Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Belatacept

Proprietary Product Name: Nulojix

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

July 2012

TGA Health Safety Regulation

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

I. Introduction to product submission

Submission details

Type of Submission	New chemical entity
Decision:	Approved
Date of Decision:	27 February 2012
Active ingredient(s):	Belatacept
Product Name(s):	Nulojix
Sponsor's Name	Bristol-Myers Squibb Australia Pty Ltd
	PO Box 39, Noble Park VIC 3174
Dose form(s):	Injection, powder for
Strength(s):	250 mg
Container(s):	Vials, Glass Type I Clear
Pack size(s):	1 or 2 vials per carton
Approved Therapeutic use:	Nulojix (belatacept) is indicated for prophylaxis of organ rejection in adults receiving a renal transplant. Nulojix is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.
Route(s) of administration:	Intravenous (IV) infusion
Dosage:	The recommended dose is 10 mg/kg on day of transplantation, prior to implantation (Day 1), Day 5, Day 14 and Day 28 and end of Week 8 and Week 12 after transplantation. The dosing for maintenance phase is 5 mg/kg every 4 weeks starting at end of Week 16 after transplantation.]
ARTG Number (s)	AUST R 179687

Product background

This AusPAR describes the application by Bristol-Myers Squibb Australia Pty Ltd to register the new biological entity, belatacept (Nulojx), as a prophylaxis of graft rejection and preservation of renal function in adults receiving a renal transplant. It represents a new class of therapeutic agents indicated for transplantation immunosuppression and is proposed to be used in conjunction with corticosteroids and a mycophenolic acid (MPA), with an interleukin 2 (IL-2) receptor antagonist in the induction therapy.

The proposed induction regimen is 10 mg/kg intravenously (IV) on Days 0, 5, 14, 28 and at the end of Weeks 8 and12 post transplantation. The maintenance regimen is intended as a 5 mg/kg IV infusion every 4 weeks starting from Week 16.

The sponsor has proposed the following indication:

Nulojix, in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for prophylaxis of graft rejection and preservation of renal function in adults receiving a renal transplant. It is recommended to add an interleukin (IL)-2 receptor antagonist for induction therapy to this belatacept-based regimen.

This indication is the same as that sought in Europe but it is noted that this indication is slightly differently worded, removing claim relating to renal function, to that proposed in the US PI.

"Nulojix (belatacept) is indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant. Nulojix is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids."

The product is intended only for use in adults and no paediatric data was included.

Belatacept differs from existing immunosuppressants in the restricted distribution of its molecular target and the specificity of its effect. Belatacept is a recombinant soluble fusion protein consisting of a modified extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) fused to a fragment (hinge-CH2-CH3 domains) of the Fc domain of a human immunoglobulin G1 antibody. As a result of these modifications, belatacept binds CD80 and CD86 more avidly than the parent CTLA4-Ig molecule.

The first product in this class of agents was abatacept (Orencia®), which was approved by TGA in September 2007 for use in adults for treatment of rheumatoid arthritis (RA) in adults and more recently (March 2010) for use in children with RA. Belatacept is a second generation higher avidity mutant of abatacept (Orencia) differing from the parent molecule by two amino acids within the region that binds CD80 and CD86.

Regulatory status

Nulojix 250 mg powder for Injection has been approved in the USA (15 June 2011) and the European Union (EU) (17 June 2011).

The following table describes the approved indications in these jurisdictions:

Table 1. Approved Indications for Nulojix in the USA and the EU.

Country	Approved Indications
European Union	NULOJIX, in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for prophylaxis of graft rejection in adults receiving a renal transplant (see section 5.1 for data on renal function). It is recommended to add an interleukin (IL)-2 receptor antagonist for induction therapy to this belatacept-based regimen.
United States	NULOJIX® (belatacept) is indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant. NULOJIX is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.

At the time this AusPAR was published, Nulojix had also been approved in Switzerland, Brazil, Colombia, Argentina, Russia and India.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

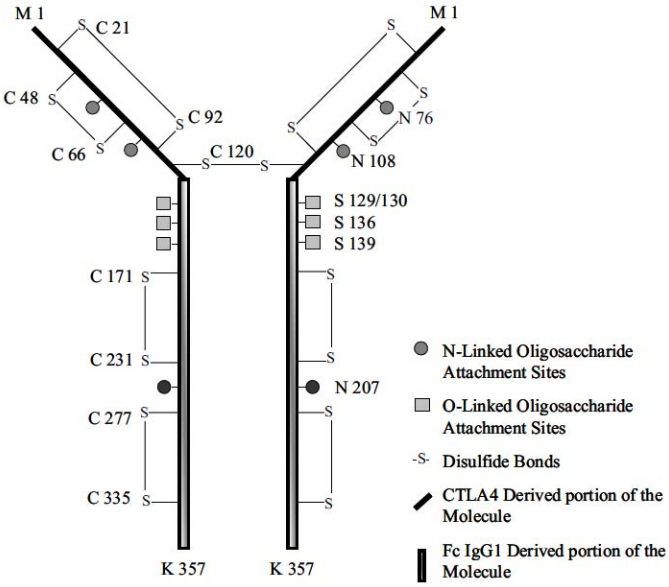
II. Quality findings

Drug substance (active ingredient)

Structure

Nulojix (belatacept) has the same overall base structure of the currently registered product Orencia (abatacept). Belatacept consists of two polypeptide chains with 357 amino acids and exists as covalent homodimer (referred to as belatacept "monomer") linked through an inter-chain disulfide bond. Belatacept represents a class of potential therapeutic agents that target the blockade of CD28-B7 (CD80, CD86), signalling key co-stimulatory signals required for T-cell activation.

Figure 1. Belatacept structure



Manufacture

Belatacept drug substance is manufactured in a recombinant Chinese Hamster Ovary (CHO) cell line using a typical biotechnology based fermentation and chromatography process. Cell banking processes are satisfactory.

The drug substance manufacturing steps are considered to be well controlled through a combination of action and alert limits for process parameters and release testing specifications

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and chemical properties

Belatacept drug substance is a clear to opalescent, colorless to pale yellow solution which contains 22.5 mg/mL to 27.5 mg/mL belatacept, 25 mM sodium phosphate and 10 mM sodium chloride, at pH 7.5. Belatacept drug substance is stored at either 2-8°C or -45 to -35°C in 2-L or

10-L polycarbonate bottles. It may undergo 4 rounds of freeze-thawing which has been supported with stability data.

The following product related variants were observed for belatacept: alanine N-terminus; lysine removal from the C-terminus; asparagine deamidation; methionine oxidation; N-linked glycosylation, O-linked glycosylation, and glycation, High molecular weight and low molecular weight species. These product related impurities were well characterised and are controlled during the purification process with appropriate specifications in place for critical quality attributes.

Four process related impurities are removed from the process stream during the downstream processing steps of the belatacept manufacturing process. Clearance studies have been performed to demonstrate clearance rates of these impurities in scaled down chromatography steps.

Bioburden and endotoxin levels are controlled and monitored throughout the drug substance manufacturing process.

Specifications

Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time and stressed conditions to characterise the stability/degradation profile of the substance and to establish a shelf life.

Drug product

Belatacept powder for concentrate for solution for infusion is a single use, sterile, non pyrogenic lyophilized product. It is also referred to as "Belatacept for Injection, 250 mg/Vial" or "Belatacept for injection." The drug product is packaged in 20-cc Type I flint glass tubing vials. Each vial is packaged with a silicone-free syringe.

Belatacept for Injection, 250 mg/Vial, is a lyophilized product for intravenous (IV) administration. Prior to use, the lyophile is constituted with either sterile water for injection, 0.9% sodium chloride injection or 5% dextrose injection to a belatacept concentration of 25 mg/mL. Prior to IV administration, the constituted solution is further diluted with 0.9% sodium chloride injection or 5% dextrose injection to belatacept concentrations ranging from 2 mg/mL to 10 mg/mL.

Formulation(s)

Each vials contains belatacept 250 mg, sucrose 500 mg, sodium phosphate monobasic 34.5 mg, sodium chloride 5.8 mg, hydrochloric acid and sodium hydroxide for pH adjustment.

No human or animal origin excipients are used in the formulation of Belatacept for Injection, 250 mg/Vial. No novel excipients are used in the formulation of Belatacept for Injection, 250 mg/Vial.

During early formulation development, the constituted belatacept solution was found to be incompatible with the siliconized plastic disposable syringes that are commonly used for the preparation and administration of parenteral products. The incompatibility was observed as translucent particles which began to appear in the drug solution after contact with the syringes.

This particle formation is due to an interaction between the protein and the silicone oil which is used on the inside of the syringe as a lubricant between the barrel and plunger.

Silicone free syringes will be provided with the drug product vial for marketing.

Specifications

Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data indicate the product is not photostable. Protection from light is provided by the outer packaging.

The proposed shelf life is 30 months when stored at 2 to 8 °C.

In-use stability data have also been submitted. The proposed shelf life and storage conditions for the reconstituted product are 24 hours when stored at 2 to 8 °C.

Stability data has been supplied to support continued quality of product which has undergone temperature deviations of room temp for 2 days and -20°C for 10 days.

Warnings are included on the labels stating "Only Use The Silicone-Free Syringe Included In The Package For Reconstitution."

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

Recommended conditions of registration for clinical delegate

As this product is a biological prescription medicine it is recommended that the following be included as a condition of registration:

Batch release testing

It is a condition of registration that batches of Nulojix belatacept (rch) 250mg powder for IV infusion vial imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

The sponsor should supply:

1. Certificates of Analysis of the active ingredient (drug substance) and final product.
2. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
3. Evidence of the maintenance of registered storage conditions during transport to Australia.
4. Five vials of each batch for testing by the Therapeutic Goods Administration OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. The conditions remain in place until the sponsor is notified in writing of any variation.

III. Nonclinical findings

Introduction

The nonclinical data consisted of a number of studies conducted with belatacept, as well as toxicity studies with abatacept. Given the higher pharmacological activity of abatacept in rodent species, this is considered appropriate. All pivotal studies were adequately conducted under Good Laboratory Conditions (GLP) conditions.

Pharmacology

Primary pharmacology

Rationale and mechanism of action

There are at least four discrete pathways that can lead to graft loss following solid organ transplantation. Most rejection episodes that occur within the first year after transplantation are termed "acute allograft rejection" and are characterised by cellular infiltrates in the graft. These rejection episodes are mediated by both CD4+ (T helper cells) and CD8+ (cytotoxic) T cells. Belatacept and its predecessor abatacept were designed to target T cell activation through modulation of the co-stimulation pathway. An effective T cell response requires antigen-specific and non-specific signals from the antigen-presenting cells (APCs). The antigen-specific signal involves allogeneic donor antigen presented in the context of MHC on APCs, to the T cell receptor, while the non-specific signal involves the interaction of CD80/CD86 on APCs with CD28 on T cells. This co-stimulation results in the production of T cell growth factor and IL-2, stimulating proliferation and differentiation of T cells as well as lowering the threshold for T cell activation. CD8+ T cells are less dependent on CD28 co-stimulation than CD4+ cells. CD28 plays a dominant co-stimulatory role in the full activation of naïve T cells but memory T cells are less dependent on CD28 co-stimulation[1]. Belatacept inhibits the physical interaction between CD80/CD86 co-stimulatory molecules and CD28, reducing T cell activation.

Effects on T cell responses

Belatacept saturated both CD80 and CD86 receptors on cultured human dendritic cells (50% inhibitory concentration (IC_{50}) 0.010 and 0.048 μg/mL; >400 times the clinical lowest level of a drug in the plasma (Ctrough)), and inhibited CD80 and CD86-mediated T cell proliferation in a co-stimulation assay (IC_{50} 0.001 and 0.0025 μg/mL, respectively). Addition of belatacept reduced CD4+ T cell proliferation and cytokine (IL-2, IL-4 and IFN-γ) release in primary and secondary allogeneic mixed lymphocyte reactions. The primary alloresponses were inhibited at belatacept concentrations required for CD86 receptor saturation but not at the lower concentrations capable of saturating CD80. Studies in mice and nonhuman primates indicate

[1] Snanoudj, R., C. Frangie, B. Deroure, H. Francois, C. Creput, S. Beaudreuil, A. Dürrbach and B. Charpentier. (2007) The blockade of T-cell co-stimulation as a therapeutic stratagem for immunosuppression: Focus on belatacept. *Biologics: Targets and Therapy* **1:** 203-213.

that inhibition of both CD80 and CD86 is required to prevent rejection of allogeneic transplants[2,3,4].

Belatacept had 5 times and approximately10 times higher affinity for CD80- and CD86-mediated T cell proliferation compared to abatacept and was more potent than abatacept at inhibiting both primary and secondary T cell proliferative responses. Furthermore, belatacept inhibited both CD4+ and CD8+ T cell proliferation, while abatacept inhibited the proliferation of CD4+ T cells only[5]. The increase in avidity for CD80 and CD86 observed with belatacept was primarily due to a decrease in off rates. The trough concentrations of belatacept observed clinically in the first month after transplantation (C_{min} >20 μg/mL) would be predicted to fully saturate CD86 and CD80 and inhibit T cell responses.

Abatacept bound similarly to the human and murine CD80 variants, had equivalent inhibitory activity in human and murine T cell co-stimulation assays and was assumed to be equipotent in animal species and humans. *In vitro*, belatacept had lower inhibitory activity than abatacept (IC_{50} ~70 times lower) in a murine T cell co-stimulation assay. Belatacept suppressed T cell dependent antibody responses (TDARs) in mice, rats, rabbits and monkeys. On a mg/kg basis, belatacept was less potent than abatacept in mice (~10 times), rats (2.9–5.3 times) and rabbits (4.6–6.9 times) while it was 2–3 times more potent than abatacept in Cynomolgus monkeys. However, at equivalent doses, exposure to belatacept was generally lower than abatacept in all tested species. To elicit a similar inhibition of TDAR to that of abatcept, based on C_{trough} levels, approximately 6% higher serum levels of belatacept are required in rats, similar serum levels of belatacept are required in rabbits and approximately 17% less serum levels of belatacept are required in monkeys. As similar C_{trough} levels were capable of inhibiting T cell responses in both humans and monkeys, the latter species is considered appropriate for toxicity studies. Due to the lower pharmacological activity in rodents, toxicity studies with abatacept were also submitted to support registration of belatacept. Given the essentially similar pharmacological profile of abatacept and belatacept, this is considered acceptable.

Effect on allograft survival in non-human primate models

The efficacy of belatacept, alone or in combination with mycophenolate mofetil (MMF) and the steroid, solumedrol, or in combination with the IL-2 receptor antagonist basiliximab, was examined in a Rhesus monkey kidney transplant model. The dosing regimen of belatacept was designed to achieve C_{trough} levels of belatacept similar to that expected clinically (20 μg/mL for the first month and 7 μg/mL for the following two months). Belatacept treatment alone prolonged animal survival (45 days compared to 5 days in control groups) but could not maintain good renal function and animals rejected the graft while still receiving treatment.

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[2] Kirk, A.D., D.K. Tadaki, A. Celniker, D.S. Batty, J.D. Berning, J.O. Colonna, F. Cruzata, E.A. Elster, G.S. Gray, R.L. Kampen, N.B. Patterson, P. Szklut, J. Swanson, H. Xu and D.M. Harlan (2001) Induction therapy with monoclonal antibodies specific for CD80 and CD86 delays the onset of acute renal allograft rejection in non-human primates. *Transplantation* **72:** 377-384.

[3] Lenschow, D.J., Y. Zeng, K.S. Hathcock, L.A. Zuckerman, G. Freeman, J.R. Thistlethwaite, G.S. Gray, R.J. Hodes and J.A. Bluestone. (1995) Inhibition of transplant rejection following treatment with anti-B7-2 and anti-B7-1 antibodies. *Transplantation* **60:** 1171-1178.

[4] Pearson, T.C., D.Z. Alexander, M. Corbascio, R. Hendrix, S.C. Ritchie, P.S. Linsley, D. Faherty and C.P. Larsen. (1997) Analysis of the B7 costimulatory pathway in allograft rejection. *Transplantation* **72:** 377-384.

[5] Larsen, C.P., T.C. Pearson, A.B. Adams, P. Tso, N. Shirasugi, E. Strobert, D. Anderson, S. Cowan, K. Price, J. Naemura, J. Emswiler, J. Greene, L.A. Turk, J. Bajorath, R. Townsend, D. Hagerty, P.S. Linsley and R.J. Peach. (2005) Rational development of LEA29Y (belatacept), a high affinity variant of CTLA4-Ig with potent immunosuppressive properties. *Am. J. Transplant.* **56:** 443-453.

Greater median survival was seen in the belatacept/MMF/solumedrol compared to an MMF/solumedrol group (>133 days compared to 30 days), though some animals rejected the allograft while still receiving the drug treatment. Significant lymphocytic infiltration was seen in the kidneys, despite good allograft function. Five of 6 animals treated with belatacept and basiliximab had stable renal function and survived for >100 days. After the cessation of treatment, all recipients rejected their allografts. When belatacept was combined with basiliximab/MMF/solumedrol, the duration of survival of allograft recipients was highly variable (28 to 625 days). It was not clear from the nonhuman primate data that the combination of all 4 compounds had greater efficacy than a belatacept/basiliximab or a belatacept/MMF/solumedrol combination. However, given the small group sizes (3–8 animals per group), no meaningful comparison can be made.

The efficacy of a belatacept/sirolimus/basiliximab combination in preventing islet allograft rejection was also assessed in Rhesus monkeys. The dosing regimen was designed to maintain C_{trough} levels of ≥20 μg/mL belatacept. The inclusion of belatacept prolonged islet allograft survival (56–200 days compared to 7 days in the sirolimus/basiliximab group). Four of the 5 belatacept treated animals had rejection free survival for the duration of the treatment period. These animals also failed to generate an anti-donor T cell response and an anti-donor antibody response while receiving belatacept treatment. Approximately 1–2 months after discontinuation of belatacept treatment, all of the surviving recipients underwent an allograft rejection episode. Overall, the data for belatacept in nonhuman primate graft models suggest the clinical use of belatacept with approved immunosuppressive agents to prevent graft rejection, has some merit.

Secondary pharmacodynamics

The Fc region of belatacept is identical to that of abatacept and contains a mutated hinge region to reduce complement fixation and minimise antibody-dependent cellular cytotoxicity (ADCC). Abatacept had no detectable binding at the human Fc receptors CD16 (FcγRIIIa/b) or CD32 (FcγRIIa, but had some affinity at CD64 (FcγRIa). However, no detectable complement-dependent cytotoxicity was seen with either abatacept or belatacept. No detectable ADCC of CD80/CD86 expressing cells was seen with belatacept. Therefore, CDC and ADCC are not expected to occur clinically. The binding kinetics of belatacept and abatacept at the neonatal Fc receptor were similar (K_D approximately 320–370 nM; approximately 29 μg/mL based on a molecular weight of 90 kDa) and placental transfer of belatacept is likely. Belatacept had no effect on the normal proliferation of a B cell line nor did it induce proliferation of primary tonsillar B cells, suggesting that belatacept does not initiate reverse signalling into B cells.

Pharmacokinetics

The pharmacokinetics of belatacept were typical for this type of compound, characterised by limited extravascular distribution and a slow elimination (half life ($t_{½}$) of 32–124 h in animals and 235 h in human subjects). The clearance of belatacept was faster and exposures (area under the plasma concentration time curve (AUC)) lower for belatacept batches with low sialic acid content. Faster clearance rates were also associated with anti-belatacept antibody formation. Extensive metabolism studies were not conducted but belatacept is expected to undergo degradation by various proteases and peptidases. Deamidation of Asn294 and Asn299 was detected in the serum of Cynomolgus monkeys. It was stated that deamidation at these sites had no impact on either *in vitro* target binding or the cell-based bioassay activity of belatacept.

Toxicology

General toxicity

General toxicity studies with belatacept consisted of a single dose toxicity study and two repeat dose toxicity studies of 1 month and 6 months duration in Cynomolgus monkeys. The choice of species is appropriate given that belatacept has similar pharmacological activity in Cynomolgus monkeys and human subjects. The use of one species is acceptable as the toxicity of the similar drug substance, abatacept, has been previously assessed in mice, rats and Cynomolgus monkeys and the findings in those studies can contribute to the safety assessment of CD28 blockade. The studies with belatacept were adequately conducted under GLP conditions, were of adequate duration for a biopharmaceutical and belatacept was administered *via* the intended clinical route (IV). The numbers of animals used were appropriate, with both sexes assessed. The dosing frequency in the pivotal study was similar to that proposed in the clinical induction regimen (weekly). A recovery period was included in both repeat dose toxicity studies with blood concentrations of belatacept and anti-drug antibodies monitored.

Toxicity studies were conducted with a belatacept drug substance from an early manufacturing process (termed Process A). Belatacept manufactured using Process C was used in Phase III clinical studies. While several comparability studies were submitted with the nonclinical part of the current submission, none directly compared the pharmacology and pharmacokinetics of belatacept manufactured by Process A and Process C. As the belatacept drug substance manufactured by different processes was generally comparable for pharmacology and pharmacokinetics, major differences in potency are not expected for belatacept batches used in the general toxicity studies and those used in the clinical studies.

Systemic exposures in the repeat dose toxicity studies were generally in excess of the maximum expected in patients, although the maximum exposures achieved were not high (Table 2). However, given that the exposure margins would be a further 3.5 fold higher compared with the anticipated long term clinical exposure from a 5 mg/kg/4 weeks dosing regimen, this may be considered acceptable. The only notable treatment-related findings were those attributed to the pharmacology of the drug (such as decreased serum IgG levels and decreased spleen and lymph node germinal centre activity). No anti-drug antibodies were detected during the treatment period but following a 3 month treatment-free period, anti-belatacept antibodies were detected in all treatment groups in the 6 month study. Overall, the toxicity profile of belatacept was similar to that previously reported for abatacept.

Table 2. Relative exposure of belatacept in repeat-dose toxicity studies

Study	Species & strain	Treatment duration [frequency]	Dose (mg/kg)	$AUC_{0-\tau}$ (mg·h/mL)	$AUC_{0-28\ days}$ (mg·h/mL)	ER_{AUC}
98699[a]	**Monkey** (Cynomolgus)	1 month [every other day]	10	8.3	116	2.4
			22	16	224	5
			50	36.1	505	11
99655[b]	**Monkey** (Cynomolgus)	6 months [weekly]	10	12	49	1
			22	29	117	2.4

Study	Species & strain	Treatment duration [frequency]	Dose (mg/kg)	$AUC_{0-\tau}$ (mg·h/mL)	$AUC_{0-28\ days}$ (mg·h/mL)	ER_{AUC}
			50	61	244	5
Clinical study DCN 930033 188	**Human** (renal transplant patients)	First month	10	48	48	–

[a]$AUC_{0-\tau}$ = AUC_{0-48h}; [b]$AUC_{0-\tau}$ = AUC_{0-168h} (average of sexes across sampling days)

In Rhesus monkeys that had received a kidney transplant, drug-related microscopic changes were restricted to the lymphoid tissues (minimal to mild lymphoid depletion). Aside from findings expected for the individual components, there were no novel or exacerbated toxicities in animals that received belatacept in combination with MMF and the corticosteroid solumedrol or with the IL-2 receptor antagonist basiliximab. While no toxicity studies were conducted with the combination of all four agents, aside from combined pharmacological activity and toxicities associated with each of the agents, no additional toxicities are predicted from their combined use.

