTLD. EBV serology is a standard test available in transplant centers that is typically assessed when patients are on the waiting list for transplantation. Through UNOS, it is known that about 75% of patients transplanted have a known EBV serostatus. These aspects of EBV serology establish a solid foundation to build upon with the belatacept communication plan.

Transplant recipients currently receive extensive education on the risks and benefits of their immunosuppression treatment and are closely supervised by the transplant center. In addition, the intravenous administration of belatacept and the frequent follow-up visits allow for a regular dialogue between the patient and the clinician, enabling early intervention when adverse events occur.

To manage the risks of PTLD and serious infections including PML, a REMS is proposed, which includes a communication plan and a medication guide. The goal of the belatacept REMS is to:

- Educate health care providers and patients on the risks of PTLD and serious infections, including PML, to minimize their occurrence.
- Educate health care providers and patients on ways to mitigate the impact of these events should they occur.

Finally, the impact of the REMS will be assessed with a comprehensive pharmacoepidemiology plan and assessment of the communication tools.

9.1 Communication Plan

The communication plan will be directed to all health care providers who will be prescribing and providing care for a renal transplant patient. The goal is to educate health care providers to minimize the occurrence of PTLD and serious infections, including PML, and mitigate the impact of events that may occur. Communication will be delivered through a multi-pronged, iterative approach including both personal and non-personal communication beginning at the time of approval. Transplant surgeons, transplant nephrologists, transplant coordinators, pharmacists, community nephrologists and those who will be infusing belatacept in the community setting will be educated.

Based upon the safety findings in the clinical program, the use of belatacept is proposed for EBV-positive recipients with a contraindication for EBV-seronegative recipients and those with unknown serostatus. The plan proposes to communicate the risks of PTLD, serious infections, and PML, and ways to minimize and mitigate these risks. The elements of the communication plan will include a dear health care provider letter, health care provider fact sheet, and education which will be delivered through personal interactions and will be web-based.

The key points of the communication plan to health care providers include the following:

PTLD minimization and mitigation:

- The risks for development of PTLD, especially in the CNS, associated with EBV serostatus, CMV infection, and use of lymphocyte-depleting agents.
- The importance of pro-active testing and updating EBV serology in patients listed for transplantation.
- Appropriate patient selection through use in only EBV-positive patients.
- CMV prophylaxis to prevent the occurrence of CMV disease, an established risk factor in the development of PTLD.
- The need for cautious use of lymphocyte-depleting therapies in the treatment of rejection episodes.
- The importance of early detection of new or worsening neurologic, cognitive, or behavioral signs or symptoms to assist in early detection and treatment of CNS pathology, including CNS PTLD and PML, in post-transplant patients.
- Awareness of treatment options, including reduction/withdrawal of immunosuppression, as well as chemotherapy and nephrectomy as appropriate, and possible consultation.

Infection minimization and mitigation:

- The risk of serious infections, including fatal infections, opportunistic infections, TB, and herpes.
- The need for effective CMV prophylaxis to reduce the risk of CMV disease.
- The need for PCP prophylaxis.
- TB screening per guidelines and appropriate management, especially patients who have moved from endemic areas.
- The importance of early detection of infectious symptoms.

PML minimization and mitigation:

- The importance of early detection of new or worsening neurologic, cognitive, or behavioral signs or symptoms to assist in early treatment of PML.
- The need for early evaluation through CNS imaging, CSF analysis for JC virus by PCR, and consultations should be considered.
- Awareness of treatment options including reduction/withdrawal of immunosuppression.

In addition, the USPI will recommend through a black boxed warning (an aspect of labeling common to all transplant immunosuppressant medicines) that belatacept treatment be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and renal transplantation.

9.2 Medication Guide

To complement the USPI, a medication guide will be included as part of the secondary packaging for belatacept to be dispensed to patients. The medication guide is intended to communicate to patients the risks and enhance the early detection and treatment of PTLD, especially the CNS presentation and serious infections including PML. The medication guide will convey important patient information based on the USPI and will stress the importance of compliance with belatacept, other immunosuppression therapy, and medications to prevent CMV infection and bacterial infections. The importance of timely patient communication of adverse events to health care providers will be stressed to expedite early intervention and reduce morbidity and mortality.