Clinical trial data indicated an increase in the incidence of central nervous system (CNS) restricted posttransplant proliferative disorder (PTLD) or progressive multifocal leukoencephalopathy (PML) in renal transplant patients that received belatacept. In healthy monkeys, belatacept, cyclosporine and the metabolites of MMF (MPA and glucuronidated MPA [MPAG]) did not cross the blood brain barrier when administered as monotherapy or in various combinations. Belatacept also had no effect on the presence of immune cells or CD80/CD86 expression in the brain. An *in vitro* study indicated belatacept had no effect on the trans-endothelial migration of T cells across a human brain endothelial cell monolayer. Therefore, there is no evidence to suggest a direct pharmacological effect on the CNS. PML and other lymphoproliferative disorders have been reported previously in patients receiving immunosuppressive drugs. This has sometimes been associated with reactivation of latent viral infections (in particular JC[6]). There was no evidence of these lymphoproliferative disorders in Cynomolgus monkeys treated for 6 months with doses resulting in 5 times the clinical AUC. Viral screening was not conducted in this study, though it was stated that latent viruses, similar to the human JC virus, can be found in monkey colonies[7]. The duration of the study may not have been sufficient for these viral effects to manifest, thereby limiting the predictive value of the study for lymphoproliferative disorders. However, lymphomas were seen in a mouse carcinogenicity study with abatacept (see *Genotoxicity and Carcinogenicity* below).

[6] The JC virus was first isolated from a brain in a patient with Hodgkin's disease. The patient was also suffering from Progressive multifocal leaukoencephalopathy(PML). The virus is named after the patient's initials. The JC virus is a double-stranded DNA viru and is strictly a human virus whose viral chromosome structure is very similar to its host chromatin. Inside its human host it can establish three kinds of infections: latent, persistent, and active infections. The infections are established depending on the strength of the host's immune system and the tissue type that is infected. Latent infections occur in the kidney tissue. Persistent infections occur in renal proximal tubule cells and active infections occur in the oligodendrocyte glial cells in the central nervous system. These cells specifically support replication of the virus. Active infections destroy oligodendrocytes and lead to a disease known as Progressive multifocal leaukoencephalopathy (PML).The JC virus infection is extremely widespread.

[7] Wachtman, L.M. and K.G. Mansfield. (2008) Opportunistic infections in immunologically compromised nonhuman primates. *ILAR J.* **49:** 191-208.

Genotoxicity and carcinogenicity

No genotoxicity studies have been conducted with belatacept, which is considered acceptable for a biotechnology-derived pharmaceutical[8]. In a previous submission, the genotoxicity of abatacept was assessed in bacterial and mammalian mutagenesis assays and in an *in vitro* clastogenicity assay. Negative results were returned in all assays.

No carcinogenicity studies have been conducted with belatacept. The sponsor relied on the previously-submitted mouse carcinogenicity study with abatacept. Mice were treated with up to 200 mg/kg/week subcutaneously (SC) abatacept for 84–88 weeks. Maximum abatacept exposures AUC from time 0 to Day 28 ($AUC_{0-28\ days}$) achieved were approximately 150 mg•h/mL (below the clinical belatacept exposure, when accounting for the higher pharmacological activity) and dosing was limited by marked mortality. Deaths were associated with malignant lymphomas, for which incidences were increased relative to control groups at all doses in both sexes. This increased incidence is possibly associated with an activation of murine leukaemia virus (MLV), resulting from immunosuppression. Lymphomas in the mouse study were systemic, including the CNS, and not restricted to the CNS as observed with the PTLD in the clinical program, suggesting some difference in their aetiology, though both are likely associated with activation of latent virus infections.

An increased incidence of female mammary tumours was also seen in mice. These included an increase in adenocarcinomas but not adenomas. There was no apparent treatment-related increase in the incidence of mammary hyperplasia. It was suggested that the drug-related increase in mammary tumours was mediated *via* activation of mouse mammary-tumour virus (MMTV), which was detected by immunohistochemical staining in selected adenocarcinomas from control and drug treated mice. While investigative studies could not confirm a role of MMTV in the higher incidence of mammary tumours, the explanation is plausible. Both MLV and MMTV are retroviruses that are integrated into the genome, with infection held in check in healthy animals by an antiviral immune response. Immunosuppression by abatacept likely reduced this antiviral immune response, allowing infection to take hold. Although these tumours may not be directly relevant to clinical use, they do indicate a risk of virally-induced malignancies during clinical use. This was also confirmed by the incidences of PTLD in clinical trials with belatacept.

Reproductive toxicity

A standard set of reproductive toxicity studies was conducted with belatacept and examined fertility (in rats), embryofetal toxicity (in rats and rabbits) and pre/postnatal development (in rats). Adequate animal numbers were used and treatment periods were appropriate. The drug substance used in all the reproductive toxicity studies was manufactured using Process C, the same as that used in clinical studies. Toxicokinetic data were collected in all studies and exposures achieved were several multiples of the maximum anticipated clinical AUC (Table 3). Taking into account the approximately 5 fold lower activity of belatacept in these species compared to humans, maximum exposures would have achieved only approximately 3–6 fold higher pharmacological activity than that expected clinically at the highest anticipated dose.

Table 3. Relative exposure in reproductive toxicity studies

Study	Species &	Dose	$AUC_{0-24\ h}$	$AUC_{0-28\ days}$	Exposure

[8] ICH Topic 9. Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008). http://www.tga.gov.au/pdf/euguide/swp64610708enfin.pdf

Study	Species &	Dose	$AUC_{0–24\,h}$	$AUC_{0–28\ days}$	Exposure
DN06032	**Rat** (SD) *[male data]*	20	9.21	258	5
		65	20.3	568	12
		200	52.6	1473	31
DN06032	**Rat** (SD) *[nonpregnant females]*	20	7.27	204	4
		65	15.1	423	9
		200	42.3	1184	25
DN06008	**Rat** (SD) *[pregnant females]*	20	5.38	151	3
		65	12.4	347	7
		200	28.2	790	16
DN06002	**Rat** (SD *[lactating females]*	20	4.63	130	3
		65	11.9	333	7
		200	32.6	913	19
DN06056	**Rabbit** (NZW) *[pregnant females]*	10	4.33	121	3
		30	10.5	294	6
		100	31.8	890	19
Clinical study DCN 930033188	**Human**	[10 mg, first month regimen]	–	48	–

Fertility and early embryonic development were unaffected in rats when either males or females were treated with ≤200 mg/kg/day IV belatacept. Belatacept binds to the neonatal Fc receptor and crossed the placenta with fetal serum levels 8–9% and 0.7–1.3% maternal serum levels in rats and rabbits, respectively. No adverse effects on embryofetal development were observed at ≤200 mg/kg/day IV belatacept in rats and ≤100 mg/kg/day IV belatacept in rabbits.

In a pre/postnatal study in rats, with the exception of one female (treated with 200 mg/kg/day IV belatacept), no adverse maternal effects were seen during gestation but clinical signs of infection began in the treatment groups in the postpartum/lactation period. At necropsy, gross lesions indicative of microbial infections were seen in the lymph nodes (enlarged) and intestinal tract (masses, adhesions and distention), with microscopic correlates of peritonitis, mucosal necrosis and necrotising inflammation with filamentous bacteria in necrotic foci. These findings were attributed to opportunistic infection, secondary to pharmacologically-mediated immunosuppression. The causative agent(s) of the opportunistic infections was not definitively determined. Postpartum infections were not seen in female rats treated with ≤200 mg/kg/day

IV abatacept in a pre/postnatal study. Pharmacology studies indicated that, on a mg/kg basis, belatacept was 3–5 times less potent than abatacept in inhibiting T cell dependent antibody responses in rats. Hence, the disparity between the two studies is surprising but might be related to differences in the ability of the two compounds to inhibit cell mediated immunity. With material from healthy human donors, belatacept inhibited both CD4+ and CD8+ T cell proliferation, while abatacept inhibited CD4+ T cell proliferation only[5]. It is unclear if this is also the case in rats but it could potentially explain the greater immunosuppression observed in rats with belatacept.

Some excretion of belatacept into milk was seen in lactating rats, with levels 9–13% those found in maternal serum, and belatacept was detected in pups from all treated groups on potsnatal day (PND21), suggesting that pups were immunosuppressed in the first 2 to 3 weeks post partum. During the preweaning period there was an increased incidence of pup death and moribundity in some litters at all doses. Pups from treated dams also had a tendency towards lower weights and signs of dehydration, coldness to touch, reduced motor activity, emaciation and ungroomed coat. These pup deaths and clinical signs were considered to be secondary to maternotoxicity and compromised maternal care. Postweaning there were no treatment-related effects on the neurobehavioural or sexual development of F_1 generation[9] rats. Gross external findings of F_2 generation[10] fetuses were unremarkable. Anti-belatacept antibodies were seen in some pups from PND62, when the serum levels of belatacept had lowered. Mean serum IgG levels were decreased at all doses on PNDs 62–64, with an uncertain relationship with treatment. There were no drug-related effects on serum Ig subtype M (IgM) levels or antibody responses on PNDs 56–112. At necropsy (PND112), there were no histopathological findings in the lymphoid tissues or male reproductive organs. The no observable adverse effect level (NOAEL) for pup development was the highest dose (200 mg/kg/day IV belatacept) but, due to early postnatal mortality, the NOAEL for F_1 pups was not established. In a pre/postnatal study in rats with abatacept, one pup from the high dose (HD) group (200 mg/kg IV abatacept) had chronic thyroid inflammation and signs of autoimmunity. This was not seen in the belatacept study and might be attributed to the lower activity of belatacept in this species.

The data suggests an increased risk for infections and a negative impact on the developing immune system and therefore belatacept should not be used in the later stages of pregnancy. As withdrawal of belatacept leads to the induction of anti-belatacept antibodies there is a theoretical risk of antibodies that cross-react with endogenous CTLA-4 leading to autoimmune reactions (see *Immunotoxicity*). Therefore withdrawal of belatacept due to pregnancy may lead to autoimmune reactions, the result of which may have adverse embryofetal effects.

Pregnancy classification

The sponsor has proposed Pregnancy Category C, a category for drugs which, owing to their pharmacological activity may cause harmful effects on the human fetus. This is considered appropriate as placental transfer of belatacept was shown in rats and minimally in rabbits and this intrauterine exposure could potentially affect the development of the immune system in the fetus. This is also the Pregnancy category for abatacept.

Local tolerance

[9] The parental generation is the first set of parents crossed. The F1 (first filial) generation consists of all the offspring from the parents - their children.

[10] The F2 (second filial) generation consists of the offspring from allowing the F1 individuals to interbreed - the grandchildren of the parental generation.

After IV injection of the proposed clinical formulation (10 mg/0.5 mL) to rabbits, there were no findings at the injection site that could be attributed to the test article. Local tolerance studies were performed in the rabbit using intra-arterial and paravenous routes, in the event of accidental exposure *via* these routes. Injection site reactions were similar between treated and control sites.

Immunotoxicity

Belatacept was developed as an immunomodulator, and effects on the immune system were assessed in pharmacology and toxicology studies. Inhibition of CD4+ T cell proliferation (human cell lines) was seen in *in vitro* studies with belatacept. *In vivo*, belatacept inhibited T cell dependent antibody responses in mice, rats, rabbits and monkeys, with varying potency, with a consequent reduction in serum IgG levels (see *Primary pharmacology*). Microscopic changes were evident in the spleen and lymph nodes, consistent with the anticipated pharmacological activity. All of these findings were reversible. In Cynomolgus monkeys, there was no effect on the absolute or relative number of peripheral blood or splenic lymphocytes expressing CD2 (pan T cells), CD4 (T helper cells), CD8 (cytotoxic T cells) or CD20 (B cells), no changes in serum levels of IgM, Ig subtype A (IgA), Tumour Necrosis Factor alpha (TNFα) or interleukin 6 (IL-6), and no drug-related increase in plasma histamine or C3a levels.

Anti-belatacept antibodies were only detected in animals during the treatment free period, when serum belatacept levels had dropped below immunosuppressive levels. It is unclear if these antibodies were neutralising. There were no obvious toxicities associated with anti-belatacept antibody production but there is a theoretical risk that antibodies against belatacept may cross-react with endogenous CTLA-4, leading to autoimmune reactions. Following up to 3 months exposure to abatacept in rats, lymphocytic inflammation of the thyroid and pancreatic islets was evident. These findings are indicative of an autoimmune response, but do not appear to be associated with anti-drug antibody production. While antibody production in animals is not always predictive of the human situation, the sponsor's Clinical Overview states that anti-belatacept antibodies were detected in up to 7% of the patients in the clinical studies, with antibody production occurring either during or at the cessation of treatment. Therefore, a risk of autoimmune reactions is possible in clinical use.

Impurities

The specifications for the belatacept drug product include two drug-related degradant fractions; a high molecular weight fraction (HMW; predominantly dimeric) (≤3%) and a low molecular weight fraction (LMW) (≤0.5%). The HMW fraction was present in batches used in the 1 month and 6 month repeat-dose toxicity studies at levels of 1.9% and 0.9%, respectively. The highest doses of the HMW fraction achieved in these studies were approximately 12 times (1 month study) and 2 times (6 month study) the clinical dose at the proposed limit in the first month (28 days), on a mg/kg basis[11]. Based on the high doses of the HMW fraction achieved in the repeat dose toxicity studies, the proposed limit of ≤3% is considered toxicologically qualified. The LMW product was not detectable in these batches (limit of detection not stated).

[11] The clinical dose in the first month of treatment is 4×10 mg/kg in 28 days (40 mg/kg in total). In the one month study, animals received a maximum of 15×50 mg/kg in 28 days (*ie* 750 mg/kg), while in the 6 month study animals received a maximum of 5×50 mg/kg in 28 days (*ie* 250 mg/kg).

Nonclinical summary

- The nonclinical data consisted of a number of studies conducted with belatacept, as well as toxicity studies with its predecessor, abatacept. All pivotal studies were adequately conducted under GLP conditions and no major deficiencies were identified.
- Belatacept is a recombinant soluble fusion protein consisting of the extracellular domain of CTLA-4 and a fragment of the Fc region of human IgG1. Belatacept is intended to inhibit the interaction of CD80/CD86 co-stimulatory molecules and CD28, reducing T cell activation. *In vitro*, belatacept inhibited both CD80 and CD86-mediated T cell proliferation and reduced cytokine release in co-stimulation assays. Belatacept suppressed T cell dependent antibody responses in mice, rats, rabbits and monkeys. At equivalent exposures, belatacept was less or equipotent to abatacept in rodents and rabbits but more potent in monkeys and humans. The trough concentrations of belatacept observed clinically in the first month after transplantation (C_{trough} >20 μg/mL) would be predicted to fully saturate CD80 and CD86, and inhibit T cell responses.
- In a non-human primate kidney transplant model, belatacept, in combination with mycophenolate mofetil (MMF) and the steroid solumedrol or in combination with the IL-2 receptor antagonist basiliximab prolonged survival and maintained good renal function for longer than treatment in the absence of belatacept. No anti-donor antibodies were detected during belatacept treatment. The study supports the proposed dosage regimen.
- No detectable complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity was seen with belatacept. Belatacept bound to the neonatal Fc receptor at clinically-relevant concentrations.
- The pharmacokinetics of belatacept were typical for an antibody, characterised by limited extravascular distribution and a slow elimination. No significant differences were seen between animals and humans.
- The toxicity of belatacept was assessed in Cynomolgus monkeys after a single dose and after repeated administration (up to 6 months duration). Treatment related findings were limited to those associated with the pharmacology of belatacept (that is, decreased serum IgG levels and decreased spleen and lymph node germinal centre activity). No novel or exacerbated toxicities were seen in Rhesus monkeys receiving belatacept in combination with MMF and solumedrol or with basiliximab. No toxicity studies were conducted with the combination of all four agents.
- No genotoxicity studies have been conducted with belatacept, which is considered acceptable. In a mouse carcinogenicity study with abatacept, a treatment related increase in the incidence of lymphomas and female mammary tumours was observed. These tumours were attributed to activation of latent viruses. Exposures achieved in the carcinogenicity study are estimated to be at or below the maximum clinical exposure of belatacept when accounting for pharmacological activity. The findings indicate a risk of virally-induced malignancies during clinical use.
- A standard set of reproductive toxicity studies was conducted with belatacept. Fertility and early embryonic development were unaffected in rats. Belatacept crossed the placenta in rats and rabbits but no adverse embryofetal development effects were seen in these species. In a pre/postnatal study in rats, infections were evident in dams in the postpartum/lactation period, secondary to immunosuppression. Pup deaths and clinical signs (dehydration, emaciation and reduced motor activity) were considered to be secondary to maternotoxicity. Excretion of belatacept into milk was seen in lactating rats with belatacept detected in pup circulation. Anti-belatacept antibodies were detected in

pups several weeks post-weaning. There were no apparent treatment related effects on the development of the F_1 generation.

- Local reactions following IV, intra-arterial or paravenous injection of the intended clinical formulation were unremarkable.
- Anti-belatacept antibodies were only detected when serum belatacept levels had dropped below immunosuppressive levels. There were no obvious toxicities associated with anti-belatacept antibody production but there is a theoretical risk that antibodies against belatacept may cross-react with endogenous CTLA-4 leading to autoimmune reactions.
- The proposed limit for a high molecular weight degradant in the drug product for Nulojix has been toxicologically-qualified.

Conclusions and recommendations

Belatacept suppressed T cell dependent antibody responses in animal species. The efficacy of belatacept, in combination with MMF and a corticosteroid, and in combination with an IL-2 receptor antagonist in a non-human primate kidney transplant model supports the proposed indication.

The most notable toxicities of clinical relevance are an increased risk of opportunistic infections and virally induced malignancies and a theoretical risk of autoimmune reactions, particularly if belatacept treatment is ceased.

Belatacept should not be used in pregnancy or when breastfeeding. Should belatacept treatment cease due to pregnancy, there is an unknown risk to the mother and fetus in the event of anti-belatacept antibody production.

If belatacept treatment is ceased, anti-belatacept antibody production may reduce the efficacy of the drug should administration re-occur.

There are no objections on nonclinical grounds to the registration of belatacept for the proposed indication.

Amendments were recommended to the draft Product Information document.

IV. Clinical findings

Introduction

Development program

The stated aim of the development program was:

> *"to address the unmet need of solid organ transplantation – to improve long-term outcomes, including both patient and graft survival".*

This aim was modified in later reports to:

> *"provide acceptable control of the alloimmune response while improving renal function and long-term patient and graft outcomes."*

Renal transplantation is the most effective treatment for end-stage renal disease (ESRD). It provides improved survival and quality of life (QoL). Maintenance of a functioning renal transplant requires life-long immunosuppressive therapy to prevent immune destruction of the graft. The current mainstays of immunosuppression are the calcineurin inhibitors (CNIs), cyclosporin (CsA) and tacrolimus. Current immunosuppressive therapy leads to 1 year patient survival rates of 91% for cadaveric and 95% for living-donor grafts and 1 year patient survival rates of 96% for recipients of cadaveric and 98% for living-donor grafts. Five year graft survival rates for cadaveric and living-donor renal transplants are 70% and 80%, respectively. Five year patient survival rates for recipients of cadaveric and living-donor renal transplants are 82% and 90%, respectively[12]. These high survival rates make it difficult to conduct comparative trials which aim at showing superiority and so non-inferiority trials have been acceptable in the development of new immunosuppressive agents.

A disadvantage of the current main drugs used in renal transplantation (calcineurin inhibitors) is that they are directly nephrotoxic and have also been associated with undesired cardiovascular and metabolic side effects that contribute to significant patient morbidity and mortality. The aim of the sponspr's research is stated to be to reduce exposure to CNIs either through CNI minimisation or replacement.

The sponsor states that they see the role of belatacept as being to provide a non-nephrotoxic therapy for use in renal transplant recipients. Belatacept can also be administered at the time of engraftment, rather than in a delayed fashion as is frequently the case with CNIs, it affords immunosuppression in a timely manner.

The pivotal studies were planned as 3 years duration with the primary efficacy outcomes being efficacy at 6 or 12 months. After 3 years subjects were enrolled into long term extension studies of variable stated duration (all still ongoing at time of submission). Reports were written at end of 1, 2 and 3 years and then, since the long term extension studies have not completed, various "pooled data" and post database lock updates were provided. The clinical summary for both safety and efficacy (dated January 2010 for database lock at July 2009) only includes data up to a 2 year duration and so does not provide a complete summary of the data submitted. It was agreed at the pre-submission planning meeting that the company would provide the 3 year study reports and an integrated summary covering the 3 year data but no integrated summary was provided, only tabulations of the up to 24 month treatment and post-database lock (24 month + up to 24 month report) without explanation. A brief clinical overview of the 3 year data was provided and presents data which is similar to the pooled data from the core studies. The

[12] United Network for Organ Sharing, UNOS

index is badly presented and inaccurate in a number of areas and so did not provide easy navigation for the evaluator.

The reporting of the trials at staged time periods has led to a very large clinical submission of over 400 volumes with multiple study reports (up to 6) with associated tabulations for each pivotal study. Also due to the unusual practice of including updates of the clinical databases after database lock the data in the subsequent reports and tabulations differs slightly from that in the 12 month data (primary efficacy outcomes). This has also led to a great deal of duplication in the reports and tabulations. This report presents the results taken from the 36 month analysis unless otherwise stated.

The product had not yet been approved in any country at the time of commencing this report. The product was submitted in the USA and EU (under centralised procedure with Sweden as rapporteur and Lithuania as co-rapporteur) in 2009 with the submissions including only 24 month data for the pivotal trials. Both agencies raised significant questions and required the submission of the 36 month follow up data for the pivotal trials. It is noted that the European Medicines Agency (EMA) issued a positive recommendation in April 2011 and the US FDA announced approval on 15 June 2011.

Guidelines

The main guideline applicable to this application is the TGA adopted EU guidance document: "Guideline on Clinical Investigation of Immunosuppressants for Solid Organ Transplantation"[13]. This guideline was adopted in July 2008. This is a general guideline relating to solid organ transplantation and is not specific to renal transplants. The guideline sets out the requirement for the primary efficacy endpoint for induction, initial and/or maintenance prophylaxis as:

- "patient death;
- Graft failure (defined by clear-cut and discrete criteria, such as permanent return to pre-transplantation treatment modality for a defined period of time eg return to dialysis for at least 4-6 weeks or more, renal re-transplantation, nephrectomy in kidney transplantation;
- Biopsy confirmed acute rejection (BCAR) (including pathologic scheme to be used for the specific type of organ transplant, severity of outcome, treatment, response to treatment, as appropriate);
- Graft (dys)-function (defined by best available clear-cut and discrete criteria) for at least kidneys, lungs and heats, such as measurement of creatinine/inulin clearance for kidney dysfunction, systolic/diastolic dysfunction for heart dysfunction, and FEV_1/FEV_{25-75}; PaO_2/FiO_2 for lung dysfunction.

The components of the composite endpoint should be reported individually and, preferably, the overall effect on the composite endpoint should not be driven by one of the components."

It should be noted that this guideline did not exist prior to the initiation of the belatacept Phase III clinical program. There is no guideline for solid organ transplantation from the FDA. The company did consult with the EMA and the FDA during the protocol development and changes to the protocols were recommended by both agencies.

[13]CHMP/EWP/263148/06 http://www.tga.gov.au/pdf/euguide/ewp26314806en.pdf

A TGA adopted EU guideline on non-inferiority studies is relevant to this application as both Phase III studies use non-inferiority design[14]. A key section of this guideline relates to the choice of non-inferiority margin:

> "The choice of delta must always be justified on both clinical and statistical grounds. It always needs to be tailored specifically to the particular clinical context and no rule can be provided that covers all clinical situations."

Definitions

The following are the definitions used in the clinical trials described in this report.

Adverse event (AE)

All AEs with an onset date from post-transplantation through 56 days after the date of the last dose of the study medication.

Acute rejection

A clinic-pathological event that requires clinical evidence and biopsy confirmation. A subject was determined to have an episode of acute rejection (AR) if 1 of more of the following conditions were met and a renal biopsy revealed histological evidence of rejection:

- An unexplained rise in SCr ≥ 25% from baseline.
- Occurrence of one or more of the following: an unexplained decreased urine output; fever and graft tenderness; a SCr that remained elevated within 14 days after transplantation and clinical suspicion of acute rejection.
- A reason other than those listed above and the subject was treated for this episode.

Biopsy-proven acute rejection (BPAR)

Includes all cases where a biopsy was read by the central pathologist as demonstrating acute rejection (based on the revised Banff 97 criteria) regardless of the reason why the biopsy was performed (such as suspected acute rejection or protocol specified biopsy).

Clinically-suspected rejection

Defined as an increase in serum creatinine (SCr) ≥ 0.5 mg/dL (44.2 mmol/L) compared to the baseline value in the absence of other factors known to adversely affect renal function.

Clinically suspected biopsy proven acute rejection (CSBPAR)

Is used throughout the studies and reports and is used interchangeably with the term "acute rejection".

Chronic allograft nephropathy (CAN)

Prevalence of CAN – imputation method

A subject was considered to have CAN if they met any of the following:

- CAN in a biopsy either prior to Month 12 (including baseline biopsy) or first post Month 12 biopsy.
- Graft loss during the first year post transplant.

[14] Guideline on the Choice of Non-inferiority Margin. EMEA/CPMP/EWP/2158/99. http://www.tga.gov.au/pdf/euguide/ewp215899en.pdf

- No biopsy available post Month 12 and CAN not observed in biopsies prior to Month 12 (including baseline biopsy); however, the measured GFR from Month 3 to Month 12. decreased at least 10 mL/min/1.73m^2. The measured GFR incorporated the missing data imputation mechanism stated in the measured GFR section.
- No biopsy available either prior to or post Month 12, and the measured GFR (incorporated missing data imputation) from Month 3 to Month 12 decreased at least 10 mL/min/1.73m^2.

Incidence of CAN – imputation method

Incidence of CAN was defined as new of worsened CAN at 12 months based on a comparison of the evidence of CAN on a 12 month biopsy to that on a baseline biopsy. A subject was considered to have CAN if they met any of the following conditions:

- if a subject had graft loss during the first year post-transplant
- new or worsened CAN was observed on a biopsy either prior to 12 months or on the first post 12 month biopsy
- No baseline biopsy was available or no post 12 month biopsy was available; however, the decrease in measured GFR Month 3 to Month 12 was at least 10 mL/min/1.73m^2

Composite endpoint of GFR

The endpoint of renal function was assessed by measurement of the clearance of a true glomerular filtration marker (non-radiolabeled iothalamate) using a validated procedure. A glomerular filtration rate (GFR) of 60 mL/min/1.73m^2, or change in GFR of at least 10 mL/min/1.73m^2 was used as the approximate equal of the threshold values of SCr of 1.5 mg/dL, or change in SCr of at least 0.3 mg/dL.

Delayed graft function

Subject was treated with dialysis within the first week (Day 1-8) post transplantation.

Dyslipidaemia

This was defined in accordance with the guidelines from the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF-K/DOQI). The incidence of dyslipidaemia was defined as the proportion of subjects who developed dyslipidaemia after randomisation and transplantation. Prevalence was defined as the proportion of subjects at any given time who met the above stated definition of dyslipidaemia.

Graft loss

Defined as either functional loss or physical loss (nephrectomy) of the graft. Functional loss was defined as a sustained level of SCr ≥ 6.0 mg/dL (530 mmol/L) as determined by the central laboratory for ≥ 4 weeks or ≥ 56* consecutive days or dialysis or impairment of renal function to such a degree that the subject undergoes retransplant. Graft loss was adjudicated by an independent Event Adjudication Committee (EAC) comprising 4 nephrologists/renal transplant surgeons.

* ≥ 56 days consecutive days of dialysis was interpreted to mean a subject with at least 1 session of dialysis per week for 8 weeks with an interruption of no more than 7 calendar days; the date of graft loss was the 56 day from commencement of the dialysis sessions.

Hypertension

- Study IM103008: defined using standard measures for subjects with chronic kidney disease: Systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 80 mmHg or

prescription of an antihypertensive medication. Hypertension was assessed only after the Week 4 visit.

- Study IM103027: defined as DBP ≥ 90 mm Hg and or SBP ≥ 140 mm Hg, or the use of any antihypertensive medication.

Major adverse cardiac event (MACE)

Defined as known cardiovascular death, myocardial infarction or stoke.

The modification of diet in renal disease (study) (MDRD) formula

A formula used to calculate renal function and is also known as the **Levey formula**.

Post-transplant diabetes mellitus (PTDM) also called now onset diabetes mellitus (NODM)

- Study IM103008: PTDM was defined according to the definition set by an international consensus guideline. A subject who did not have diabetes prior to randomisation was determined to have NODM if:
  - Subject received an anti-diabetic medication for a duration of ≥ 30 days, or
  - At least 2 fasting plasma glucose (FPG) tests indicated FPG ≥ 126 mg/dL (7.0 mmol/L)
  - NODM was assessed only after the Week 4 visit.
- Study IM103027: Defined as the need for treatment of hyperglycaemia with either an oral agent or insulin for a total or > 4 week or haemoglobin A1c (HbA1c) > 7% in a subject not known to be diabetic prior to transplantation.

Presumed acute rejection

Defined as an elevation in SCr (≥ 0.5 mg/dL [44.2 mmol/L] compared to baseline value in the absence of other factors known to adversely affect renal function that led the investigator to suspect that the subject had experienced acute rejection, and in whom either:

- The biopsy did not confirm acute rejection (and the subjects was treated for acute rejection) or
- The subject was treated for acute rejection without a biopsy to confirm the diagnosis.

Subclinical rejection

Defined as histological findings by the central pathologist consistent with AR but lacking its clinical correlate.

Tuberculosis (TB)

Subjects at risk for tuberculosis, including subjects who:

- Had current clinical, radiographic or laboratory evidence of active or latent TB.
  Note: A negative chest radiograph was required for all subjects. A purified protein derivative (PPD) test was required if it reflected local standard of care practice.
- Had a history of active TB within the last 2 years, even if it was treated, or > 2 years ago, unless there was documentation of adequate treatment according to locally accepted clinical practice
- In the opinion of the investigator and based upon an appropriate evaluation, had a risk of reactivation of TB that precluded the use of conventional immunosuppression.

Use of anti-rejection therapy

A subject is said to have had an episode of treated acute rejection if anti-rejection therapy was administered to the subject during an episode of rejection (clinically-suspected or biopsy-proven).

Good clinical practice (GCP) aspects

The study reports indicate that all laws and regulatory requirements were adhered to for all countries where studies were conducted. The studies were conducted in accordance with the relevant guidelines[15].

The protocols, amendments and subject informed consent documents were reviewed and approved by appropriate Institutional Review Boards and/or Institutional Ethics Committees prior to study start. All subjects or their legally acceptable representatives gave written informed consent.

Studies were monitored by the company or a contract research organisation (CRO) and internal audits were conducted in each study in compliance with GCP.

Pharmacokinetics

Introduction

The pharmacokinetics was determined from initial single escalating doses in standard pharmacokinetic studies in healthy volunteers and subjects receiving renal transplant and in steady state dosing in renal transplant recipients. Most of the PK data was determined through the collection of samples from the core clinical studies to establish the population pharmacokinetics.

The studies conducted and the summary of population pharmacokinetic results are summarised in the following tables.

Tabulations of the results of single dose and steady state dosing are also presented.

[15] GCP as defined by the International Conference on Harmonisation (ICH), The ethical principles underlying the European directive 2001/20/EC, and US Code of Federal Regulations, Title 21, Part 50 (21CFR50).

Table 4. Clinical Pharmacology Studies. Table continued across 4 pages.

Study ID	Man. Process	Objectives of study	Study Design	Type of Subjects	No of Subjects	Duration of Treatment	Belatacept Dosage; Route	PK Objectives
Phase I – IV formulation								
IM103 001	A	S, T, PK, Im	R, DB, PC	Healthy volunteers	Bel = 30 P = 10	Single dose	Bel: 0.1, 1, 5, 10, 20 mg/kg or Placebo IV over 1 hour	Sequential escalating single dose
IM103 024	B, C	PK, S, Im	R, OL, PG	Healthy volunteers	Bel: Process B = 15 Bel: Process C = 15	Single dose	Belatacept 10 mg/kg IV over 30 mins	Comparison of manufacturing Process B vs Process C
Phase II in Renal Transplant Recipients								
IM103 010	C	E, S, Im, PK	R, OL, AC, PG	Renal transplant	Bel = 83 CNI = 88	12 months	Bel maintenance dose: 5mg/kg every 2 wks in 1st 2 months and then every 3 wks IV over 30 min	PK samples predose at wk 4,24, and 52 and post dose at wk 20 and at time of AR
IM103 034	C	E, S, Im, PD	R, OL, PG	Renal transplant	Bel + MMF =35 Tacrolimus + MMF = 31 Bel + Sirolimus = 27 all +	12 months	**Bel MI**: 10 mg/kg on Day 1 &5, then every 2 wks through month 3, then every 4 wks through month 6, then 5 mg/kg every 4 weeks through month 12	Receptor occupancy assessment

Study ID	Man. Process	Objectives of study	Study Design	Type of Subjects	No of Subjects	Duration of Treatment	Belatacept Dosage; Route	PK Objectives
					thymoglobulin induction		IV over 30 mins	
IM103 047	C	PK, PD, S	OL	Renal transplant	12 (10 completed)	3 years PK 4 weeks	**Bel LI**: 10 mg/kg on Day 1 & 5, then every 2 wks through month 1, then every 4 wks through month 3, then 5mg/kg every 4 weeks IV over 30 mins	PK samples taken from wk 12 to wk 16 Steady state – Cmax, Tmax, Cmin, T-half, CLT, Vss
IM103 100	A, B, C	E, S, Im, PK	R, OL, PTB AC, PG	Renal transplant	Bel MI = 74 Bel LI = 71 CsA = 73 LTE Bel = 102 CsA = 26	12 months With long term extension study until drug marketed	**Bel MI**: 10 mg/kg on Day 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 through month 12 **Bel LI**: 10 mg/kg on Day 1, 5, 29, 57, 85, then 5mg/kg every 4 or 8 wks through month 12 IV over 30 min	PK parameters at steady state: Cmax, AUC(0-6hr), Cmin, AI
Phase III – Renal Transplant Recipients								
IM103 008	C	E, S, Im, PK	R, OL, PTB, AC, PG	Renal Transplant STD	Bel MI = 219 Bel LI = 226 CsA = 221	3 years	**Bel MI**: 10 mg/kg on Day 1 &5, then every 2 wks through month 3, then every 4 wks through month 6, then 5 mg/kg	PK values for Pop PK

Study ID	Man. Process	Objectives of study	Study Design	Type of Subjects	No of Subjects	Duration of Treatment	Belatacept Dosage; Route	PK Objectives
				criteria donors			every 4 wks through month 12 **Bel LI**: 10 mg/kg on Day 1 & 5, then every 2 wks through month 1, then every 4 wks through month 3, then 5mg/kg every 4 wks through month 36 IV over 30 mins	
IM103 027	C	E, S, Im, PK	R, OL, PTB, AC, PG	Renal Transplant EXT criteria donors	Bel MI = 184 Bel LI = 178 CsA = 184	3 years	**Bel MI**: 10 mg/kg on Day 1 &5, then every 2 wks through month 3, then every 4 wks through month 6, then 5 mg/kg every 4 wks through month 12 **Bel LI**: 10 mg/kg on Day 1 & 5, then every 2 wks through month 1, then every 4 wks through month 3, then 5mg/kg every 4 wks through month 36 IV over 30 mins	PK values for Pop PK
Phase II & III PK sub-studies in Renal Transplant Recipients								
IM103 100 LTE PK	C	PK	R, OL, AC, PG	Renal Transplant	Bel: every 4 wks = 14 Bel: every 8 wks = 12	Every 4 wks = 28 days Every 8 wks = 56 days	Bel: maintenance phase - 5 mg/kg every 4 or 8 wks	PK values – 4 wk vs 8 wk.

Study ID	Man. Process	Objectives of study	Study Design	Type of Subjects	No of Subjects	Duration of Treatment	Belatacept Dosage; Route	PK Objectives
IM103008/IM103027 MPA PK	C	PK	Same as IM103008 & IM103027	Same as IM103008 & IM103027	Bel + MMF = 21 CsA + MMF = 20	1 day	Same as IM103008 & IM103027 MMF maintained at a fixed dose in the range of 250 mg – 1.5 g BD for at least a wk prior to day	Belatacept MMF interaction study
E = Efficacy; S = Safety; T = tolerability, Im = Immunogenicity R = randomised; DB = double blind; PTB = partially blinded; PC = placebo controlled; AC = active controlled; OL = open-label; PG = parallel group Bel = belatacept; MI = more intensive regimen; LI = less intensive regimen; P = placebo; CNI = calcineurin inhibitor; MMF = mycophenolate mofetil; CsA = cyclosporin								
Phase II – Other indications								
IM103002	A	E, S, Im, PK/PD	R, DB, PC, PG	Rheumatoid arthritis	Bel: 92 Abatacept = 90 Placebo = 32	Dose on Day 1, 15, 29, 57	Belatacept or abatacept 0.5, 2, 10 mg/kg or placebo IV	Cmax, Tmax, AUC(0-T), T-half
Phase I – SC route of administration								
IM103029	C	PK, S, Im	R, DB, PC, PG	Healthy volunteers	Bel = 30 Placebo = 12	Single dose	Belatacept 50, 75, 100, or 150 mg or placebo SC	PK parameters following single SC administration
IM103038	C	S, Im	Follow up to IM103	Healthy volunteers	Bel = 24 Placebo = 9	Not applicable	Not applicable	Observational study only

Study ID	Man. Process	Objectives of study	Study Design	Type of Subjects	No of Subjects	Duration of Treatment	Belatacept Dosage; Route	PK Objectives
			029					
IM103 046	C	Bioavail, PD, S, Im	R, PC, PG	Healthy volunteers	Bel SC = 31 Bel IV = 10 Placebo = 6	Single dose	Belatacept 50, 100, 125, 150, 200, 250 mg Belatacept 125 mg IV	PK parameters following single SC administration

E = Efficacy; S = Safety; T = tolerability, Im = Immunogenicity

R = randomised; DB = double blind; PTB = partially blinded; PC = placebo controlled; AC = active controlled; OL = open-label; PG = parallel group

Bel = belatacept; MI = more intensive regimen; LI = less intensive regimen; P = placebo; CNI = calcineurin inhibitor; MMF = mycophenolate Mofetil;

Single dose study in healthy volunteers

Study IM103001 was a randomised (within dose), double blind placebo controlled, sequential escalating single dose study in which a total of 40 normal, healthy subjects (in groups of 8) received one of 5 dose levels; 0.1, 1.0, 5.0, 10, or 20 mg/kg of belatacept or placebo. Belatacept was administered as a single intravenous dose infused over 1 hour. Blood samples were taken pre-dose and on Day 1, 2, 4, 7, 15, 22, 50, 78 and end of study on Day 106.

The pharmacokinetic results are shown below (n = 6 subjects/dose).

Table 5. Pharmacokinetic results

BMS- 224818 Dose Level					
PK Parameter	**0.1 mg/kg**	**1 mg/kg**	**5 mg/kg**	**10 mg/kg**	**20 mg/kg**
C_{max}[a] (µg/mL)	2.32 (13.6%)	28.2 (20.2%)	126 (14.9%)	260 (9.9%)	466 (10.3%)
$AUC_{(INF)}$[a] (µg•h/mL)	143 (14.4%)	2232 (16.0%)	10341 (21.8%)	22049 (15.1%)	41380 (4.4%)
T_{max}[b] (h)	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.5 (1.0, 2.0)
$T_{1/2}$[c] (h)	86.4 (14.7)	137 (24.3)	176 (25.8)	197 (36.6)	222 (37.1)
CLT[c] (mL/h/kg)	0.71 (0.12)	0.45 (0.07)	0.49 (0.11)	0.46 (0.07)	0.48 (0.02)
V_{SS}[c] (mL/kg)	80.2 (14.8)	79.6 (19.1)	102.0 (15.4)	98.8 (10.1)	117 (12.6)

a Geometric mean (CV)

b Median (minimum, maximum)

c Arithmetic mean (SD)

C_{max}=peak plasma concentration; **$AUC_{(INF)}$**= area under the plasma concentration time curve from time zero to infinity; **T_{max}**=time of C_{max}; **$T_{1/2}$**=half life; **CLT**=total clearance ; **Vss**= volume of distribution at steady state.

Steady state dosing. renal transplant

Study 103047 was a single-group, multiple dose study in de novo transplant subjects who were treated with a belatacept less intensive regimen (10 mg/kg on Days 1 and 5 and Weeks 2, 4, 8 and 12, then 5 mg/kg once every 4 weeks for 3 years). In addition all subjects received basiliximab induction therapy and maintenance therapy with mycophenolate and corticosteroids. PK samples were collected primarily within 4 months of belatacept treatment; between Weeks 12 and 16. Samples were taken on pre-dose and 30 minutes (end of infusion), at

2 hours postdosing and at 3, 7, 14, 21 and 28 days following the Week 12 infusion. For C_{max} evaluation, postinfusion samples were collected on Days 1 and 5 and in Week 16

A summary of the PK data is presented in the tables below.

Table 6. Summary Statistics of Belatacept Pharmacokinetics Parameter Following an IV Infusion Dose of 10 mg/kg at Week 12 (N=10)

C_{max}[a] (µg/mL) Geo. Mean (CV%)	T^{maxa} (h) Median (min-max)	$AUC_{(TAU)}$ (µg•h/mL) Geo. Mean (CV%)	C_{min} (µg/mL) Geo. Mean (CV%)	$T_{1/2}$ (h) Mean (SD)	CLT (mL/h/kg) Geo. Mean (CV%)	V_{ss} (L/kg) Mean (SD)
238.33 (27)	0.60 (0.5-2.5)	21241 (35)	7.29 (61)	235.43 (76.414)	0.47 (27)	0.11 (0.033)
a N=9						

C_{min}=minimum plasma concentration; **$AUC_{(TAU)}$**= area under the plasma concentration time curve over a dosing interval.

Population pharmacokinetic results

Table 7. Typical Values of Parameter Estimates for the Final Population PK Model at the Reference Value of Covariates

Name [Units]	Estimate[a]	Standard Error (RSE%)[b]	95% CI[c]
Fixed Effects			
CLTV, ref [L/h]	0.0366	0.000308 (0.84)	0.0360 - 0.0372
VCTV, ref [L]	3.59	0.0326 (0.91)	3.52 - 3.66
QTV, ref [L/h]	0.0568	0.00168 (2.96)	0.0537 - 0.0599
VPTV, ref [L]	5.11	0.151 (2.95)	4.82 - 5.40
CL ~ BBWT (ref = 75 kg)	0.736	0.0348 (4.73)	0.668 - 0.804
VC ~ BBWT (ref = 75 kg)	0.708	0.0408 (5.76)	0.632 - 0.784
VP ~ BBWT (ref = 75 kg)	0.854	0.058 (6.79)	0.741 - 0.967
Q ~ BBWT (ref = 75 kg)	0.464	0.107 (23.1)	0.250 - 0.678
Q ~ BWT	2.07	0.311 (15.0)	1.44 - 2.70

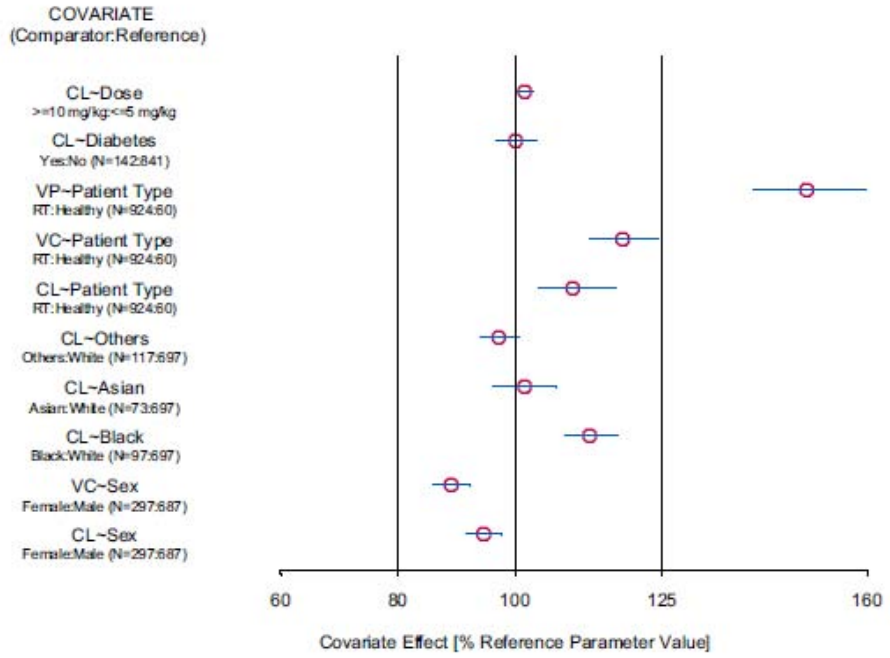
Name [Units]	Estimate[a]	Standard Error (RSE%)[b]	95% CI[c]
CL ~ AGE (ref = 50 yr)	-0.185	0.0192 (10.4)	-0.222 - -0.148
VP ~ PTTYPE (ref =Healthy)	0.335	0.0311 (9.28)	0.274 - 0.396
Random Effects			
ZCL [-]	0.0456 (0.214)	0.00258 (5.66)	0.0404 - 0.0508
ZVC [-]	0.0313 (0.177)	0.0035 (11.2)	0.0246 - 0.0380
ZVP [-]	0.0830 (0.288)	0.00782 (9.42)	0.0674 - 0.0986
ZCL:ZVC	0.0258 (0.683)	0.00254 (9.84)	0.0207 - 0.0309
ZCL:ZVP	0.0167 (0.271)	0.00341 (20.4)	0.00998 - 0.0234
ZVC:ZVP	0.0277 (0.543)	0.0036 (13.0)	0.0207 - 0.0347
Residual Error			
θ_{PROP} [-]	0.246	0.00463 (1.88)	0.237 - 0.255
θ_{ADD} [µg/mL]	0.143	0.0256 (17.9)	0.0936 - 0.192

a Random Effects parameter estimates are shown as variance (standard deviation) for diagonal elements (*ZP,*) and covariance (correlation) for off-diagonal elements (*ZP1:ZP2*)

b RSE% is the relative standard error (standard error as a percentage of estimate)

c Confidence intervals of Random Effects parameters are for variance or covariance, all confidence intervals are from 500 bootstrap runs

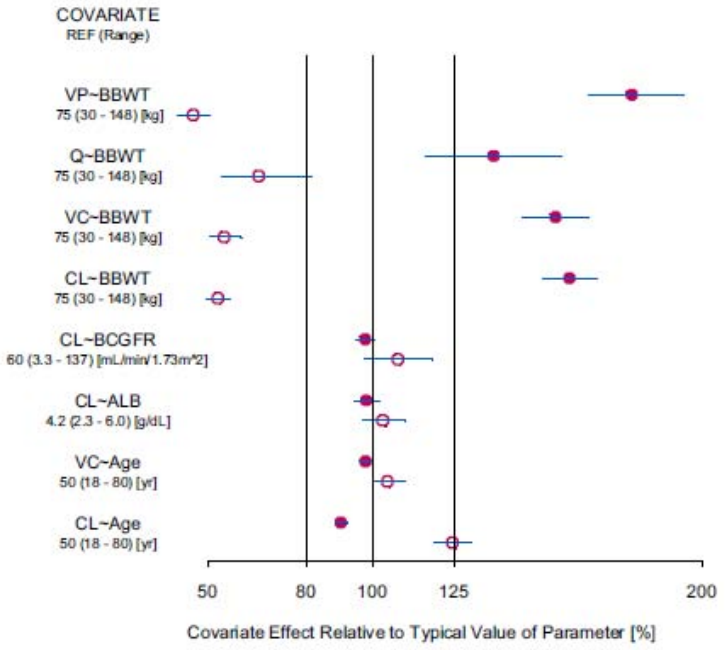
Figure 2a. Covariate effects for baseline categorical covariates in the full population PK model.