The distribution of the medication guide is facilitated by the IV administration of belatacept. For de novo use, belatacept will be initiated in a hospital, just before or in the operating room on the day of the transplant surgery. Subsequent infusions will take place in a transplant center, infusion center, or in home settings by a health care provider. The IV administration of belatacept provides an important opportunity for predictable, regular, in-person contact between patient and health care providers and for dispensing the medication guide, which will be given upon hospital discharge post-transplant and at the time of monthly maintenance infusions.

The medication guide will also be provided to health care providers as part of the communication plan.

Prior to finalizing and implementing the medication guide, a patient comprehension study will be conducted using transplant recipients and patients with end stage renal disease. The study will help evaluate the level of understanding of the key messages and provide guidance for any necessary changes. Post approval, the comprehension of the communication plan by health care providers and patients will be evaluated.

Through a communication plan designed to educate health care providers and patients of known and potential risks of belatacept and an assessment plan that leverages features of the transplant community, the proposed REMS can be expected to further maintain the positive benefit risk profile of belatacept.

10 CONTINUED ASSESSMENT OF BELATACEPT AFTER APPROVAL

Further assessment and monitoring of the benefit-risk profile of belatacept post-marketing are planned via clinical trials, a comprehensive pharmacovigilance program including pharmacoepidemiology studies (post marketing observational studies), spontaneous reports of AEs, and targeted questionnaires for enhanced characterization of PTLT and select infections.

10.1 Post-Marketing Pharmacoepidemiology Studies

BMS plans to conduct 4 post-marketing observational studies in the US:

- 1) An approximately 6,000 patient (comprised of 3,000 belatacept and 3,000 CNI patients) prospective cohort study that will characterize and estimate incidence and relative risk of PTLT, including CNS PTLT, and hospitalized infections compared to CNIs. This study will also evaluate real world outcomes, including death, graft loss, rejection episodes, and treatment.
- 2) A study using the data routinely collected by UNOS will allow for frequent assessments of the relative risks of PTLT with belatacept compared with the CNIs. This study is aimed at enhancing signal detection with respect to PTLT. Since all transplants are captured in UNOS data, this study will accrue belatacept patients more quickly than the cohort study. The cohort study and the complementary PTLT study will have interim reports to the FDA semi-annually for the first 2 years and annually thereafter until their final reports, which will be 7 years after approval.
- 3) A patterns of use study will describe belatacept use relative to CNIs in terms of a number of factors such as EBV serostatus and use of CMV prophylaxis, which are routinely captured in the UNOS database. BMS will provide data to the FDA semi-annually for the first 3 years and annually thereafter up to 7 years after launch. This study will help assess the impact of the REMS.
- 4) A study using an existing transplant pregnancy registry to monitor any possible teratogenic or developmental effects of belatacept.

The overall plan of pharmacoepidemiology studies will enable the assessment of adherence to the recommended use of belatacept, describe the patterns of treatment practice (including information on EBV serostatus), enable quantitative assessment of risks associated with belatacept in the context of other immunosuppressive regimens in transplantation, and complement the information about belatacept risk that derives from ongoing clinical trials and spontaneous AE reports and their supplemental questionnaires. Taken together, the elements of the pharmacovigilance plan form a robust program of safety surveillance for belatacept.

10.2 Additional Clinical Trials

After a drug's approval, the development of a transplant medicine continues through additional clinical studies and scientific evaluation. The belatacept program will focus on generation of long-term controlled clinical data, minimization of immunosuppression, and further characterization and management of acute rejection episodes. The Phase 3 clinical trials are designed as 3 year studies, and have been amended with long-term extensions to continue to collect additional safety and efficacy data for a minimum of 5 years. The Phase 2 long-term extension study remains ongoing as a leading cohort of subjects treated with belatacept and has already accrued more than 5 years of follow-up. The clinical trials will allow for further characterization of AR and evaluation of the management of AR to enhance our understanding and provide better guidance to clinicians.

Clinical studies with other dosing regimens aimed at reducing and optimizing the overall immunosuppressive burden are either ongoing or under consideration. A steroid avoidance study (IM103034) is ongoing, a subcutaneous dosing program that may reduce peak and total belatacept exposure is planned, and studies using reduced MMF dosing are under consideration.

All of the proposed risk management activities provide a comprehensive approach that will afford an ongoing assessment of the continued favorable benefit risk profile.

11 BENEFITS AND RISKS CONCLUSIONS

11.1 Summary of Benefits

The goal of renal transplantation is to optimize renal function and thereby improve the health, longevity and quality of life of transplant recipients. The results of a rigorously-conducted development program demonstrate that belatacept offers substantial clinical benefit to renal transplant recipients. Belatacept, at the recommended LI dose, results in subject and graft survival that is comparable to CsA at 1 and 2 years. Furthermore, belatacept avoids the toxicities of the CNIs and offers clinically meaningful and durable benefits in renal function, reduces the incidence of new-onset diabetes, and improves blood pressure control and lipid parameters, all of which are important health benefits as well as critical determinants of renal transplant outcomes.

The non-inferiority assessment of subject and graft survival was supported by near complete ascertainment of vital status in both Phase 3 studies. Month 12 results ruled out that belatacept LI was more than 1.5% worse in recipients of standard criteria donor kidneys and more than 4.3% worse in recipients of extended criteria donor kidneys than CsA on the proportion of subjects who died or experienced graft loss. In addition, the comparability of belatacept to CsA in terms of subject and graft survival was demonstrated over an extended period of follow-up (2 years since transplantation).

Belatacept treatment resulted in clinically important renal function improvements that indicate better overall transplantation effectiveness and improved allograft health as compared to treatment with CsA. The durability of the effect is seen in extended follow-up, and supported by the findings of less structural damage seen in the biopsies of belatacept-treated subjects. The magnitude of the renal function differences (13 - 15 mL/min/1.73 m² in recipients of standard criteria donor kidneys and 4 - 7 mL/min/1.73 m² in recipients of extended criteria donor kidneys according to measured GFR) is several times greater than the annual rate of decline in GFR observed in CsA-treated subjects (~ 2 mL/min/1.73 m²/year) further supporting the clinical significance of the renal function differences, and suggesting a favorable impact on graft survival.

In addition to the renal function benefits, treatment with belatacept resulted in less NODAT, lower blood pressure, and a more favorable lipid profile. Favorable effects on these well validated risk factors can be expected to further reduce morbidity and mortality from CV disease, the leading cause of death in kidney transplant recipients, beyond that resulting from renal function improvements alone.

Belatacept treatment was associated with an increased short-term risk of AR, and these episodes were often of high histologic grade. The extended follow-up in the belatacept clinical program suggests that the risk of AR is temporally limited to the first 6 months after transplantation. In addition, the impact of these episodes was limited as few subjects experienced severe renal dysfunction, death, or graft loss after AR.

The cumulative impact of the differential effects of belatacept is represented in an analysis of progression to advanced renal dysfunction, graft loss, or death over time which showed that by 2 years, fewer belatacept than CsA subjects had progressed to Stage 4 or 5 CKD. These data demonstrate that in recipients of both standard criteria and extended criteria donor kidneys, belatacept may alter the natural history of the transplanted kidney and delay the time to GFR decline and graft loss relative to CsA.

The results of a comprehensive development program demonstrate that belatacept at the recommended clinical dose offers kidney transplant recipients graft and subject survival that is comparable to a CsA-based regimen, with clinically important benefits with regard to renal function and CV risk. The renal, metabolic, and CV effects associated with belatacept are established predictors of improved graft survival, fewer CV events, and enhanced subject survival. Thus, long-term transplant outcomes can be expected to be improved with belatacept treatment. These benefits of belatacept were observed with both dose regimens, and consistently across all recipient and donor sub-groups, including recipients of standard criteria and extended criteria donor kidneys. Efficacy endpoint results in the EBV-seropositive cohort in each study were consistent with the overall results in both Phase 3 studies.

11.2 Summary of Risks

The risks of belatacept were characterized in 949 belatacept-treated transplant recipients in 3 core studies with a median exposure of 2 years, in which some subjects were

followed for over 7 years from the time of transplantation. Thus, the clinical program permits a thorough characterization of the short- and longer term risks of belatacept.