Source: Population PK and Exposure-Response Report[56]

The uncertainty (95% confidence interval) around the estimated effects is represented by the error bars.

Figure 2b. Covariate effects for baseline categorical covariates in the full population PK model.



Source: Population PK and Exposure-Response Report[56]

The open and solid circles show the estimated effects of continuous covariates at the minimum and maximum of the covariate values, respectively. The uncertainty (95% confidence interval) around these estimated effects is represented by the error bars.

Methods

Analytical methods

A bioanalytical assay (Enzyme-linked immunosorbent assay (ELISA)) was developed and validated by the sponsor (BMS) for the determination of belatacept in human serum samples. Both manual and automated methods were developed and validated for all sites measuring belatacept. The assays have a validated range of reliable response of 3.0 to 80 ng/mL with a lower limit of quantification (LLOQ) of 3.0 ng/mL. Belatacept was stable in human serum for up to 25 hours and after 13 freeze thaw cycles and stable at approximately -70°C or below for at least 120 days.

A urine assay was also developed to investigate whether belatacept was excreted in the urine in renal transplant patients who develop proteinuria. The urine ELISA method was identical to the serum ELISA method but utilised standards and quality controls (QCs) that were human urine matrix-based. The range of reliable response for belatacept was 3.0 to 80 ng/mL in human urine, with a LLOQ of 3.0 ng/mL. Belatacept was stable in human urine at room temperature for up to 26 hours after 3 freeze-thaw cycles and stable at approximately -70°C or below for at least 174 days.

The immunogenicity assay is described in the summary of *Immunogenicity* below.

Pharmacokinetic data analysis

The population pharmacokinetic (PPK) analysis for belatacept was conducted with 749 and 12,139 serum concentrations values from 60 healthy subjects and 924 renal transplant (RT) subjects who received IV infusions of belatacept in the following studies – IM103001 and IM103024 in healthy volunteers and IM103100, IM103008 and IM103027 in renal transplant subjects. The data included the serum concentrations up to 1 year (for IM103100 data beyond one year).

Statistical analysis

The PPK model was developed in 3 stages. First, a base model was developed to describe the pharmacokinetics of belatacept without consideration of covariate effects. Second, a full covariate model was developed by incorporating the effects of all pre-specified parameter relationships and finally a parsimonious final model was developed by retaining only the statistically significant and clinically meaningful covariate parameter relationships.

Covariate parameter relationships were examined for the following covariance baseline and time varying body weight, age, gender, race, calculated GFR, albumin, diabetes, subject type, and dose (≤ 5 mg/kg versus ≥ 10 mg/kg).

Model evaluation was conducted by visual and quantitative predictive performance check methods.

Absorption

Bioavailability

Not applicable to IV formulation.

Bioequivalence

Belatacept is produced as a secreted protein in large scale cell culture using a CHO cell line. The cell culture from the production bioreactor is harvested by microfiltration and ultrafiltration. The cell-free harvest material is adjusted for pH and then clarified through depth and sterilising grade filters in preparation for downstream processing using a series of chromatographic and filtration steps. The purpose of these steps is to purify the belatacept protein, to reduce the high

molecular weight (HMW) belatacept material and to control the sialic acid content of the belatacept drug substance. The downstream processing steps also include a viral inactivation step and a viral filtration step to clear potential adventitious viral agents.

During the clinical development program there were changes to the manufacturing processes. These different processes are called "Process A", "Process B, and "Process C". Process C was used in the Phase III clinical studies and is the process intended for commercial production. Initial clinical trials were conducted using product using Process A and Process B.

No human study was done comparing Process A to Process B based on studies conducted in monkeys but a cross study comparison of the clinical data from IM103100 and IM103001 demonstrated similarity between the product from these processes.

A PK study (IM103024) was conducted comparing a single IV dose of 10 mg/Kg belatacept derived from Process B and Process C in 30 healthy volunteers. Plots of mean (standard deviation (SD)) serum concentration of belatacept versus time profiles by manufacturing processes were similar and statistical assessment of C_{max}, $T_{1/2}$ and V_{ss} values were similar. The 90% confidence interval (CI) of belatacept C_{max} ratio between Process C and Process B was contained within the limit of 80-125%. Although the 90% CIs of belatacept area under the plasma concentration time curve over a dosing interval ($AUC_{(0\text{-}T)}$) and $AUC_{(INF)}$ ratios between Process C and Process B were not contained within the limit of 80-125%, the difference of $AUC_{(0\text{-}T)}$ and $AUC_{(INF)}$ was small (10.6% and 11.9% higher in Process C respectively). Also, the inter-individual variability was numerically less in subjects receiving belatacept from Process C (19% for $AUC_{(0\text{-}T)}$ and 20% for $AUC_{(INF)}$, respectively) than that in subjects receiving belatacept from Process B (29% for both $AUC_{(0\text{-}T)}$ and $AUC_{(INF)}$). The small differences in AUC values are not considered to be clinically significant and so the two processes were considered to be comparable.

Process C drug product was produced in 2 vial strengths (100 mg and 250 mg), which are identical with regard to the proportions of active and inactive ingredients. The belatacept molecules for the 2 vial strengths were shown to be analytically comparable. Both vial sizes were used in the Phase III studies, however only the 250 mg vial presentation is intended to be comparable.

Influence of food

Not applicable.

Distribution

The volume of distribution is low, 0.1 L/kg, with a volume of distribution at steady state (V_{ss}) similar to that of the vascular space. This is consistent with the low distribution of large protein molecules. Since belatacept is neither lipophilic nor a known transporter substrate and has a low volume of distribution, it is unlikely that it crosses the blood brain barrier.

Elimination

Excretion

Limited data suggest that belatacept is excreted in urine at generally low or variable concentrations in renal transplant subjects with proteinuria.

It is presumed that the drug is cleared through the non specific mechanisms of clearance known for therapeutic proteins, that is, through their interaction with specific receptors on the target cell surfaces, as well as interactions with the FcγR1 receptors on the hepatic sinusoidal epithelial cells and through non-specific proteolysis in the Kupffer cells in the liver and macrophage activity in spleen.

The homeostasis of Fc-containing molecules, such as antibodies of the human IgG1 isotype, is maintained through a specific interaction with the neonatal Fc receptor (FcRn), and the PK of such molecules is affected by their binding to FcRn, which protects them from elimination. There is evidence that very high doses of IgG may lead to increases in the rate of IgG elimination due to saturation of FcRn. Belatacept binds to FcRn with approximately one-third the affinity of IgG1 thought this lower affinity does not appear to affect the PK of belatacept relative to that of IgG1, as the $T_{1/2}$ of belatacept is similar to that of IgG1. Thus, the FcRn mediated pathway likely plays a significant role in the PK of belatacept.

Belatacept has an apparent terminal elimination half-life of approximately 8-10 days.

Metabolism

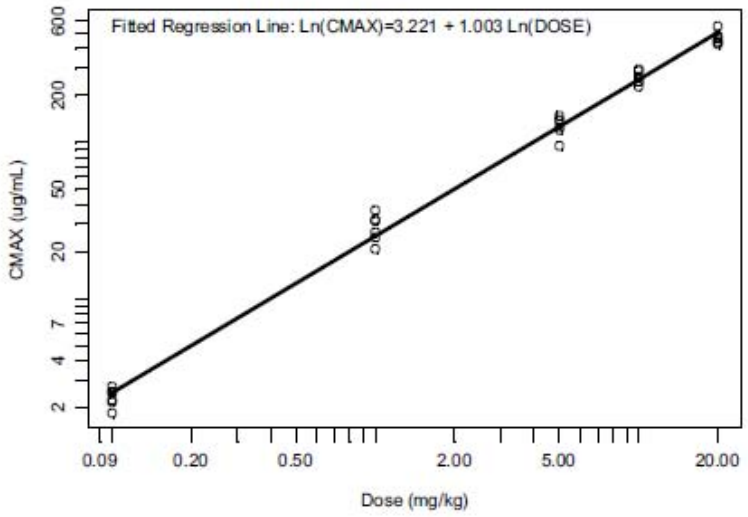
Belatacept metabolism has not been studied in humans. Like most therapeutic proteins, belatacept is not expected to be metabolised by cytochrome P450 enzymes (CYP) and not expected to have significant interactions with molecules metabolised by CYP. The expected consequence of metabolism of biotechnology derived proteins is degradation to small peptides and individual amino acids that are then recycled into other proteins.

Dose proportionality and time dependency

Dose proportionality

The PK of belatacept was linear and the exposure to belatacept increased proportionally in health subjects after single intravenous infusion dose of 1 to 20 mg/kg.

Figure 3. Relationship between C_{max} and dose of belatacept. IM103001



Time dependency

Over a 1 year period the overall mean variability (day to day range) for belatacept C_{max}, C_{avg} and C_{min} were 15% (14-16%), 23% (14-27%) and 47% (19-57%), respectively.

Trough levels of belatacept were stable throughout the 36 months of the study and through 5 years of exposure in Study IM103100 LTE. Based on population PK analysis of 944 renal transplant recipients up to 1 year post transplant, the PK of belatacept appeared to be time in-variant.

Intra- and inter-individual variability. Target drug concentrations

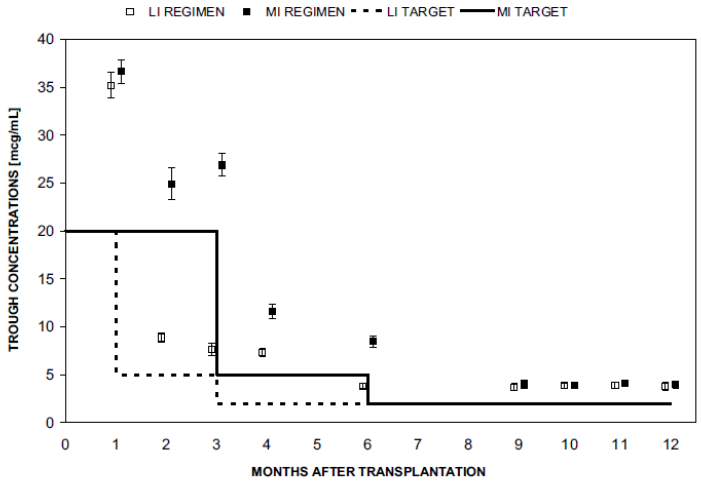
The dosing of belatacept (in combination with other agents) is designed to achieve a tiered approach to effectiveness with greater immunosuppression in the initial phase and a sustained

level through the maintenance phase. The target concentrations selected were approximately 20 µg/mL for 30 days followed by approximately 7 µg/mL to day 90 (initial phase), and approximately 2 or 0.25 µg/mL in the maintenance phase to Day 365. These concentrations were in the upper portion of the exposure-response curve and produced approximately 80% inhibition of the alloresponse during the 3 months post transplant and approximately 50% or greater inhibition of the alloresponse during the maintenance phase. These concentrations were confirmed to produce maximal /near maximal (approximately 2-20 µg/mL) to approximately 60% (0.25 µg/mL) CD86 receptor occupancy and maximal CD80 receptor occupancy *in vitro*.

Table 8. Target C_{min} and Predicted CD86 Receptor Occupancy for the LI and MI Regimens in Phase III Studies IM103008 and IM103027

Time Post Transplant	Month 1	Month 2-3	Month 4-6	Month 7-12
	LI Dosing Regimen			
Target Cmin (µg/mL)	20	5	2	2
% of Patients Achieving Cmin[a]	>90%	>80%	> 90%	>90%
Expected CD86Receptor Occupancy	85%	72%	59%	59%
	MI Dosing Regimen			
Target Cmin (µg/mL)	20	20	5	2
% of Patients Achieving Cmin	>90%	>79%	>80%	>90%
Expected CD86Receptor Occupancy	85%	85%	72%	59%
a Based upon nominal dose and time				

Figure 4. Belatacept serum through concentration (Cmin) (gemoteric mean and 95% CI) for L1 and M1 regimens in Phase III studies. Observed data pooled from IM103008 and IM103027.



Source: Supplemental Table S.3.3.1.1B

Note: PK samples for trough concentrations for Month 1, 2, 3, 4, 6, 9, 10, 11, and 12, were collected on Day 5, 56, 84, 112, 168, 252, 280, 308, and 336, respectively; no trough samples were collected for Months 5, 7 and 8

Target concentrations for the LI and MI regimens were 20 µg/mL for up to Month 1 and 3, respectively; followed by 5 µg/mL for Months 2-3 and 4-6, respectively; and 2 µg/mL beyond Month 4 and 6, respectively, post-transplantation

Pharmacokinetics in target population

The PK of belatacept was similar in healthy subjects and renal transplant recipients.

Table 9. Pharmacokinetic Parameters in Healthy Subjects and Renal Transplant Recipients After 5 and 10 mg/kg Intravenous Infusions

	Belatacept Pharmacokinetic Parameters					
	C_{max} µg/mL Geo Mean (%CV)	$AUC_{(TAU)}$ µg·h/mL Geo. Mean (%CV)	$AUC_{(INF)}$ µg·h/mL Geo. Mean (%CV)	$T_{1/2}$ days Mean (SD)	CLT mL/h/kg Mean (SD)	V_{ss} L/kg Mean (SD)
Healthy Subjects After 10 mg/kg Single Dose (N=15)	292.1 (26)	--	25975.1 (20)	9.8 (2.7)	0.39 (0.07)	0.10 (0.02)
Renal Transplant Recipients After 5 mg/kg Single Dose (N=12)a	124.6 (27)	--	10219.7 (28)	8.2 (2.4)	0.51 (0.14)	0.12 (0.03)

Belatacept Pharmacokinetic Parameters						
Renal Transplant Recipients after 5 mg/kg Multiple doses (N=14)	136.3 (20)	13587.1 (27)	--	--	--	--
Renal Transplant Recipients After 10 mg/kg Multiple Doses (N=10)	238.3 (27)	21241.1 (35)	- -	9.8 (3.2)	0.49 (0.13)	0.11(0.03)

Source: IM1030244, IM1030477, IM10310010

Dosing interval for TAU = 4 weeks

a Assessed as single dose PK since the terminal half life of belatacept is approximately 8 days, and the 8-week dosing interval represents a wash-out of >5 half-lives between doses and was adequate to characterize the elimination phase of belatacept.

The variability of belatacept exposure in renal transplant recipients was generally low. The target C_{min} (trough level) of 20 µg/mL during the first month, 5 µg/mL during the second and third month (also through sixth month for the MI regimen), and 2 µg/mL thereafter and during the maintenance phase were achieved. The pattern of C_{min} was consistent in the Studies IM103008, IM103027, IM103100 and IM103047 and was consistent with the administered dosing which was constructed to ensure highest immunosuppression in the period immediately post transplant.

Minimal systemic accumulation of belatacept occurred upon multiple infusions of 5 or 10 mg/kg dose in renal transplant recipients once monthly.

Special populations

Children

No paediatric data (< 18 years of age) were submitted.

Elderly

Based on the population PK analysis, the effect of age on the clearance of belatacept was not clinically relevant. Belatacept PK data was available from 847 < 65 years and 137 subjects > 65 years of age. The age range was 18-80 years.

Gender

Based on the population PK analysis, the effect of gender on the clearance of belatacept was not clinical relevant. Belatacept PK data was available from 687 male subjects and 297 female subjects.

Weight

In the Phase III studies, dose of belatacept did not require modification during the course of the study when changes of body weight were less than ± 10%.

Figure 2b shows that for the baseline continuous covariates, the effects of baseline body weight (BBWT) on all PK parameters exceed the 80-125% range relative to the typical value of

parameters, and thus the covariate effects are considered as clinically relevant, supporting a weight based dose of belatacept. CL and VC increase with increasing weight supporting a weight based dose.

Race

The effect of race was only analysed according to the US classifications of race which is not relevant to the Australian population mix. Based on the population PK analysis, the effect of race was not clinically relevant. Belatacept PK data was available from 696 Caucasian subjects, 97 Black subjects, 73 Asian/Pacifica Islander subjects, 6 American/Alaskan Native subjects, 5 Hispanic/Latino subjects, 1 subject with missing data and 106 subjects classified as "Other".

Impaired renal function

Based on a population PK analysis of 984 subjects, the effect of baseline renal function (classified by baseline GFR corrected for body surface area (cGFR)) and the effect of time varying renal function (classified by time varying cGFR post transplant) on the clearance of belatacept were not clinically relevant. There is minimal change in the PK of belatacept as renal function improves over time after renal transplant. The subjects evaluated in the population PK analysis include subjects with normal through to severe renal impairment. The range of baseline serum creatinine concentration was from 0.8 to 21.7 mg/dL and the range of baseline cGFR was from 3.3 to 138 mL/min/1.73m^2.

Limited data suggest that belatacept or belatacept related biomaterial is excreted in urine at generally low and variable concentrations in renal transplant subjects with proteinuria. Up to Month 36 post transplant, the proportion of subjects with protocol defined proteinuria was 10%, 8% and 6% in IM103008; and 14%, 15% and 12% in IM103027 in the belatacept more intensive (MI), less intensive (LI) and cyclosporin (CsA) groups, respectively, based on proteinuria defined as central laboratory determined 2+ urine protein for at least 2 consecutive visit dates.

The sponsor's conclusion was that although belatacept may be detected in the urine of renal transplant recipients with some degree of proteinuria, renal function does not play a significant role in the overall clearance of belatacept.

The population PK analysis contained an evaluation of PK for 87 patients on one occasions with dialysis and one occasion not on dialysis and indicated no effect of dialysis on the clearance of belatacept.

One subject in Study IM10345 who experienced PML underwent plasmapheresis for approximately 1.5 hours on 2 occasions. Serum samples for belatacept concentrations were collected before and after plasmapheresis. Serum belatacept concentrations were reduced by 53-63% per cycle of plasmapheresis. Overall there was a 79% reduction in serum belatacept concentration after 2 cycles of plasmapheresis as the belatacept concentration decreased from 20600 ng/mL to 4300 ng/mL. This suggests that plasmapheresis may accelerate removal of belatacept from the systemic circulation.

Impaired hepatic function

Based on the population PK analysis, the effect of hepatic function (classified by serum albumin) on the clearance of belatacept was not clinically relevant. The subjects evaluated in the population PK analysis ranged from normal to mild hepatic impairment. The range of serum albumin was from 2.3 to 6 g/dL.

Evaluator's overall comments on pharmacokinetics in special populations

Given the intended patient population the population pharmacokinetic analysis approach appears to provide adequate description of effect of belatacept.

Interactions

Formal interaction studies were not conducted to investigate the impact of background immunosuppressive therapy (MMF + corticosteroids) on the PK of belatacept. It is known that CsA lowers mycophenolic acid (MPA) exposure by inhibiting the enterohepatic recirculation of MPA and so an evaluation of the PK of MPA and mycophenolic acid glucuronide (MPAG) was conducted in renal transplant recipients who received belatacept or CsA based treatment with mycophenolate Mofetil (MMF) (IM IM103008 / IM103027 PK substudy). MMF was one of the drugs used in the background immunosuppressive therapy in both the Phase III studies (IM103008 and IM103027).

MPA C_{max} was approximately 22% higher and $AUC_{(TAU)}$ as approximately 41% higher in subjects receiving belatacept compared to subjects receiving CsA, and MPAG C_{max} was approximately 26% lower and $AUC_{(TAU)}$ approximately 30% lower in subjects receiving belatacept compared to subject receiving CsA. The observed difference in the exposure to MPA between MMF + CsA and for MMF + belatacept was consistent with other reported data on the impact of enterohepatic recirculation alterations by CsA on the exposure of MPA after MMF dosing (range 10-60%).

The degree of increase in plasma MPA exposure seen in stable renal transplant subjects receiving the belatacept based regimen during the maintenance phase was also similar to the relatively higher MPA exposure (6-43%) reported in renal transplant recipients who received a belatacept based regimen compared with a CsA based regimen 2-12 weeks post transplant (Kamar et al 2007 abstract from Phase II study)

Table 10. Pharmacokinetic Parameters in Healthy Subjects and Renal Transplant Recipients After 5 mg/kg Intravenous Infusions

Belatacept Pharmacokinetic Parameters					
	Cmax (µg/mL) Geo Mean (%CV)	**AUC(INF) (µg•h/mL) Geo. Mean (%CV)**	**T-HALF (d) Mean (SD)**	**CLT (mL/h/kg) Mean (SD)**	**Vss (L/kg) Mean (SD)**
Healthy Subjects After 5 mg/kg Single Dose (N=6)	126 (14.9)	10341 (21.8)	7.3 (1.1)	0.49 (0.11)	0.10 (0.015)
Renal Transplant Recipients After 5 mg/kg Single Dose(N=12)	124.6 (27)	10219.7 (28)	8.2 (2.4)	0.51 (0.14)	0.12 (0.03)

Source: IM1030013, IM10310010

Like most therapeutic proteins, belatacept is not metabolised by liver CYP450 metabolising enzymes and so belatacept is not expected to have a significant interactions with other drugs that are metabolised by CYP450. No drug-drug interaction studies to assess CYP mediated metabolism were conducted.

Evaluator's overall comments on pharmacokinetic interactions

The PK profile has been predominantly determined using the population pharmacokinetic model. The population of renal transplant recipients have been well documented within this model and provides appropriate information.

Exposure relevant for safety evaluation

The use of the two dose regimens in the core clinical efficacy studies provides information on the effect of dose on safety assessment.

Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics have been appropriately studied in the intended population.

Pharmacodynamics

Introduction

An extensive report of the pharmacodynamic studies was provided in the current submission. Only key features of this report are summarised here.

Receptor Occupancy

CD86 receptor occupancy was assessed with a flow cytometric based CD86 receptor competition assay, utilising PE-conjugated anti-human CD86 mAb clone HA5 (HA5-PE) and APC-conjugated mAb clone 2D4 (2D4D4-APC). HA5-PE binds free CD86 unoccupied by belatacept, while 2D4-APC binds all CD86 detecting total CD86 expression on $CD14^+$ monocytes. Samples were processed in duplicate and acquired on FACSCanto™ flow cytometer using Diva™ analysis software.

In Study IM103034 receptor occupancy was evaluated at baseline prior to belatacept infusion and over time following transplant in 57 subjects. Subjects received belatacept 10 mg/kg IV on Days 1 and 5, then every other week through Month 6 and then maintenance dose of 5 mg/kg every 4 weeks until 12 months.

Approximately 94% saturation of CD86 receptors on the surface of antigen presenting cells in the peripheral blood was observed at predose on Day 5 following the Day 1 infusion of the 10 mg/kg dose. Receptor occupancy tapered to 65% by Month 12. At these belatacept concentrations, *in vitro* data suggested complete saturation of CD8 receptors by belatacept.

Figure 5a. Total CD86 receptor expression over time.

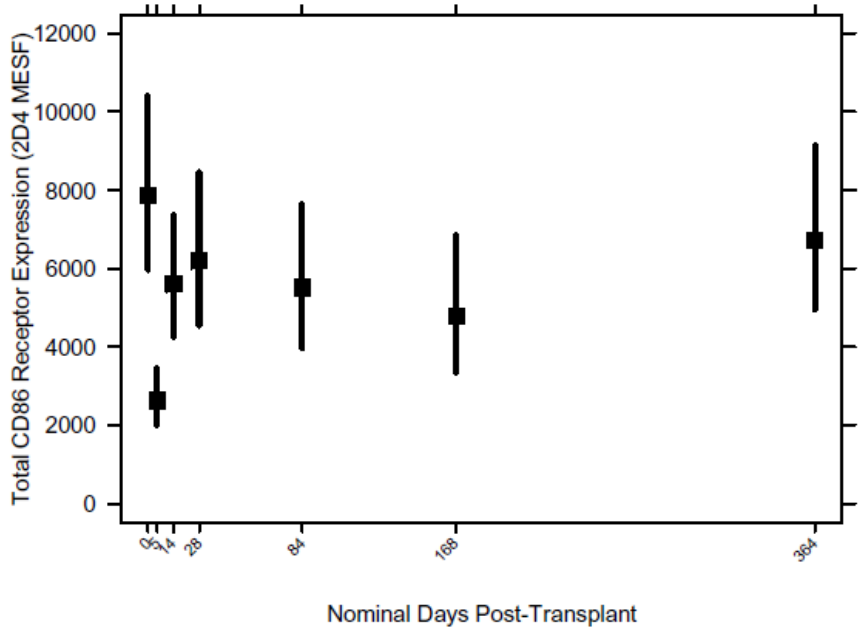
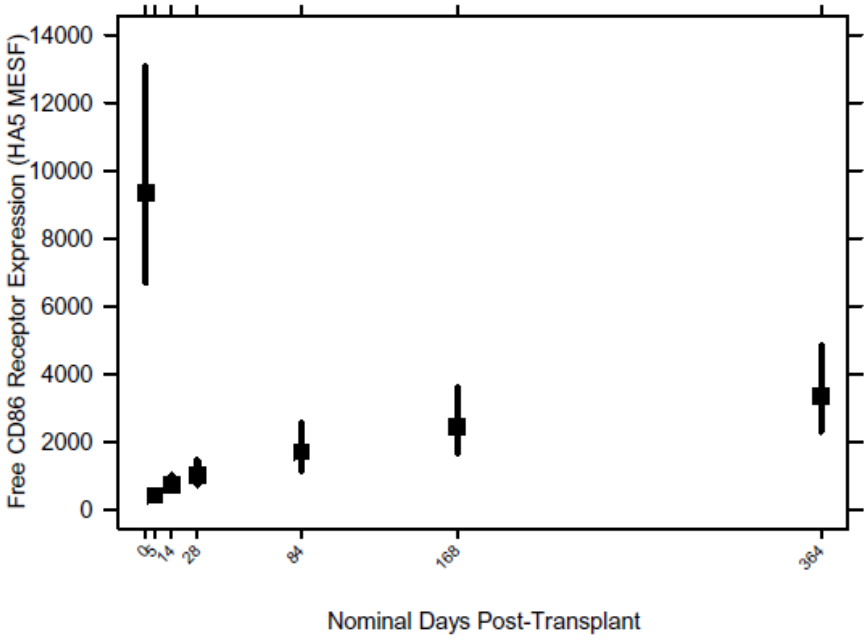


Figure 5b. Free CD86 receptor expression over time.



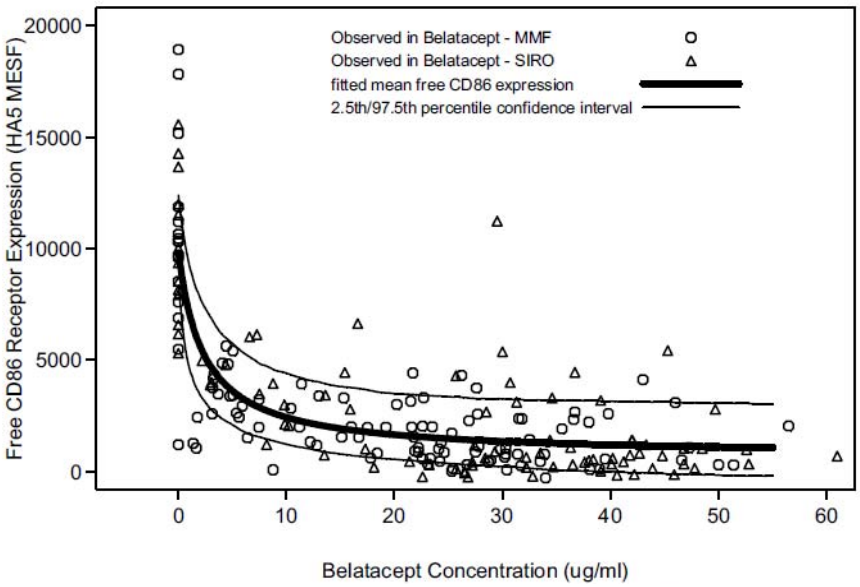
Source: IM103034 Clinical Study Report[11]
Filled squares indicate mean CD86 receptor expression at each time point
Lines indicate 95% confidence interval coverage around the mean

Relationship between plasma concentration and effect

CD86 Receptor Occupancy PK-PD relationship

The PK-PD relationship of free CD86 levels and the belatacept concentration is shown in Figure 6 below.

Figure 6. PK-PD relationship of belatacept concentration versus free CD86 receptor expression in Study IM103034.



Receptor occupancy rapidly increases as belatacept concentrations increase and stabilises at concentration of > 20 µg/mL. For the recommended dosing regimen (LI) the PK-PD relationship predicted approximately 90% saturation of CD86 receptors on the surface of antigen-presenting cells in the peripheral blood following the initial administration of belatacept.

During the first month post transplant approximately 85% saturation of CD86 was maintained. The level of CD86 saturation was approximately 70% during Months 2-3; while beyond Month 4 the level of CD86 receptor saturation was maintained at approximately 60%. Receptor occupancy for the MI regimen was similar to the LI regimen at ≤ 1 month; however, receptor occupancy was approximately 85% and 75% during Months 2-3 and 4-6, respectively. Beyond Month 6, the level of CD 86 receptor saturation was similar to the LI regimen at approximately 60%.

The high level of CD86 receptor occupancy by belatacept in the early period following the transplantation is critical to block T cell co-stimulation and thereby inhibit graft rejection during the early post transplant period when the risk of immunologic acute rejection is highest.

Anti-donor HLA antibodies

The incidence of developing anti-donor HLA antibodies was evaluated in the pivotal clinical trials using flow cytometry. Overall, few subjects had anti-donor HLA antibodies at baseline or after treatment with belatacept.

Numerically fewer subjects in each belatacept treatment group (4-5%) had detectable circulating antibodies directed against donor-specific HLA antigens following transplantation than subjects in the cyclosporin (CsA) treatment arm (8-12%).

Data from the Phase III studies demonstrated that among the belatacept treated subjects who had an AR episode within the first 24 months of the study only 4-5% of the subjects with AR with AR had detectable anti-donor HLA antibodies at any time. In the CsA treatment group, 15-22% of subjects who experienced AR within the first 24 months had detectable anti-donor HLA antibodies post transplantation.

The presence of anti-donor HLA antibodies at baseline did not appear to predispose subjects to acute rejection as the majority of subjects in all treatment groups with detectable anti-donor HLA antibodies at baseline did not experience acute rejection.

Evaluator's overall conclusions on pharmacodynamics

The biomarker data elucidate the pharmacodynamics of belatacept and support the dosing regimens tested in the efficacy studies. The data supports the recommended doses as providing a sufficient level of target saturation to inhibit the immune responses to the graft, including humoral response without impacting immune-regulatory T cells.

Efficacy

Introduction

The efficacy data is derived primarily from 3 studies: two Phase IIIstudies in renal transplant recipients, the first (IM103008) in subjects who received kidneys based on standard donor criteria and the second (IM103027) in subjects who received kidneys based on extended donor criteria. In addition a Phase II study (IM103100) was included in which the prime aim was efficacy in renal transplant recipients.

In all the clinical studies there was extensive immunogenicity testing of all subjects on belatacept. The immunogenicity results were reported separately from the clinical study reports and are discussed in the section on pooled data.

Also each clinical study collected PK samples for contribution to population PK analysis. These results have been reported and are not included in this section.

The key focus of assessment of efficacy by the company in their summaries and overview were restricted to the 3 pivotal studies. A number of additional Phase II studies were included in the submission primarily to add to the safety assessment. The details of these studies are included only in Table 11 below.

Table 11. Summary of clinical efficacy studies. Table continued across 3 pages.

Study ID	No. of centres (Location)	Design	Dosage regimen* (Background therapy)	Study objective	Subjects by arm: Entered (Completed 12m, 36m)	Duration	Gender: M/F (Age)	Type of subject	Primary endpoint
Pivotal Trials– Renal Transplant									
IM103 008 Phase III	104 (worldwide)	R, OL, PTB AC, PG	Bel MI vs Bel LI vs CsA Basiliximab induction and maintenance MMF + corticosteroids	Bel vs CsA	Bel MI: 219 (173, 153) Bel LI: 226 (181, 173) CsA: 221 (173,143)	3 years	462/204 (≥18yrs)	De novo Renal transplant recipients with standard criteria donors (SCD)	• Composite endpoint of subject & graft survival at 12 m • Composite endpoint of measured GFR <60 or decrease >10 at 12 m • Incidence of AR at12m
IM103 027 Phase III	79 (worldwide)	R, OL, PTB, AC, PG	Bel MI vs Bel LI vs CsA Basiliximab induction and maintenance MMF + corticosteroid	Bel vs CsA	Bel MI: 184 (134, 109) Bel LI: 175 (131, 114) CsA: 184 (125,100)	3 years	364/179 (≥18yrs)	Renal transplant recipients with extended criteria donors (ECD)	• Composite endpoint of subject & graft survival at 12m • Composite endpoint of measured GFR <60 or decrease >10 at 12 m • Incidence of AR

Study ID	No. of centres (Location)	Design	Dosage regimen* (Background therapy)	Study objective	Subjects by arm: Entered (Completed 12m, 36m)	Duration	Gender: M/F (Age)	Type of subject	Primary endpoint
									at12m
IM103 100 Phase II Long term extensive study	41 (USA, EU, Canada) 20	R, OL, PTB, AC, PG	Bel MI vs Bel LI vs CsA Basiliximab induction and maintenance MMF + steroids) (MMF + another IMPDH + steroids)	Bel vs CsA	Bel MI: 79 (58) Bel LI: 74 (58) CsA: 73 (53)	12 months ongoing to product approval	151/90 (≥18yrs)	De novo Renal transplant recipients	Acute rejection at 6 months • Composite endpoint of subject & graft survival at yearly intervals • immunogenicity
R = randomised; PTB = partially blinded; DB = double blind; PC = placebo controlled; AC = active controlled; OL = open-label; PG = parallel group; Bel = Belatacept; CsA = Cyclosporin;									
Other Trials = Phase II									
IM103 010	34 (worldwide)	R, OL, PG	Bel vsCNI MMF , MPA, SRL or AZA ± steroids	Conversion	Bel: 84 CNI: 89	12 months	126/47 (18-72 yrs)	Maintenance renal transplant	Change in cGFR from baseline to 12 months
IM103 034	25 (USA,	R, OL, PG	Bel MI TAC	Steroid avoidance	Bel + MMF: 33	12 months	68/22 (18-72	De novo renal transplant	Acute rejection at 6 months

Study ID	No. of centres (Location)	Design	Dosage regimen* (Background therapy)	Study objective	Subjects by arm: Entered (Completed 12m, 36m)	Duration	Gender: M/F (Age)	Type of subject	Primary endpoint
	Spain, Italy)		thymoglobulin induction and maintenance MMF or SRL	regimens	Bel +SRL: 26 TAC + MMF: 30		yrs)		
IM103 045	49 (worldwide)	R, PTB, AC	Bel MI + MMF + basiliximab vs Bel MI + MMF vs Bel LI + MMF vs TAC +MMF vs TAC + orticosteroids	Bel vs TAC	Bel :146 TAC: 102	12 months (ongoing)	42/8 (28-68 yrs)	De novo liver transplant	Incidence of acute rejection, graft loss and death at 12 months

R = randomised; PTB = partially blinded; DB = double blind; PC = placebo controlled; AC = active controlled; OL = open-label; PG = parallel group Bel = Belatacept; CsA = Cyclosporin; CNI = calcineurin inhibitor; TAC = tacrolimus, SRL = sirolimus; MMF = mycophenolate mofetil; MPA = mycophenolic acids; AZA = azathioprine

* Dosing regimens:

IM103008 and **IM103027 -** Belatacept MI and LI same in 2 Phase III studies:

Bel MI: 10 mg/kg on Day 1 &5, then every 2 wks through month 3, then every 4 wks through month 6, then 5 mg/kg every 4 wks through month 36

Bel LI: 10 mg/kg on Day 1 & 5, then every 2 wks through month 1, then every 4 wks through month 3, then 5mg/kg every 4 wks through month 36

Study ID	No. of centres (Location)	Design	Dosage regimen* (Background therapy)	Study objective	Subjects by arm: Entered (Completed 12m, 36m)	Duration	Gender: M/F (Age)	Type of subject	Primary endpoint

CsA: twice daily for trough serum 150-300 ng/mL during month 1, then 100-250 ng/mL thereafter

IM103100

Bel MI: 10 mg/kg on Day 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 through month 12

Bel LI: 10 mg/kg on Day 1, 15, 29, 57, 85, then 5mg/kg every 4 or 8 wks starting on Day 113 through month 12

CsA: 7±3 mg/kg then dose to meet target serum levels (month 1 150-400 ng/mL, thereafter 100-350 ng/mL)

IM103010

Bel: 5mg/kg on Days 1, 5, 15, 29, 43, 57, then every 28 days; **CNI**: 40-60% of baseline dose on Day 15, 20-30% of baseline on Day 22 and stopped on Day 29

IM103034

Bel MI: 10 mg/kg Day 1 &5, then every 2 wks through month 3, then every 4 wks through month 6, then 5 mg/kg every 4 wks;

TAC: 0.1 mg/kg to achieve stable 12 hr trough level of 8-12 ng/mL on Days 1-30, then 5-10 ng/mL

IM103045

Bel MI: 10 mg/kg on Days 1, 3, 5 & at wks 2, 4, 8, 1, 12, 16, 20, 24, then 5 mg/kg every 4 wks.

Bel LI: 10mg/kg on Days 1, 3, 5 & at wks 2, 4, 8. 12, then 5 mg/kg every 4 wks

TAC: BID dosing, 1st dose ≥ 6 hrs post transplant to achieve stable 12 hr trough level 6-12 ng/mL

Dose response studies

The selection of the belatacept less intensive (LI) and more intensive (MI) dose regimens is stated to be based on a systematic, stepwise approach developed from the *in vitro* pharmacodynamic data and in vivo efficacy data from a primate transplant study. The initial regimens were tested in the Phase II study IM103100 then refined for use in the Phase IIIstudies (IM103008 and IM103027).

In Study IM103100, the belatacept LI (without Day 5 dosing) and MI regimens with either every 4 weeks (q-4 week) or every eight weeks (q-8 week) maintenance schedule were tested.

- **Bel MI**: 10 mg/kg on Day 1, 5 and 15, then every 2 weeks through to Month 3, then every 4 weeks through to Month 6, then 5 mg/kg every 4 or 8 weeks through to Month 12
- **Bel LI**: 10 mg/kg on Day 1, 15, 29, 57 and 85, then 5 mg/kg every 4 or 8 weeks through to Month 12

The target C_{trough} of belatacept was largely achieved for both LI and MI regimens, except that the C_{trough} of approximately 11 µg/mL on Day 15 fell below the target of 20 µg/mL for the LI regimen (without Day 5 dosing). While both regimens gave comparable results to CsA in the prevention of death and graft loss, the LI regimen without Day 5 dosing was associated with a higher frequency of subclinical rejection (17/71, 24%) than either the belatacept MI regimen (11/74, 15%) or the CsA regimen (13/72, 18%). The rates of subclinical AR were also numerically higher when subjects were treated with the belatacept q-8 week maintenance schedule compared to the q-4 week schedule.

Table 12. Comparison of 4 week versus 8 week maintenance therapy

Summary Statistics for Belatacept Pharmacokinetic Parameters		
PK Parameter	**4-week (n=14)**	**8-week (n=12)**
C_{max} (µg/mL) Geom. Mean (CV%)	136.3 (20)	124.6 (27)
$AUC_{(0\text{-}T)}$ (µg•h/mL)[a] Geom. Mean (CV%)	13587.1 (27)	10106.5 (27)
$AUC_{(INF)}$ (µg•h/mL)[b] Geom. Mean (CV%)	NR	10219.7 (28)
T_{max} (h) Median (min, max)	0.50 (0.48, 2.03)	0.55 (0.50, 1.92)
$T_{1/2}$ (h) Mean (SD)	NR	196.6 (57.2)
CLT (mL/h/kg) Mean (SD)	NR	0.51 (0.14)
V_{ss} (L/kg)	NR	0.12 (0.03)

Summary Statistics for Belatacept Pharmacokinetic Parameters		
Mean (SD)		
C_{min} (µg/mL) Mean (SD)	6.32 (2.83)	NR

a AUC(0-T) for 4 week schedule is $AUC^{(TAU)}$ where TAU = 4 weeks; T for 8-week schedule = 8 weeks.

b It is reasonable to calculate $AUC_{(INF)}$, CLT, and V_{ss} for subjects on the 8 week schedule were calculated since the terminal half life of belatacept is approximately 8 days and the 8 week duration represents a wash-out of 7 half-lives between doses and was adequate to characterize the elimination phase of the drug.

NR = Not reported

As the optimal dosing schedule could not be determined from the Phase II study, both dosing regimens were investigated in the Phase III studies with the following modification:

A q-4 week maintenance schedule was used for both regimens and

an additional dose of 10 mg/kg was given on Day 5 in the LI regimen to attain belatacept C_{trough} of 20 µg/mL during Month 1 post transplantation.

The MI regimen resulted in a 2 fold higher exposure to belatacept than the LI regimen during Months 2 to 7 posttransplantation.

Main (pivotal) studies

Study IM103008

Title: Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT). This study was reported in a series of reports; at 12 month, 24 month and 36 months. No report is available for the long term extension study (up to 5 years). This resulted in an extremely large volume of data (over 170 volumes of data). The summary below is for up to the 36 months analysis unless otherwise stated.

Deaths and Graft survival data are discussed under *Safety* below.

Methods

Primary objective

To evaluate the effects of belatacept, relative to cyclosporin (CsA), on:

- Composite endpoint of subject and graft survival by 12 months, 24 and 36 months.
- Composite endpoint of measured glomerular filtration rate (GFR) < 60 mL/min/1.73m^2 at month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73m^2 from month 3 to month 12
- Incidence of acute rejection (AR) by 12 months

Secondary objectives

To assess the effects of belatacept, relative to cyclosporin, on:

- Composite endpoint of subject and graft loss, and acute rejection by 12, 24 and 36 months
- Subject and graft survival by 24 and 36 months

- Individual components of the primary composite endpoint of measured GFR < 6 mL/min/1.73m^2 at month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73m^2 from month 3 to month 12
- Proportion of subjects with a measured GFR < 30 mL/min/1.73m^2 at 24 months
- Measured GFR at 3 and 24 months and change from baseline (3 months) to 12 months and to 24 months
- Proportion of subjects with a measured GFR < 30 mL/min/1.73m^2 at 12 and 24 months
- Proportion of subjects with a measured GFR < 60 mL/min/1.73m^2 at 12 and 24 months
- Calculated GFR at 6, 12, 24 and 36 months, and change from 6 months to 12, 24 and 36 months
- Measures of acute rejection by 6, 12, 24 and 36 months, including the incidence and severity of acute rejection, the use of polyclonal antilymphocyte preparations for impaired renal function and anticipated delayed graft function (DGF), the initial use of lymphocyte-depleting therapy (LDT) for treatment of acute rejection, the incidence of steroid-resistant acute rejection, the incidence of complete recovery (serum creatinine (SCr) returning to baseline) following acute rejection, the incidence of subclinical rejection, the incidence of all treated acute rejection episodes regardless of histological findings, and the time to onset of acute rejection
- Posttransplant diabetes mellitus (PTDM) by 12, 24 and 36 months
- Measures of hypertension at 12, 24 and 36 months, including serum total, non-high-density lipoprotein (HDL), low-density lipoprotein (LDL), HDL cholesterol and triglycerides, incidence and prevalence of dyslipidaemia and controlled dyslipidaemia and intensity of treatment regimen
- Overall safety of belatacept, relative to CsA
- Quality of Life (QoL) using SF-36[16] and Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD) scales.

Tertiary objectives

To assess the effects of belatacept, relative to cyclosporin on:

- Incidence of delayed graft failure (DGF)
- Proportion of subjects with Stage 1 through Stage 5 chronic kidney disease at 12 and 24 months as assessed by measured GFR
- Proportion of subjects with < 60 mL/min/1.73m2 calculated GFR at Month 12 or subjects with a decrease in calculated GFR from Month 3 to Month 12 of at least 10 mL/min/1.73m2

[16] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4-week recall) and acute (1-week recall).