Belatacept was generally well tolerated. Overall rates of deaths, serious infections, and discontinuations due to AEs were numerically lower with belatacept LI, the recommended clinical dose, than with CsA. The risks associated with belatacept use are PTLD involving the CNS, and serious infections, including PML, which are consistent with belatacept's immunosuppressant properties.

The observed risk of CNS PTLD with belatacept treatment is concentrated in EBV-negative recipients, and thus can be mitigated by avoiding use in this subpopulation. In contrast, the observed risk of CNS PTLD in EBV-positive recipients is approximately 13 times lower than in EBV-negative recipients. In addition, CNS PTLD occurred less frequently with the belatacept LI regimen than the belatacept MI regimen. Only 1 case of PTLD with belatacept has occurred after 18 months, although a substantial amount of follow-up time accrued after 18 months. This suggests that the risk of this malignancy may decline over time, which is consistent with its known epidemiology.^{63,83}

Whereas most types of infections were reported at similar frequencies in belatacept and CsA-treated subjects, TB, herpes and PML were more common in belatacept subjects. The increases in these specific types of infections were not indicators of a widespread reduction in overall immunity since the rates of CMV infections were comparable across groups, and the rate of serious infections was lower in subjects treated with belatacept LI than CsA. Furthermore, there was no evidence that belatacept treatment diminished the ability of transplant subjects to respond to medical treatment for infections.

Based on these safety data and the higher drug exposure observed with the belatacept MI regimen, selection of the belatacept LI regimen is an inherent step towards reducing the risk of belatacept therapy. Additionally, belatacept use will be limited to EBV-seropositive patients via the proposed contraindication for the use of belatacept in EBV-seronegative recipients and those with unknown serostatus. Furthermore, a comprehensive approach to risk minimization and ongoing characterization of benefit-risk has been developed, as outlined in Section 9.

11.3 Overall Assessment of Benefit-Risk

Belatacept was developed as a novel immunosuppressant to address the medical need for new therapies that can avoid CNI-related toxicities while maintaining their favorable short-term outcomes.

The effects of belatacept LI relative to CsA on the key attributes of benefit and risk are summarized in [Figure 19](#). For each attribute, the absolute difference in frequency between the belatacept LI group, the recommended clinical dose, and CsA are shown for both Phase 3 studies, with a solid line representing the confidence interval of the difference.

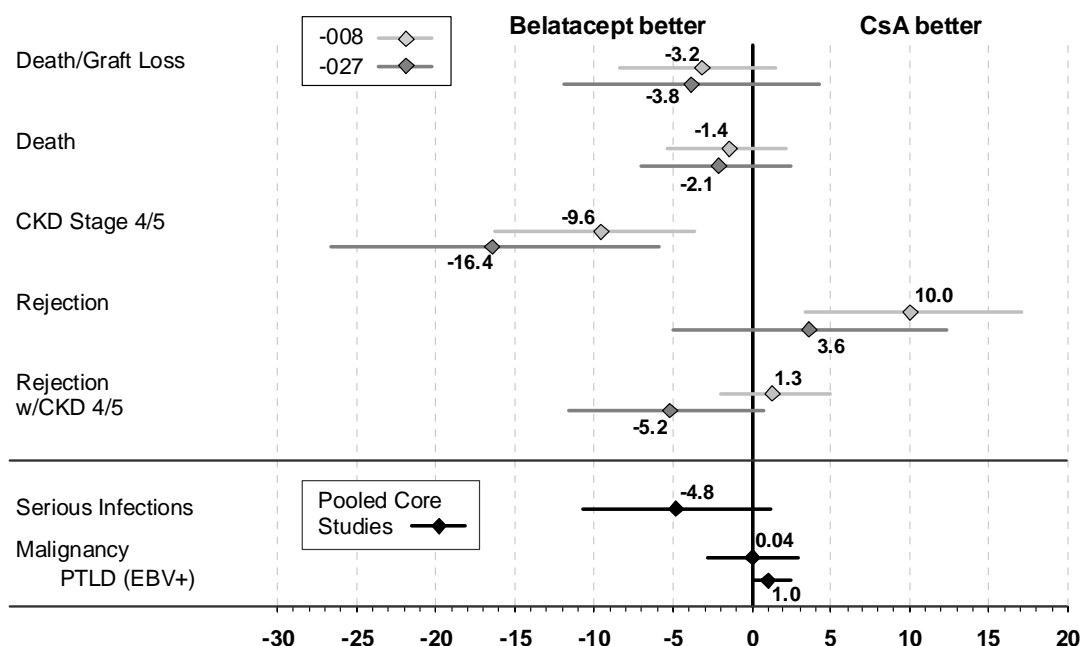
The top portion presents key efficacy endpoints at 12 months. The bottom panel presents pooled data from the 3 core studies on safety findings of particular interest, including serious infections, malignancy and PTLT. Events of serious infections and malignancies are presented up to BLA database lock and events of PTLT are presented to 14-Dec-2009. Note that PML is not reflected here as the single case in a renal transplant recipient occurred in the belatacept MI treatment group. In addition, the PTLT risk depicted is limited to EBV-positive recipients, consistent with the proposed contraindication.