- Proportion of subjects with Stage 1 through Stage 5 chronic kidney disease at 36 months as assessed by measured GFR
- Slope and intercept of calculated GFR from 3 months to 12, 24 and 36 months
- Composite cardiovascular disease endpoint (adjudicated cardiovascular death, myocardial infarction, ischemic stroke, and revascularisation [surgical or percutaneous] procedures) by 12, 24 and 36 months
- Composite cardiorenal disease endpoint (death, graft loss, non-fatal myocardial infarction, and stroke) by 12, 24 and 36 months
- Framingham Risk Score at 12, 24 and 36 months
- Incidence of discontinuation of study drug
- Anti-donor human leukocyte antigen (HLA) antibodies
- Angiotensin II type (AT_1) receptor antibodies
- C4d positivity in biopsy specimens

Study design

This is a Phase III randomised, active controlled, parallel-group study conducted at 104 sites in the following countries: USA (34 sites), India (10), France (7), Argentina (6), Brazil (6), Canada (6), Mexico (6), Australia (4), Germany (4), Italy (3), South Africa (3), Spain (3), Belgium (2), Switzerland (2), Poland (2) and one site in each of Austria, Czech Republic, Hungary, Israel, Sweden and Turkey.

Study participants

Study inclusion criteria were:

- Recipient of a living donor or deceased donor kidney transplant with an anticipated cold ischemic time (CIT) < 24 hours
- Male or female (not nursing, not pregnant) subjects ≥ 18 years of age
- Women of child-bearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the study in such a manner that the risk of pregnancy is minimised
- Willing to provide signed, written informed consent

Exclusion criteria were:

- Genetically-identical donor recipient pairs (ie identical twins) or donor < 10 years of age
- Subjects receiving an extended criteria donor organ as defined by donor age ≥ 60 years, or donor age 50-59 years and 1 of the following:
  - Cerebrovascular accident (CVA) + hypertension + serum creatinine (SCr) > 1.5 mg/dL, or
  - CVA + hypertension
  - CVA + SCr > 1.5 mg/dL
  - Hypertension + SCr > 1.5 mg/dL
  - Anticipated CIT ≥ 24 hours
  - Donor with cardiac death (non-heart beating donor)

- Underlying renal disease of: primary focal segmental glomerulosclerosis, Type I or II membranoproliferative glomerulonephritis, or haemolytic uraemic syndrome / thrombotic thrombocytopenic purpure syndrome
- Subjects undergoing primary (first-time) transplant with current panel reactive antibodies (PRA) ≥ 50%, or subjects undergoing retransplantation with a PRA ≥ 30%
- Previous graft loss due to acute rejection
- A positive T-cell lymphocytotoxic cross match
- Prior solid organ transplant (subjects undergoing kidney retransplantation are eligible pending other study criteria being met), or undergoing multi-organ (for example, kidney-pancreas) or concurrent solid organ or cell (islet, bone marrow, stem cell) transplants, or subjects who were deemed likely to have a second solid organ or cell transplant (for example, pancreas or islet transplant) in the next 3 years by the investigator
- Subjects receiving paired kidneys (dual or en bloc kidney transplants)
- Subjects who were or whose allograft donor was known to be hepatitis C or hepatitis B surface antibody-positive or polymerase chain reaction (PCR)-positive for hepatitis C or hepatitis B, or with known human immunodeficiency virus (HIV) infection
- Subjects at risk for TB (see Definitions)
- Had any active infection or other contraindication that would have normally excluded transplantation
- Impaired haematological, hepatic, or renal function, as determined by laboratory values
- Had a life expectancy severely limited by disease state or other underlying medical condition, a history of cancer (or other non-melanoma skin cell cancers cured by local reaction) within the last 5 years, and/or a mammogram that was suspicious for malignancy and in whom the possibility of malignancy could not have been reasonably excluded following additional clinical, laboratory, or other diagnostic evaluations
- History of substance abuse (alcohol or drug) within the past 5 years or psychotic disorders that were not compatible with adequate study follow-up
- Active peptic ulcer disease, chronic diarrhoea or gastrointestinal malabsorption
- History of true allergy to iodinated X-ray contrast agents
- Were currently receiving immunosuppressive agent(s) (such as methotrexate, infliximab, etanercept) for other indications, such as an autoimmune disease, or having co-morbidities such that treatment with immunosuppressive agents was likely during the trial
- Difficult IV access or other reasons that would have likely precluded assessment of the co-primary endpoint of measured GFR or subjects who were unlikely or unwilling to undergo the protocol-specified 12 month allograft biopsy
- Used any investigational drug within 30 days prior to the Day 1 visit or who had been previously treated with belatacept
- Prisoners or subjects who were compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (such as infectious disease) illness must not have been enrolled into this study.

Treatments

Subjects were randomised 1:1:1 to receive belatacept in either a More Intensive (MI) or Less Intensive (LI) regimen or to receive cyclosporin (CsA). All subjects also received a background regimen of basiliximab induction and maintenance therapy with mycophenolate mofetil (MMF) and corticosteroid maintenance therapy.

Belatacept – MI regimen

Subjects received intravenous (IV) belatacept (10 mg/Kg) on:

- Day 1 (intended to be given pre-operatively) and Day 5 during the first week
- then every other week through 3 months (Weeks 2, 4, 6, 8, 10 and 12)
- then every 4 weeks until 6 months (Weeks 16, 20 and 24)

After 6 months, subjects were to receive belatacept at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial at 36 months.

Belatacept – LI regimen

Subjects received intravenous (IV) belatacept (10 mg/Kg) on:

- Day 1 (intended to be given pre-operatively) and Day 5 during the first week
- and then every other week for 2 weeks (Weeks 2, and 4)
- and then every 4 weeks for 2 months (Weeks 8, and 12)

After 3 months, subjects were to receive belatacept at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial at 36 months.

Subjects in the LI regimen were administered 2 placebo infusions (dextrose 5% in water for injection or 0.9% normal saline solution) on Weeks 6 and 10 in order to preserve blinding between the LI and MI groups.

The infusion dose was based on the subject's actual body weight at study Day 1 and was not modified during the course of the study unless the subjects body weight changed by ± 10%. Belatacept was administered to the subject at a relatively constant rate over 30 minutes. The Day 1 and Day 5 (post-operative Day 4) doses were administered approximately 96 hours apart (± 6 hours).

Cyclosporin

CsA was administered in 2 divided doses on a consistent schedule in relation to time of day and meals. The initial daily dose was 7 ± 3 mg/kg. Subsequent doses were adjusted to maintain a pre-defined range of trough serum concentrations:

- First month: target level 150-300 ng/mL
- After first month: target level of 100-250 ng/mL.

Dosing of CsA could be initiated as early as 12 hours prior to transplant or postoperatively. Dosing could be delayed through Day 7 if in the clinical judgement of the investigator the administration of CsA was not in the best interest of the subject due to postoperative impairment of allograft function.

Background immunosuppressive therapy

Corticosteroids

All subjects received daily corticosteroids for the duration of the study. Corticosteroids were initiated at 500 mg IV preoperatively (Day 1) and were reduced to no less than 2.5 mg, oral (PO) daily for Days 15 – Month 6. The dose was to remain at no less than 2.5 mg PO daily through Month 36.

Mycophenolate Mofetil (MMF)

All subjects in this study were initially treated with MMF (2 g/day) orally in 2 divided doses. A higher dose (3 g/day) could be administered to African-Americans at the investigator's discretion. IV dosing was permitted if needed due to intercurrent illness. The first dose of MMF was administered preoperatively. Subsequent doses were administered as soon as the subject was able to tolerate medications by mouth and could be adjusted based on lab values (WBC) and subject tolerability.

Basiliximab

All subjects received induction therapy (2 doses) of basiliximab IV. The first dose (20 mg) was administered on Day 1 (day of transplant) and the second dose was given on Day 5 if the subject had not received and was not expected to receive LDT.

Treatment of rejection

During the first 12 months post transplant, the use of LDT (thymoglobulin or antithymocyte gamma globulin [ATGAM ®]) was permitted only for subjects randomised to CsA who experienced impaired renal allograft function and anticipated DGF following transplantation. After 12 months use of LDT was allowed for the treatment of AR in both belatacept and CsA treated subjects. Subjects with AR up to and including Banff Grade IIA were to be treated with corticosteroids. Treatment with LDT was recommended but not mandated for those with Banff Grade IIb and III rejection.

Study duration

The study duration is described variably in the different study reports and tabulated lists. It was planned to run for 3 years with analyses conducted at 12, 24 and 36 months. After the 36 months visit (Day 1092) the subjects were enrolled into a long term extension study which is continuing.

Outcomes/endpoints

The primary efficacy outcome was planned for evaluation at 12 months because of the likelihood of rejection occurring in the first 12 months. The follow up period of 36 months was to assess long term efficacy and safety.

Efficacy assessments

Each belatacept regimen was compared to the CsA based regimen on the following 3 co-primary efficacy measures:

- Composite endpoint of subject and graft survival by 12 months, using a non-inferiority design with a margin of 10% (see definitions)
- Composite endpoint of measured GFR < 60 mL/min/1.73m^2 at Month 12 or a decrease in measured GFR > 10 mL/min/1.73m^2 from Month 3 to Month 12, using a superiority test. (see definitions)
- Incidence of acute rejection (AR) by 12 months, using a non-inferiority design with a margin of 20% (see definitions)

Secondary objectives

A key secondary objective of this study was to evaluate the effects of belatacept relative to CsA on biopsy proven CAN at 12 months. A decrease in the proportion of subjects with chronic allograft nephropathy (CAN), in conjunction with an improvement in renal function, was expected to be a measure of a substantial medical benefit by belatacept in renal transplant recipients. Both prevalence (all subjects with CAN, including those with new onset or worsening CAN) and incidence (new onset) of CAN were evaluated primarily by biopsies obtained at 1 year posttransplant. Biopsy proven CAN was determined by a blinded central histopathologist using the Banff 97[17] working classification of kidney transplant pathology.

Other secondary outcomes were assessed as follows:

- New onset diabetes mellitus (NODM) [also known as post-transplant diabetes mellitus (PTDM)] (see definitions)
- Subject death or graft loss
- Hypertension (see *Definitions* above)
- Dyslipidaemia (see *Definitions* above)

Sample size

Sample size was calculated for each of the primary endpoints. A sample size of 220 subjects per group would afford 95% power to ascertain that a lower bound of the 97.3% (Dunnett's adjustment for the 2 belatacept regimens) 2-sided confidence intervals (CIs) for the absolute difference (between each belatacept regimen and the CsA regimen) in the first co-primary endpoint (subject and graft survival) did not exceed -10%, if the true subject and graft survival rate at Month 12 was 92% for the CsA regimen for all 3 regimens.

For the renal function endpoint, the sample size of 220 subjects per group afforded 99% power to detect a decrease of 25% in the proportion of subjects meeting the measured GFR endpoint for each belatacept regimen as compared with the CsA regimen, assuming 75% (estimated from the Phase II study) of CsA subjects met the renal function endpoint and 25% drop-outs per treatment group.

For the AR co-primary endpoint, 220 subjects per group provided 99% power to ascertain that the upper bound of the 97.3% 2-sided CIs for the absolute difference (between each belatacept regimen and CsA regimen) would not exceed 20%, assuming the true AR rate by 12 months was 15% for all 3 regimens.

Overall 220 subjects per treatment group afforded 93% power to detect 1 belatacept regimen that met all co-primary endpoints with overall Type 1 error controlled at the 0.05 significance level (using Dunnett adjustment).

Randomisation

Randomisation was by a centralised call-in system. Subject randomisation was stratified by study site. No further information is provided on the method of randomisation.

[17] Raeusen LC, Solez K, Colvin T, et al. The Banff 97 Working Classification of Renal Allograft Pathology. Kidney Int. 1999; 55: 713-723

Blinding (masking)

The study was fully blinded through 12 months with respect to assignment of belatacept dose regimen MI and LI but open label with respect to allocation to treatment with belatacept or cyclosporin. Subjects in the LI regimen were administered 2 placebo infusions (dextrose 5% in water for injection or 0.9% normal saline solution) on Weeks 6 and 10 in order to preserve blinding between the LI and MI groups.

The assigned dosing group (MI or LI) of the belatacept treated subjects was blinded to subjects and study site personnel. At the study site only the pharmacist had knowledge of the randomised dose.

No subjects were unblinded in the first 12 month period.

Statistical methods

Co-primary endpoints

Subject and Graft Survival at Month 12: summarised within each treatment group using point estimates of the proportion of subjects surviving with the graft, and the corresponding 95% CIs. Two-sided 97.3% CI were generated for the difference between each belatacept regimen and CsA to assess the effect of belatacept. If the lower bound of the CI (belatacept-CsA) as > -10%, then the corresponding belatacept regimen as considered non-inferior to CsA.

Composite endpoint of measured GFR: proportion of subjects with a measured GFR < 60 mL/min/1.73m^2 at Month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73m^2 from Month 3 to Month 12. A continuity-corrected chi-square test (at a significance level of 0.027) was performed to assess the effect of each belatacept regimen on renal function compared to CsA. Two sided 97.3% CIs were generated for the difference in the proportion of subjects meeting the composite renal function endpoint between each belatacept regimen and CsA.

Acute rejection: summarised using point estimates for the proportion of subjects who experienced AR by 12 months in each group, and the corresponding 95% CIs. Two-sided 97.3% CIs were generated for the difference between each belatacept regimen and CsA to assess the effect of belatacept. If the upper bound of the CI (belatacept – CsA) was < 20%, then the corresponding belatacept regimen was considered non-inferior to CsA.

Key secondary endpoint

Measured GFR at Month 12: using an analysis of variance (ANOVA) model with factor for randomisation group (treatment) to assess the difference between each belatacept group and CsA. Each test comparing a belatacept group to CsA was conducted at a level of 0.027 (two-sided).

Prevalence of CAN at Month 12: summarised using point estimates of the respective proportion, 95% CIs within each treatment group, and 97.3% CIs between each belatacept group and CsA (belatacept-CsA). A continuity corrected Chi-square test (at the significance level 0.027) was performed to assess the effect of each belatacept regimen compared with CsA.

Hypertension related endpoints: the primary assessment of hypertension was based on the intensity of anti-hypertensive therapy at Month 12. The intensity of anti-hypertensive therapy was taken as the number of unique antihypertensive medications that the subject was taking on the target day. The intensity of anti-hypertensive therapy for a non hypertensive subject at a particular time point was zero. Analysis was performed using a cumulative logit model with treatment groups as the covariate. Odds ratios between each of the belatacept treatment groups and CsA, as the corresponding 97.3% CIs obtained by exponentiating the constructed 97.3% CIs for the treatment effect estimates were provided. Chi-square test (Wald Chi-square) was used to

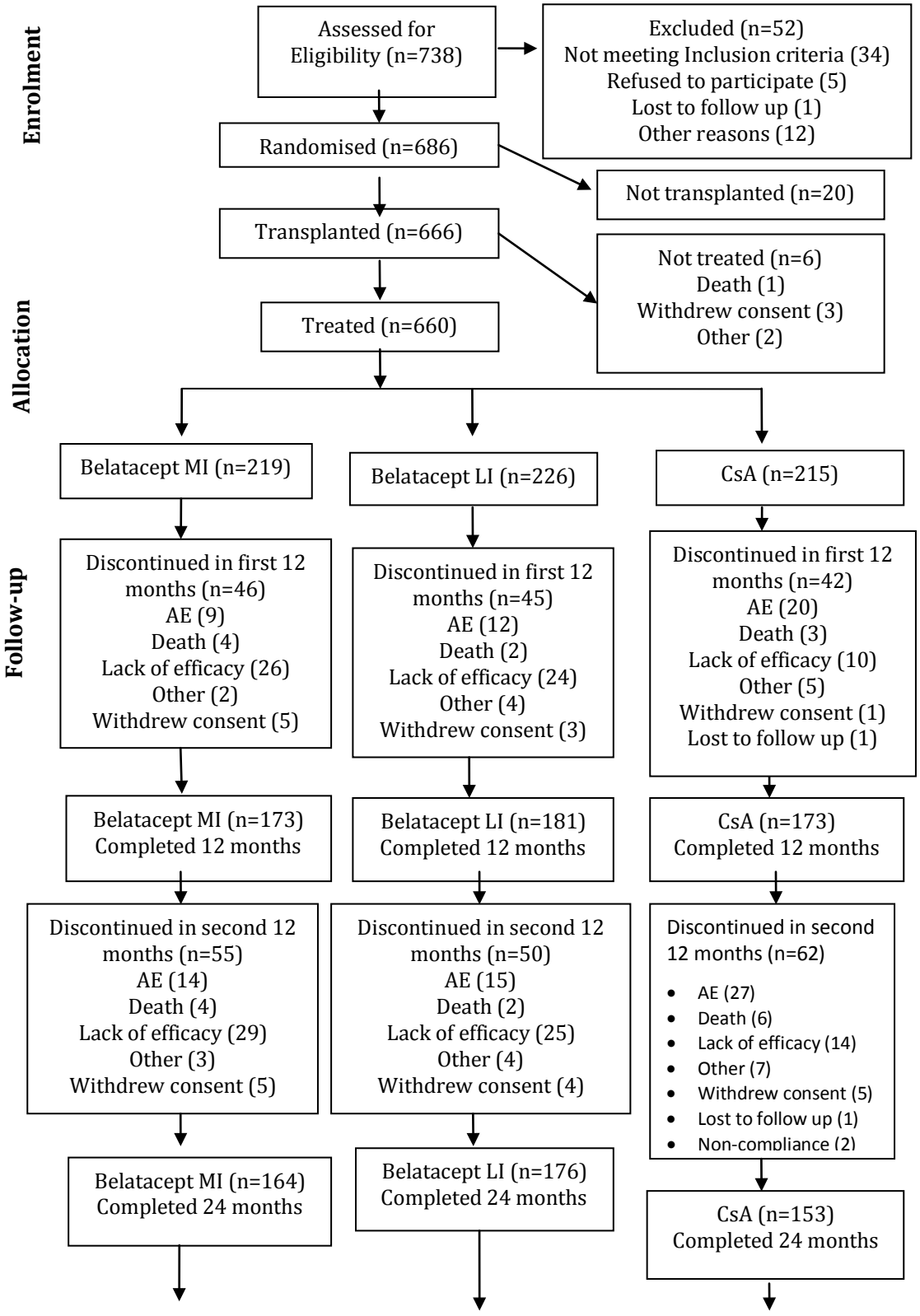
test the treatment differences between each belatacept treatment group and CsA group at the 0.027 significance level.

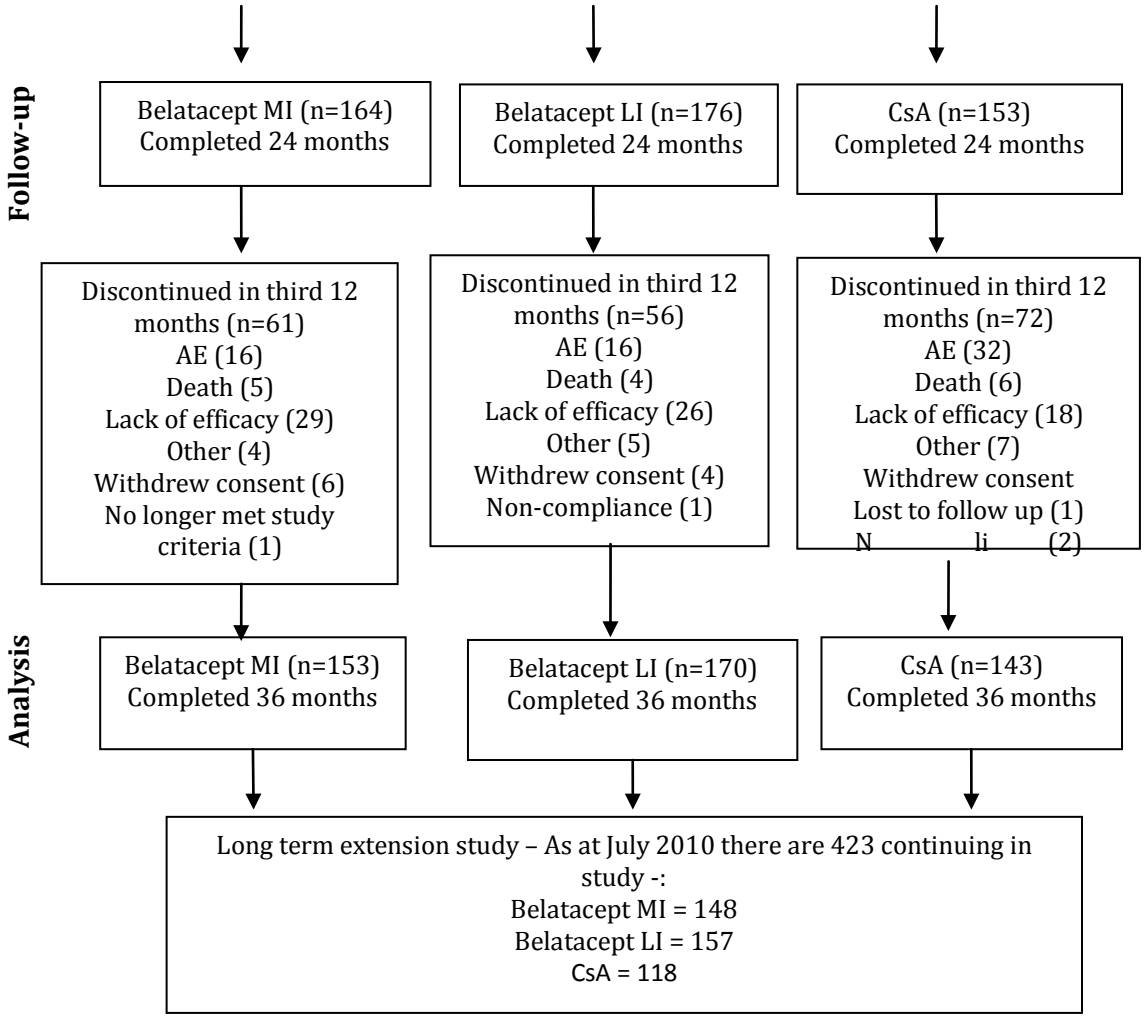
New Onset Diabetes Mellitus (NODM): was summarised with the 95% CIs. Continuity adjusted Chi-square test was performed at a significance level of 0.027 for comparison between each of the belatacept group and CsA at specified time points. Hba1C is descriptively summarised.

Results

Participant flow

Figure 7. Participant flow. Figure continued across two pages.





Recruitment

No information is provided on how subjects were identified and recruited. The study sites were initiated on a staggered timeframe from April 2005 (USA) to March 2007 (India). The Australian sites were initiated during April 2006.

The study started on (first subject first visit) in January 2006 and study completed (last subject last visit) in June 2008 for Month 12 analysis.

Conduct of the study

The study was monitored by 2 CROs and internally audited by BMS (16 out of 104 sites). No major problems at any sites are identified.

There were 9 protocol amendments during the course of the study. Only one was of major significance; in December 2006 an amendment to the protocol added a pharmacokinetic substudy to characterise the PK of belatacept in renal transplant subjects as part of the population PK analysis (details in *Pharmacokinetic* section of this report).

The subjects in the trial were seen at different times depending on their treatment allocation. Subjects receiving belatacept were seen at the clinic on each treatment day (due to infusion) but for subjects randomised to CsA treatment, the subjects were only required to attend the clinic visits at Weeks 2, 4, 8 and 12; then at every 3 months. At the non-3 month interval visits (that is,

Weeks 6, 10, 16, 20, 28 32 and so on) a telephone contact was conducted to collect adverse event (AE) information.