In renal transplant recipients of organs from standard or extended criteria donors, belatacept was comparable to CsA on the proportion of subjects who survive with a functioning allograft, and on overall mortality. In addition, belatacept resulted in clinically meaningful reductions in the proportion of patients with advanced renal dysfunction, defined as Stage 4 or 5 CKD. While rejection rates were higher with belatacept than CsA, the rates of rejection that led to severe renal dysfunction or graft loss were low and were similar in the belatacept and CsA groups. Additional benefits of belatacept therapy not depicted in this figure include less NODAT, lower blood pressure, and a better lipid profile.

The risks associated with belatacept are CNS PTLT and infections, including PML. The impact of these safety concerns on the subject and the graft were captured in the primary survival endpoint, indicating that while clinically important, the absolute risk of these safety events did not outweigh the overall benefits of belatacept to the subject or the allograft.

Based upon these data, the benefit-risk profile of belatacept is favorable among EBV-positive recipients who receive the belatacept LI regimen.

Figure 19: Comprehensive Benefit-Risk Assessment: Absolute Difference between Belatacept LI and Cyclosporine (%)



The top portion presents key efficacy endpoints at 12 months. The bottom panel presents pooled data from the 3 core studies on safety findings of particular interest, including serious infections, malignancy and PTLD. Events of serious infections and malignancies are presented up to BLA database lock and events of PTLD are presented up to 14-Dec-2009.

11.4 Conclusions

Belatacept represents a new treatment option for renal transplant recipients addressing the current unmet need for an immunosuppressive that provides short-term outcomes comparable to the CNIs while avoiding their renal, CV, and metabolic toxicities that compromise transplant recipient health and outcomes. The risk of PTLD will be reduced via the proposed contraindication for the use of belatacept in EBV-seronegative recipients and those with unknown serostatus. A comprehensive REMS is proposed to minimize the risks of belatacept and monitor its safety in clinical practice. Based upon its

demonstrated efficacy and manageable safety profile, belatacept is recommended for approval for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.

12 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AR	acute rejection
BLA	Biologic Licensing Application
BMS	Bristol-Myers Squibb
Cavg	average concentration
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD	chronic kidney disease
Cmin	trough serum concentration
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CNS	central nervous system
CRF	case report form
CsA	cyclosporine A
CTS	Collaborative Transplant Study
CV	cardiovascular
DMC	Data Monitoring Committee
EBV	Epstein Barr virus
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HDL	high density lipoprotein
HLA	human leukocyte antigen
IND	Investigational New Drug Application
IV	intravenous
LI	less intensive (belatacept regimen)
MDRD	Modification of Diet in Renal Disease (study) (i.e., Levey formula)
MI	more intensive (belatacept regimen)
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MPAG	glucuronic acid of MPA

Abbreviation	Definition
NODAT	new onset diabetes mellitus after transplantation
PD	pharmacodynamics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PRA	panel reactive antibodies
PTLD	post-transplant lymphoproliferative disorder
RA	rheumatoid arthritis
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SC	subcutaneous
SCr	serum creatinine
SD	standard deviation
SUR	Safety Update Report
TB	tuberculosis
UNOS	United Network of Organ sharing
US	United States
USPI	United States Package Insert
USRDS	United States Renal Data System

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