Samples for urinalysis, haematology, and blood chemistry analysis were taken at baseline, Day 5 and protocol specified monthly or 3 monthly visits.

Two Data Monitoring Committees (DMC) reviewed data from the study on an ongoing basis. One committee reviewed all cardiovascular events and one committee reviewed subject and graft survival.

Baseline data

Baseline characteristics are generally balanced among the treatment groups.

Table 13. Baseline Characteristics of Transplant Recipients: All Randomised and Transplanted Subjects (ITT). Table continued across two pages.

Baseline Characteristics	Belatacept MI N = 219	Belatacept LI N = 226	Cyclosporine N = 221
Mean Age (y)	43.6	42.6	43.5
Gender	**(n, %)**	**(n, %)**	**(n, %)**
Male	151 (68.9)	146 (64.6)	165 (74.7)
Female	68 (31.1)	80 (35.4)	56 (25.3)
Race (n, %)			
White	132 (60.3)	133 (58.8)	139 (62.9)
Black	15 (6.8)	23 (10.2)	17 (7.7)
Asian	27 (12.3)	29 (12.8)	27 (12.2)
Other	45 (20.5)	41 (18.1)	38 (17.2)
Geographic Region	**(n, %)**	**(n, %)**	**(n, %)**
North America	95 (43.4)	92 (40.7)	94 (42.5)
South America	35 (16.0)	36 (15.9)	33 (14.9)
Europe	55 (25.1)	64 (28.3)	58 (26.2)
Rest of World (Asia/Pacific)	32 (14.6)	33 (14.6)	34 (15.4)
Africa	2 (0.9)	1 (0.4)	2 (0.9)
Highest PRA < 20% (n, %)	165 (75.3)	164 (72.6)	168 (76.0)
Reported Cause of End Stage Renal Disease	**(n, %)**	**(n, %)**	**(n, %)**

Baseline Characteristics	Belatacept MI N = 219	Belatacept LI N = 226	Cyclosporine N = 221
Glomerulonephritis	48 (21.9)	73 (32.3)	55 (24.9)
Diabetes	31 (14.2)	22 (9.7)	26 (11.8)
Polycystic Kidneys	31 (14.2)	31 (13.7)	30 (13.6)
Hypertensive Nephrosclerosis	21 (9.6)	22 (9.7)	22 (10.0)
Renovascular and Other	4 (1.8)	4 (1.8)	4 (1.8)
Congenital, Familial, and Metabolic	9 (4.1)	7 (3.1)	7 (3.2)
Tubular and Interstitial Diseases	10 (4.6)	12 (5.3)	13 (5.9)
PRA – panel reactive antibodies			

Transplant Characteristics			
Transplant Characteristics	**Belatacept MI**	**Belatacept LI**	**Cyclosporine**
	N = 219	**N = 226**	**N = 221**
Type of Transplant (n, %)			
Living-related	91 (41.6)	99 (43.8)	91 (41.2)
Living-unrelated	41 (18.7)	30 (13.3)	33 (14.9)
Cadaveric	87 (39.7)	97 (42.9)	97 (43.9)
Mean Cold Ischemia Time (h)			
Living transplant	1.4	1.3	1.5
Cadaveric transplant	15.4	16.7	16.7
Total Number of HLA-Mismatches (n, %)			
0-2	50 (22.8)	60 (26.5)	56 (25.3)
3-4	121 (55.3)	113 (50.0)	110 (49.8)
5-6	42 (19.2)	48 (21.2)	49 (22.2)

Numbers analysed

ITT dataset = 666 = all subjects randomised and transplanted – used for primary efficacy and safety analysis = 219 belatacept MI, 226 belatacept LI, 221 CsA

Per-Protocol (PP) dataset = 646 at 12 months = all randomised and transplanted subjects who did not violate terms of the protocol that might affect efficacy outcomes – used for secondary efficacy analysis = 217 belatacept MI, 221 belatacept LI, 208 CsA

As treated dataset = 660 at 12 months – all randomised subjects who received a renal transplant and at least 1 dose of study medication = 219 belatacept MI, 226 belatacept LI, 215 CsA

At database lock for the 36 month report (July 2010) there were 423 subjects continuing in the study.

Outcomes

Results are presented only for the ITT dataset. Results for PP and as treated datasets are similar. The results presented in the 36 month report are different to those presented in the 12 month clinical study report and 24 month CSR. The 24 month CSR states that it includes updates to the database received after database lock for the Month 12 CSR. The differences are slight but results presented here are taken from the 36 month analysis.

Table 14. Summary of Key Efficacy Outcomes at Month 36 ITT dataset. Table continued across two pages.

	Belatacept MI N = 219	Belatacept LI N = 226	CsA N = 221
Subject and Graft Survival (n, %)[a]			
Month 12*	**209 (95.4)**	**218 (96.5)**	**205 (92.8)**
Difference from CsA (97.3% CI)	2.2 (-2.9, 7.5)	3.2 (-1.5, 8.4)	-
Graft Loss (n, %)	4 (1.8)	5 (2.2)	8 (3.6)
Death (n, %)	6 (2.7)	4 (1.8)	7 (3.2)
Imputed as Graft Loss or Death	0	0	1 (0.5)
Month 24	**206 (94.1)**	**214 (94.7)**	**200 (90.5)**
Difference from CsA (97.3% CI)	3.6 (-2.2, 9.6)	4.2 (-1.3, 10.1)	-
Graft Loss (n, %)	7 (3.2)	5 (2.2)	8 (3.6)
Death (n, %)	7 (3.2)	8 (3.5)	13 (5.9)
Imputed as Graft Loss or Death	0	0	1 (0.5)

Month 36	**202 (92.2)**	**208 (92.0)**	**196 (88.7)**
Difference from CsA (97.3% CI)	3.5 (-2.8, 10.0)	3.3 (-2.9, 9.8)	-
Graft Loss (n, %)	10 (4.6)	9 (4.0)	10 (4.5)
Death (n, %)	9 (4.1)	10 (4.4)	15 (6.8)
Imputed as Graft Loss or Death	0	0	1 (0.5)
Composite Endpoint for Measured GFR (mL/min/1.73 m²): **< 60 or decr ≥ 10 from Month 3 to 12 (n, %)[a]**	**115 (55.0)**	**116 (54.2)**	**166 (77.9)**
Difference from CsA (97.3% CI)	-22.9 (-32.6, -12.9)	-23.7 (-33.3, -13.7)	-
P-Value	< 0.0001	< 0.0001	
Measured GFR < 60 (n, %)	91 (43.5)	92 (43.0)	144 (67.6)
Decrease in measured GFR ≥ 10 from Month 3 to Month 12 (n, %)	48 (23.0)	50 (23.4)	60 (28.2)
Mean (SD) measured GFR with imputation[b] (mL/min/1.73 m²)			
Month 12	**65.0 (30.0)**	**63.4 (27.7)**	**50.4 (18.7)**
Estimated difference from CsA (97.3% CI)*	14.6 (8.9, 20.4)	13.0 (7.3, 18.7)	-
P-Value	< 0.0001	< 0.0001	
Month 24	**65.0 (27.2)**	**67.9 (29.9)**	**50.5 (20.5)**
Estimated difference from CsA (97.3% CI)*	14.5 (8.5, 20.5)	17.5 (11.5, 23.4)	-
P-Value	< 0.0001	< 0.0001	
Month 36 not performed per protocol			
Mean (SD) calculated GFR with imputation[b] (mL/min/1.73 m²)			
Month 12*	**65.2 (23.5)**	**65.4 (22.9)**	**50.1 (21.0)**
Difference from CsA (97.3% CI)	15.1 (10.1, 20.1)	15.3 (10.3, 20.3)	-

Month 24	**65.5 (24.8)**	**65.4 (25.2)**	**47.9 (23.0)**
Difference from CsA (97.3% CI)	17.6 (12.0, 23.3)	17.5 (12.0, 23.1)	-
Month 36	**65.2 (26.31)**	**65.8 (27.00)**	**44.4 (23.58)**
Difference from CsA (97.3% CI)	20.8 (14.8, 26.9)	21.4 (15.4, 27.4)	-
Acute Rejection (n, %)[a,c]			
Month 12*	**49 (22.4)**	**39 (17.3)**	**16 (7.2)**
Difference from CsA (97.3% CI)	15.1 (7.9, 22.7)[d]	10.0 (3.3, 17.1)	-
Month 24	**53 (24.2)**	**39 (17.3)**	**20 (9.0)**
Difference from CsA (97.3% CI)	15.2 (7.5, 23.0)[d]	8.2 (1.2, 15.4)	-
Month 36	**53 (24.2)**	**39 (17.3)**	**21 (9.5)**
Difference from CsA (97.3% CI)	14.7 (7.0, 22.6)[d]	7.8 (0.6, 15.0)	-
Prevalence of CAN (n, %) at 12 months	**40 (18.3)**	**54 (23.9)**	**71 (32.4)**
Difference from CsA (97.3% CI)	-14.2 (-23.2, -5.0)	-8.5 (-17.9, 0.9)	–
Delayed Graft Function (n, %) at 12 months			
Living transplant	5 (3.8)	5 (3.9)	7 (5.6)
Cadaveric transplant	30 (34.5)	26 (26.8)	33 (34.0)

CAN – chronic allograft nephropathy, CI – confidence interval, CsA – cyclosporine, GFR – glomerular filtration rate, LI – less intensive, MI – more intensive, SD – standard deviation

a Co-primary endpoint

b. Imputation method: No imputation for subjects with graft loss or death, however, if a value was available, it was used in the analysis. For other missing data, measured GFR at other time points or cGFR at the same time point was used to impute the missing values at Month 12 or 24. For cGFR for missing data due to graft loss or death, cGFR after graft loss or death was imputed as 0 by Month 36.

c. Acute Rejection (AR) defined as central biopsy proven rejection that was either (1) clinically suspected by protocol defined reasons or (2) clinically suspected by other reasons and treated.

d Did not meet the 20% protocol-specified margin for non-inferiority to CsA

Summary

12 month efficacy outcomes

Subject and graft survival in the Belatacept MI and LI groups at Month 12 was comparable to that of CsA, meeting the pre-specified 10% non-inferiority margin

Both belatacept regimens (MI and LI) resulted in improvement in renal function at Month 12 as assessed by measured GFR and calculated GFR

- For the composite endpoint for measured GFR, MI and LI regimens were significantly (P<0.0001) better than CsA for the composite endpoint (measured GFR <60 mL/min/1.73 m2 at Month12, or with a decrease in measured GFR <60 mL/min/1.73 m2 from Month 3 to Month 12).
- Mean measured GFR at Month 12 was 14.6 (MI) and 12.9 (LI) mL/min/1.73 m2 higher than in CsA. Results based on calculated GFR were consistent

The proportion of subjects with AR at Month 12 was higher in the belatacept MI (22%) and LI (17%) groups compared with the CsA group (7%).

- The LI regimen met the 20% protocol specified margin for non-inferiority to CsA. The MI regimen did not meet the 20% protocol specified margin for non-inferiority to CsA.
- Rates of Banff grade Iia, Iib and III rejections were more frequent in the belatacept treated subjects. Most rejections occurred by Month 6
- Rates of corticosteroid-resistant rejections (5.9%, 4.4%, 0%) and initial use of LDT to treat rejection (5.9%, 4.4%, 0.9%) were higher in belatacept MI and LI treated subjects than in CsA treated subjects, respectively. Ten subjects (1, 1, and 8 in the MI, LI and CsA groups respectively) received LDT for anticipated delayed graft function (DGF).

Rates of subclinical rejection on the Month 12 protocol biopsy were similar and low across treatment groups (MI: 4%, LI: 5% and CsA: 5%).

The prevalence of CAN at Month 12 was 18%, 24% and 32% in the belatacept MI, LI and CsA groups, respectively.

Rates of DGF were comparable across the treatment groups.

36 month efficacy outcomes

Death and Graft Loss:

Comparable rates of death (4%, 4% and 7% respectively) and graft loss (5%, 4%, and 5% respectively) from transplantation up to Month 36 were observed across the belatacept MI, LI and CsA treatment groups

Renal Function:

The difference in renal function, as assessed by cGFR, between belatacept and CsA seen at Months 12 and 24 was maintained; at Month 36 differences between both belatacept groups and CsA were approximately 21 mL/min/1.73m^2. Measured GFR was not obtained at Month 36 as designed in the protocol.

The annual rate of change in cGFR from Month 3 to Month 36 was 1.0, 1.2, and -2.0 mL/min/1.73m^2/year for the belatacept MI, LI and CsA groups, respectively.

Chronic kidney disease stage based on cGFR at Month 36 showed greater proportions of subjects with Stage 1 and 2 and fewer subjects with Stage 4 and 5 in the belatacept groups compared with CsA.

Subjects receiving belatacept experienced a delay in the time to progression to advanced renal dysfunction (CKD Stage 4 and 5), graft loss or death as compared with subjects treated with CsA. By 3 years after transplantation, approximately 25% CsA subjects and 10% of belatacept subjects had reached this endpoint.

Acute rejection:

Up to 36 months, AR occurred in 24% (MI), 17% (LI) and 10% (CsA). Most cases of AR occurred by Month 6. More cases of AR were classified as Banff Grade IIb and III in the MI or LI, 1 new case occurred in the CsA group.

Through Month 36 there were comparable rates of the composite endpoint of BPAR, death, graft loss and loss to follow up between treatment groups.

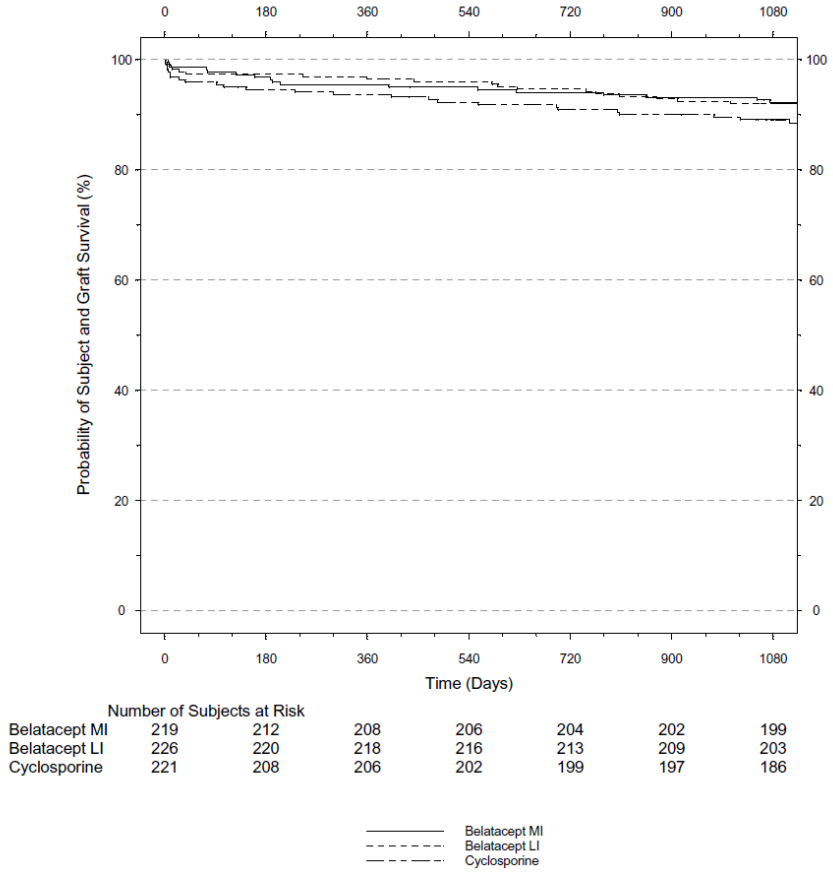
Impact of AR by month 24 on outcomes up to month 36

The overall rate of death by Month 36 in subjects with AR was 9% (5 subjects) in the belatacept MI group, 13% (5 subjects) in the belatacept LI group and 0% in the CsA group; in subjects without AR the rate was 2% (4 subjects) in the belatacept MI group, 3% (5 subjects) in the belatacept LI group and 8% (15 subjects) in the CsA group.

The overall rate of graft loss by Month 36 in subjects with AR was 9% (5 subjects) in the belatacept MI group, 13% (5 subjects) in the belatacept LI group and 5% (1 subject) in the CsA group; in subjects without AR the rate was 3% (5 subjects) in the belatacept MI group, 2% (4 subjects) in the belatacept LI group and 5% (9 subjects) in the CsA group.

Renal function (cGFR as observed or with imputation) at Month 36 was lower in subjects with AR than without AR in all treatment groups.

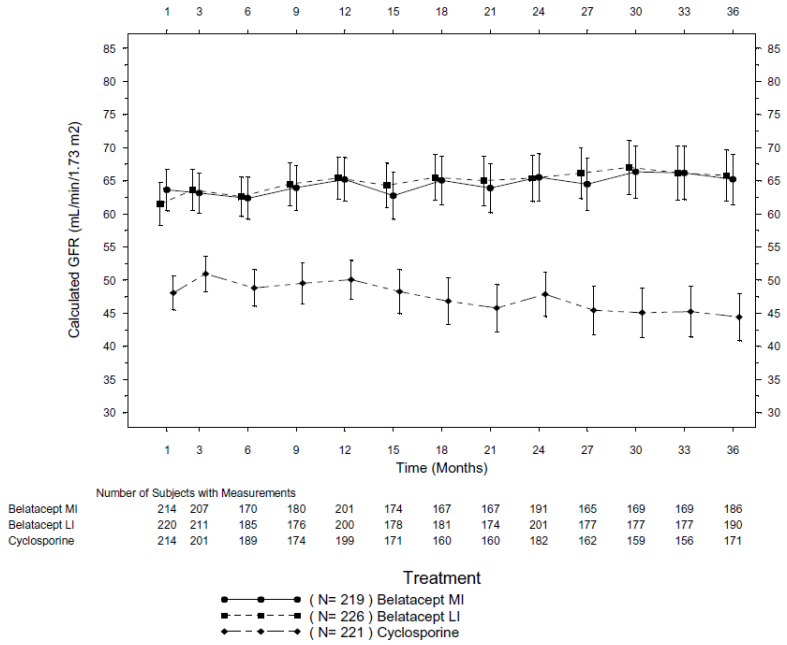
Figure 8. Kaplan-Meier estimates of subject and graft survival: All randomised and transplanted subjects.



Number of Subjects at Risk

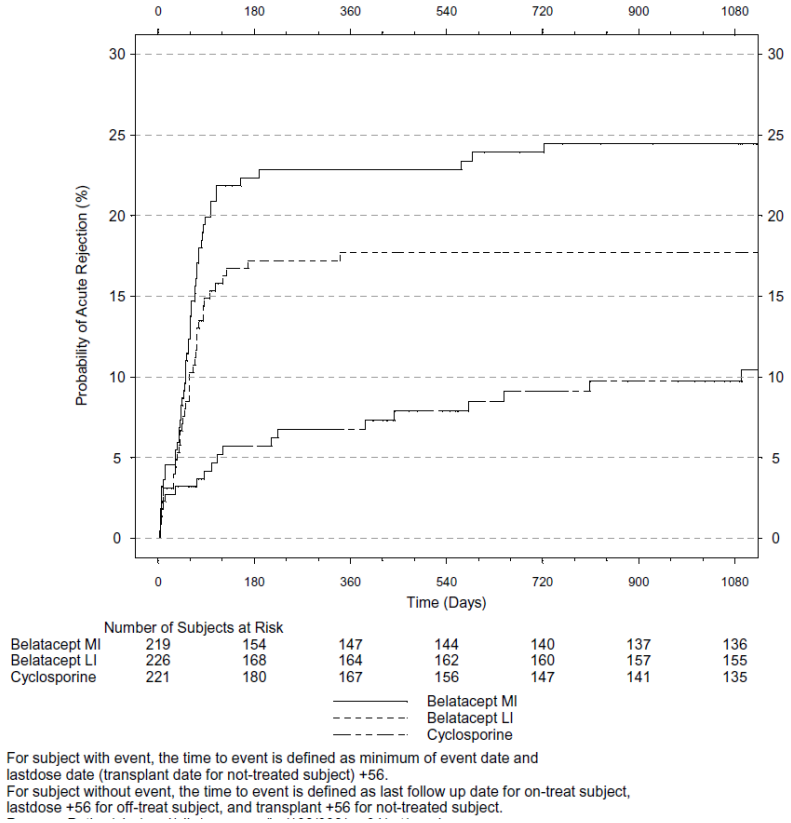
Belatacept MI	219	212	208	206	204	202	199
Belatacept LI	226	220	218	216	213	209	203
Cyclosporine	221	208	206	202	199	197	186

Figure 9. Summary of cGFR with imputation posttransplantation: All randomised and transplanted subjects.



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

Figure 10. Kaplan-Meier estimates of acute rejection. All randomised and transplanted subjects. On-treatment Analysis.



Composite endpoint of acute rejection, death or graft loss

Table 15. Composite endpoint

Composite endpoint	Belatacept MI	Belatacept LI	Cyclosporin
ITT No subjects	219	226	221
No at 12 months (%)	55 (25)	44 (20)	30 (14)
No at 24 months (%)	57 (28)	53 (20)	52 (18)
No at 36 months (%)	62 (28)	47 (21)	44 (20)

Differences between treatment groups are driven by the AR frequencies, the majority of which occurred by Month 6.

Metabolic effects:

By Month 36, the incidence of NODM was 10%, 7% and 11% in the belatacept MI, LI and CsA groups, respectively

At Month 36, BP was lower in belatacept groups compared to CsA by approximately 6 to 8 mmHg (SBP) and approximately 3 mmHg(DBP)

Belatacept-treated subjects were less likely to use antihypertensive medications compared to CsA treated subjects; in the belatacept MI group there was a 40% reduction (p=0.0092) and in

the belatacept LI group a 50% reduction in the odds of using antihypertensive medication (p= 0.0002)

Mean non-HDL cholesterol levels increased from baseline to Month 36 in the CsA group and decreased in the belatacept groups (decreased by approximately 3 mg/dL in belatacept versus increased by approximately 16 mg/dL in CsA (p<0.0001)

Triglyceride levels at Month 36 decreased in the belatacept groups (adjusted mean change: 32 to 43 mg/dL), and increased by approximately 1 mg/dL in the CsA group.

Mean LDL cholesterol levels increased in the belatacept LI and the CsA group with a larger increase in the CsA group.

At Month 36, mean HDL cholesterol levels increased slightly in all treatment groups (by approximately 3 to 4 mg/dL in the belatacept groups and by approximately 5 mg/dl in the CsA group).

The proportions of subjects using lipid-lowering therapy were lower in belatacept versus CsA treated subjects (46% to 48% in the belatacept groups and 57% in the CsA group).

Table 16. Effects on Cardiovascular and Metabolic Endpoints at/by Month 36

	Belatacept MI	Belatacept LI	CsA
	N = 219	**N = 226**	**N = 221**
	N = 156	**N = 168**	**N = 162**
Incidence of NODM (n, %)	**16 (10.3)**	**11 (6.5)**	**18 (11.1)**
P-Value	0.9481	0.2043	---
Estimated Diff. From CsA (97.3% CI)	-0.9 (-8.8, 7.1)	-4.6 (-12.0, 2.5)	---
Mean (SD) Blood Pressure (mmHg)	**N = 166**	**N = 180**	**N = 145**
Systolic	126.0 (16.14)	127.7 (16.48)	133.5 (17.93)
Estimated Diff. From CsA (97.3% CI)	-7.5 (-11.7,-3.3)	-5.8 (-10.0,-1.6)	---
Diastolic	76.1 (11.20)	76.6 (9.75)	79.5 (9.16)
Estimated Diff. From CsA (97.3% CI)	-3.4 (-6.0, -0.9)	-2.9 (-5.4, -0.4)	---
Use of Anti-hypertension Medications (n, %)	**N = 192**	**N = 199**	**N = 182**
1-2 Medications	101 (52.6)	111 (55.8)	95 (52.2)
≥3 Medications	60 (31.3)	52 (26.1)	74 (40.7)

	Belatacept MI	Belatacept LI	CsA
Odds Ratio[a]	0.6	0.5	---
P-Value	0.0092	0.0002	---
	Belatacept MI	**Belatacept LI**	**CsA**
Dyslipidemia	**N = 168**	**N = 175**	**N = 146**
Non-HDL cholesterol: adjusted mean (SE)change from baseline	-3.2 (2.928)	-2.7 (2.869)	16.3 (3.141)
Estimated Diff. From CsA (97.3% CI)	-19.5 (-29.0,-9.9)	-19.0 (-28.5, -9.6)	---
P-Value -	<0.0001	<0.0001	--
Use of Antihyperlipidemic Medications (n, %)	**N = 192**	**N = 199**	**N = 103**
≥1 Medication	92 (48)	92 (46)	103 (57)
% Diff. From CsA (97.3% CI)	-8.7 (-19.9, 2.7)	-10.4 (-21.4, 1.0)	---
a Compared with CsA, belatacept MI provides a 40% reduction and belatacept LI provides a 50%reduction in the odds of requiring more anti-hypertensive medications at Month 36.			

Table 17. Adjusted Mean Change from Baseline to Month 36 in Lipid Values

Parameters	Belatacept MI	Belatacept LI	Cyclosporine
	N = 219	**N = 226**	**N =221**
Non-HDL Cholesterol (mg/dL)	**N = 168**	**N = 175**	**N = 146**
Baseline Mean (SD)	124.7 (40.45)	123.8 (47.63)	125.5 (38.45)
Month 36 (SD)	121.5 (37.29)	121.6 (40.12)	141.2 (42.66)
Adjusted mean change from baseline to Month 36 (SE)	-3.2 (2.928)	-2.7 (2.869)	16.3 (3.141)
Total Cholesterol (mg/dL)	**N = 168**	**N = 175**	**N = 146**
Baseline Mean (SD)	169.7 (43.91)	169.6 (48.28)	169.2 (40.35)

Parameters	Belatacept MI	Belatacept LI	Cyclosporine
Month 36 (SD)	170.5 (42.14)	169.7 (44.72)	189.9 (45.09)
Adjusted mean change from baseline to Month 36 (SE)	0.9 (3.237)	0.2 (3.172)	20.5 (3.473)
Triglyceride (mg/dL)	**N = 140**	**N = 145**	**N = 117**
Baseline Mean (SD)	173.7 (129.21)	168.7 (98.41)	179.6 (172.21)
Month 36 (SD)	141.6 (80.18)	129.8 (64.16)	176.1 (99.66)
Adjusted mean change from baseline to Month 36 (SE)	-32.1 (6.415)	-42.8 (6.305)	1.1 (7.020)
HDL Cholesterol (mg/dL)	**N = 168**	**N = 175**	**N = 146**
Baseline Mean (SD)	45.0 (14.75)	45.8 (15.41)	43.7 (13.25)
Month 36 (SD)	49.0 (16.91)	48.1 (14.53)	48.8 (14.53)
Adjusted mean change from baseline to Month 36 (SE)	4.1 (0.963)	2.6 (0.944)	4.6 (1.034)
LDL Cholesterol (mg/dL)	**N = 140**	**N = 145**	**N = 117**
Baseline Mean (SD)	90.5 (34.14)	91.2 (39.31)	91.6 (30.68)
Month 36 (SD)	90.9 (32.49)	96.1 (36.86)	107.1 (39.10)
Adjusted mean change from baseline to Month 36 (SE)	0.0 (2.938)	5.0 (2.887)	15.9 (3.214)

Quality of Life

Improvements from baseline to Month 36 were observed in physical component scores and mental component scores for belatacept MI (6.1, 4.5 points), belatacept LI (6.5, 5.1 points) and CsA (4.9, 2.6 points) respectively but were not statistically significantly different.

Differences between treatment groups on SF-36 mean scores at Month 36 and mean change from baseline were small and not consistently statistically significant.

The ridit analyses[18] showed that subjects in the belatacept groups had lower probability of symptom occurrence and symptom distress (MTSOSD) compared to CsA at Month 36 ($p<0.0001$ for belatacept LI).

[18]Ridit scoring is a way of recoding variables in a data set so that one has a measure not of their absolute values but their positions in the distribution of observed values.

Evaluator's note: One minor concern is the higher level of withdrawal due to lack of efficacy in each year with belatacept compared to CsA which was not commented on by the sponsor.

Study – IM103027

Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosupression Trial – Extended Criteria Donors (BENEFIT-EXT).

This study was reported in a series of reports; at 12 month, 24 month and 36 months. The summary below is for up to the 36 months analysis unless otherwise stated.

Methods

Objectives

The primary objective was to evaluate the effects of belatacept, relative to CsA, on:

- Measured GFR at 12 months
- Biopsy proven CAN at 12 months

Secondary objectives: to assess the effects of belatacept, relative to CsA on:

- Composite endpoint of death, graft loss and acute rejection by 12, 24 and 36 months
- Subject and graft survival by 24 and 36 months
- Individual components of the primary endpoint of measured GFR < 60 mL/min/1.73m^2 at Month 12 or a decrease in measured GFR ≥ mL/min/1.73 m^2 from Month 3 to Month 12
- Proportion of subjects with a measured GFR < 60 mL/min/1.73 m^2 at 24 months
- Measured GFR at 3 and 24 months and change from baseline (3 months) to 12 months and to 24 months
- Proportion of subjects with a measured GFR < 30 mL/min/1.73 m^2 at 12 and 24 months
- Proportion of subjects with a calculated GFR < 60 mL/min/1.73 m^2 at 24 and 36 months
- Calculated GFR at 6, 12, 24 and 36 months and change from 6 months to 12, 24 and 36 months
- Measures of acute rejection by 6, 12, 24, and 36 months, including the incidence and severity of acute rejection, the use of polyclonal antilymphocyte preparations for impaired renal function and anticipated delayed graft function (DGF) for treatment of acute rejection, the incidence of steroid-resistant acute rejection, the incidence of complete recovery (serum creatinine [SCr] returning to baseline) following acute rejection, the incidence of subclinical rejection, the incidence of all treated acute rejection episodes regardless of histological findings, and the time to onset of acute rejection
- New onset diabetes mellitus (NODM, also called post transplant diabetes mellitus [PTDM]) by 12, 24 and 36 months
- Measures of hypertension at 12, 24 and 36 months, including SBP and DBP, incidence and prevalence of hypertension and controlled hypertension, and intensity of treatment regimen
- Measures of dyslipidaemia at 12, 24 and 36 months, including serum total, non-high-density lipoprotein (non-HDL), low density lipoprotein (LDL) and HDL cholesterol, and triglycerides, incidence and prevalence of dyslipidaemia and controlled dyslipidaemia and intensity of treatment regimen
- Overall safety of belatacept relative to CsA

- QoL

Tertiary objectives: to assess the effects of belatacept, relative to CsA on:

- Incidence of delayed graft function (DGF)
- Proportion of subjects with Stage 1 through Stage 5 chronic kidney disease at 12 and 24 months as assessed by measured GFR
- Proportion of subjects with < 60 mL/min/1.73m^2 calculated GFR at Month 12 or subjects with a decrease in calculated GFR from Month 3 to Month 12 of at least 10 mL/min/1.73m^2
- Proportion of subjects with Stage 1 through Stage 5 chronic kidney disease at 36 months as assessed by calculated GFR
- Slope and intercept of calculated GFR from 3 months to 12, 24 and 36 months
- Composite cardiovascular disease endpoint (adjudicated cardiovascular death, myocardial infarction, ischaemic stroke and revascularisation [surgical or percutaneous] by 12, 24 and 36 months
- Composite cardiorenal disease endpoint (death, graft loss, non-fatal myocardial infarction, and stroke) by 12, 24 and 36 months
- Framingham Risk Score at 12, 24 and 36 months
- Incidence of discontinuation of study drug
- Anti-donor human leukocyte antigen (HLA) antibodies
- AT_1 receptor antibodies
- C4d positivity in biopsy specimens

Study design

This is a Phase III randomised, active controlled, parallel group study conducted in 79 sites worldwide in the following countries: USA (28 sites), France (9), Brazil (6), Germany (5), Argentina (5), Spain (5), Canada (4), Italy (3), Hungary (2), Austria (2), Poland (2), Belgium (1), Chile (1), Czech Republic (1), Norway (1), South Africa (1), Sweden (1), UK (1) and Australia (1).

Study participants

The study subjects were recipients of a kidney from a donor with 'extended criteria'. The specific eligibility criteria for the donor were based on the 'expanded criteria' for organ donation issued by UNOS.

Inclusion criteria:

- First time recipient of a deceased donor kidney transplant
- Donor and/or donor kidney met at least 1 of the following extended criteria for organ donation:
  - Donor age ≥ 60 years
  - Donor age 50 -59 years and 1 of the following:
    - Cerebrovascular accident (CVA) + hypertension + SCr > 1.5 mg/dL
    - CVA + hypertension
    - CVA + SCr > 1.5 mg/dL

    - Hypertension + SCr > 1.5 mg/dL
  - Anticipated CIT ≥ 24 hours (subjects not to be randomised if actual CIT is < 20 hours)
  - Donor with cardiac death (non-heart beating donor)
- Male or female (non nursing, not pregnant (subjects ≥ 18 years of age
- Women of child bearing potential must be using adequate contraception throughout study and for 8 weeks after study completion
- Willing to provide signed, written informed consent

Exclusion criteria:

- Genetically identical donor recipient pairs (ie identical twin) or donor < 10 years of age
- Underlying renal disease of primary focal segmental glomerulosclerosis, Type I or II membranoproliferative glomerulonephritis, or haemolytic uremic syndrome/thrombotic thrombocytopenic purpure syndrome
- Subjects undergoing primary (first time) transplant with a current panel reactive antibodies (PRA) ≥ 30%
- A positive T cell lymphocytotoxic cross match
- Prior solid organ transplant or undergoing multi-organ (for example, kidney-pancreas) or concurrent solid organ or cell (islet, bone marrow, stem cell) transplants, or subjects who were deemed likely to have a second solid organ or cell transplants (for example, pancreas or islet transplant) in the next 3 years by the investigator
- Subjects receiving paired kidneys (dual of en bloc kidney transplants)
- Subjects who were known to be hepatitis C or hepatitis B surface antibody-positive or polymerase chain reaction (PCR)-positive for hepatitis C or hepatitis B, or with known human immunodeficiency virus (HIV) infection
- Subjects with active tuberculosis (TB) requiring treatment within the previous 3 years or any subject who previously required triple (or more) combination therapy for TB. Subjects with a known positive purified protein derivative (PPD) were not eligible for the study unless they completed treatment for latent TB and had a negative chest X-ray at the time of enrolment. Further qualification of PPD results given in protocol
- Had any active infection or other contraindication that would have normally excluded transplantation
- Impaired haematological, hepatic or renal function, as determined by laboratory values
- Had a life expectancy severely limited by disease state or other underlying medical condition, a history of cancer (other than non-melanoma skin cell cancers cured by local resection) within the last 5 years, and/or a mammogram that was suspicious for malignancy and in whom the possibility of malignancy could not have been reasonably excluded following clinical, laboratory, or other diagnostic evaluations.
- History of substance abuse (drug and alcohol) within the past 5 years, or psychotic disorders that were not compatible with adequate study follow-up
- Active peptic ulcer disease, chronic diarrhoea or gastrointestinal malabsorption
- History of true allergy to iodinated X-ray contrast agents

- Were consistently receiving immunosuppressive agents (such as methotrexate, infliximab or etanercept) for other indications, such as autoimmune disease, or having co-morbidities such that treatment with immunosuppressive agents was likely during the trial
- Difficult IV access or other reasons that would have likely precluded assessment of the co-primary endpoint of measured GFR or subjects who were likely or unwilling to undergo the protocol-specified 12 month allograft biopsy
- Used any investigational drug within 30 days prior to the Day 1 visit of who had been previously treated with belatacept
- Prisoners or subjects who were compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (such as infections disease) illness

Treatments

Subjects were randomised 1:1:1 to receive belatacept in either a More Intensive (MI) or Less Intensive (LI) regimen or to receive cyclosporin (CsA). All subjects also received a background regimen of basiliximab induction and maintenance therapy with mycophenolate mofetil (MMF) and corticosteroid maintenance therapy

Belatacept MI regimen: Subjects receive IV belatacept (10 mg/kg) on:

a) Day 1 (pre-operative) and Day 5 during the first week

b) Every other week through 3 months (Weeks 2, 4, 6, 8, 10 and 12)

c) Evert 4 weeks until 6 months (Weeks 16, 20 and 24)

After 6 months, subjects were to receive belatacept at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial at 36 months

Belatacept LI regimen: Subjects received IV Belatacept (10 mg/kg) on:

a) Day 1 (pre-operative) and Day 5 during the first week

b) Then every other week for 2 weeks (Weeks 2 and 4)

c) Then every 4 weeks for 2 months (Weeks 8 and 12)

After 3 months, subjects were to receive belatacept at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial at 36 months.

Subjects randomised to the LI regimen were administered 2 placebo infusions (dextrose 5% in water for injection or 0.9% normal saline solution) on Weeks 6 and 10 in order to preserve blinding between the LI and MI groups.

The infusion dose was based on the subject's actual body weight at study Day 1 and was not modified during the course of the study unless there was a ± 10% change in body weight.

Cyclosporin

The daily dose of CsA was administered in 2 divided doses on a consistent schedule in relation to time of day and meals. The initial daily dose was 7 ± 3 mg/kg. Subsequent doses were adjusted to maintain a pre-defined range of trough serum concentrations:

- First month: target level 150 – 300 ng/mL
- After first month: target level 100 – 250 ng/mL

Local laboratory values for CsA trough levels were utilised to maintain serum trough concentrations in the pre-specified range. Administration of CsA was initiated in all subjects on Day 7, as soon as, but not until there was evidence of adequate allograft function (defined as a

decrease in SCr of at least 1 mg/dL compared to the initial post-transplant value or urine output ≥ 250 mL in a 12 hour (or less) period post transplant.

Lymphocyte depleting therapy (LDT)

The use of LDT (thymoglobulin or antithymocyte gamma globulin [ATGAM] was permitted only for subjects randomised to CsA who experienced impaired renal allograft function and anticipated delayed graft function (DGF) following transplantation.

LDT was permitted in both belatacept and CsA treated subjects who experienced rejection at any time during the study.

Background immunosuppressive therapy

Corticosteroids: all subjects received daily corticosteroids for the duration of the study. Corticosteroids were initiated at 500 mg IV, pre-operatively (Day 1) and were reduced to no less than 2.5 mg PO daily for Days 15 – Month 6. Corticosteroid dose was to remain at no less than 2.5 mg PO daily through to Month 36.

Mycophenolate Mofetil (MMF): all subjects were initially treated with MMF (2 g/day) orally in 2 divided doses. A higher dose (3 g/day) could be administered to African-Americans at the investigator's discretion. IV dosing was permitted if needed. The first dose of MMF was administered preoperatively. Subsequent doses were administered as soon as the subject was able to tolerate medications by mouth. The dose and schedule was adjusted on the basis of laboratory values (such as decrease in white blood cells (WBCs)) and subject tolerability.

Basiliximab: all subjects received an induction therapy (2 doses) of basiliximab IV. The first dose (20 mg) was administered on Day 1 (the day of transplantation). The second dose (20 mg) was given on Day 5 (Post-operative Day 4) if the subject had not received or was not expected to receive a lymphocyte depleting treatment.

Study duration

The duration of the study was 3 years (36 months) with a subsequent 8 week follow up period for safety evaluation. At the end of the 36 months, subjects could elect to enrol in a long term extension study which is ongoing.

Outcomes/endpoints

Primary efficacy endpoints:

Each belatacept regimen was compared to CsA based regimen on the following 2 co-primary efficacy outcomes:

- Composite endpoint of subject and graft survival by 12 months, using a non-inferiority design with a margin of 10%
- Composite endpoint of measured GFR < 60 mL/min/1.73 m^2 at Month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73 m^2 from Month 3 to Month 12, using a superiority test

Secondary endpoints:

- Acute rejection: The incidence of acute rejection as independent secondary outcome and as composite with subject and graft survival.
- Preservation of renal function: Direct measurement of renal function (measured GFR) and creatinine-based assessment of renal function (calculated GFR) were performed.

The endpoint of renal function was assessed by measurement of the clearance of a true glomerular filtration marker (non-radiolabeled iothalamate) using a validated procedure. A GFR of 60 mL/min/1.73m^2 or change in GFR of at least 10 mL/min/1.73m^2 was used as the

approximate equal of the threshold values of SCr of 1.5 mg/dL, or change in SCr of at least 0.3 mg/dL. The change component of the composite renal endpoint was assessed from Month 3 to Month 12, since post-transplant renal function is largely stable by Month 3.

Sample size

A sample size of 180 subjects per group would afford 83% power to ascertain that the lower bound of the 97.3% (Dunnett's adjustment for the 2 belatacept regimens) two-sided CIs for the absolute difference (between each belatacept regimen and the CsA regimen) in the first co-primary endpoint (subject and graft survival) did not exceed 10%, if the true subject and graft survival at Month 12 was 80% for the CsA regimen and 83% for each of the 2 belatacept regimens.

For the renal function endpoint, the sample size of 180 subjects per group would afford 98% power to detect a decrease of 25% in the proportion of subjects meeting the measured GFR endpoint for each belatacept regimen compared to the CsA regimen, assuming 75% (estimated from the Phase II study) of CsA subjects met the renal function endpoint and 25% drop outs per treatment group.

Overall, 180 subjects per group would afford at least 80% power to detect 1 belatacept regimen that met both co-primary endpoints with overall Type 1 error controlled at the 0.05 significance level (using Dunnett adjustment).

Randomisation

Subjects were randomised 1:1:1 to receive either a MI or LI regimen or to receive CsA. No details of randomisation are provided.

Blinding (masking)

The study was fully blinded through 12 months with respect to assignment of belatacept dose regimen (MI or LI) but open-label with respect to allocation to treatment (belatacept or CsA). Lack of full blinded is justified as precluded because of the need for periodic dose-level monitoring needed in CsA-treated subjects.

Statistical methods

Primary and key secondary efficacy analysis:

The co-primary and key secondary analysis include, in the order of hierarchy:

- Assessment of non-inferiority for the difference between belatacept and CsA in subject and graft survival at 12 months
- Test of the difference between belatacept and CsA on the composite endpoint of renal function
- Test of the difference between belatacept and CsA on the incidence of CAN by 12 months

A sequential testing procedure was employed for testing the 2 co-primary and key secondary hypothesis according to the hierarchy specified above. A primary measure was tested between a particular belatacept group and the CsA group only if the test between that belatacept group and the CsA group was statistically significant in favour of the belatacept group for all preceding measures. In all of the tests, the nominal Type I error rate was set at 2.7% therefore this sequential testing procedure preserved the overall experiment-wise Type 1 error rate at 2.7% for each belatacept treatment group versus the CsA group and at 5% overall for the entire study. All tests for treatment comparison were two-sided.

Subject and Graft Survival at Month 12: summarised within each treatment group using point estimates of the proportion of subjects surviving with the graft and the corresponding 95% CIs.

Two-sided 97.3% CIs were generated for the difference between each belatacept regimen and CsA to assess the effect of belatacept. If the lower bound of the CI (belatacept-CsA) was > -10%, then the corresponding belatacept regimen was considered non-inferior to CsA.

Measured GFR

The co-primary endpoint was the proportion of subjects with a measured GFR < 60 mL/min/1.73 m^2 at Month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73 m^2 from Month 3 to Month 12.

To account for missing observations that would generate biased estimates, a primary imputation method followed by 2 secondary methods were used to impute missing values.

A continuity-corrected chi-square test (at the significance level 0.027) was performed to assess the effect of each belatacept regimen on renal function compared with CsA. Two-sided 97.3% CIs were generated for the difference in the proportion of subjects meeting the composite renal function endpoint between each belatacept regimen and CsA. Point estimates and 95% CIs of the proportion of subjects satisfying each of the components of the composite endpoint were presented. The analysis was performed on the ITT population.

Measured GFR (with imputed missing values) at Month 12 were also analysed using an ANOVA model with factor for randomisation group (treatment) to assess the difference between each belatacept group and CsA. Each test comparing a belatacept group to CsA was conducted at a level of 0.027 (two-sided).

Acute Rejection at Month 12: summarised within each treatment group using point estimates of the proportion of subjects who had experienced AR by Month 12 and the corresponding 95% CIs. Two-sided 97.3% CIs were also generated for the difference between each of the belatacept regimens and CsA regimen to assess the effect of belatacept. If the upper bound of the CI (belatacept – CsA) was < 20%, then the corresponding belatacept regimen were considered not inferior to CsA. If the upper bound of the CI was < 0, then a continuity-corrected chi-square test (at a two-sided significance level of 0.027) was also performed to assess the superiority of belatacept over CsA. Similar methods (proportions and CIs) were used to summarise other measures of AR such as steroid-resistant acute AR and treated AR.

Prevalence of CAN

Similar to the imputation methods for measured GFR, the imputation method also sought to reduce bias and maintain power of the ITT analysis by replacing missing information about CAN at Month 12 for a subject on the basis of available biopsy information and graft function for the same subject.

Prevalence of CAN at Month 12 was summarised using point estimates of the respective proportion, 95% CIs within each treatment group and 97.3% CIs between each belatacept group and CsA (belatacept-CsA). A continuity corrected Chi square test (at the significance level 0.027) was performed to assess the effect of each belatacept regimen compared with CsA.

Incidence of CAN at 12 months: analysed using similar methods as presented for the summary of prevalence of CAN at 12 months. The summary presented the point estimates of the respective proportion, 95% CIs within each treatment group and 97.3% CIs between each belatacept group and CsA (belatacept-CsA).

Calculated GFR and Serum Creatinine: were summarised descriptively. Recovery of SCr in subjects with AR was calculated using 2 different algorithms:

- The last central laboratory measurement prior to onset of AR was considered the baseline and the first central laboratory measurement after 84 days (3 months) was considered the resolution value

- The lowest central lab measurement on or after transplantation date and prior to onset date of the first episode of AR was considered the baseline value and the lowest central laboratory measurement after onset date of the first episode of AR up to Month 12 was considered as the resolution value.

New onset diabetes mellitus: was summarised with 95% CIs. Continuity adjusted chi-square test was also performed at the significance level of 0.027 for comparisons between each belatacept group and CsA at the specified time points.

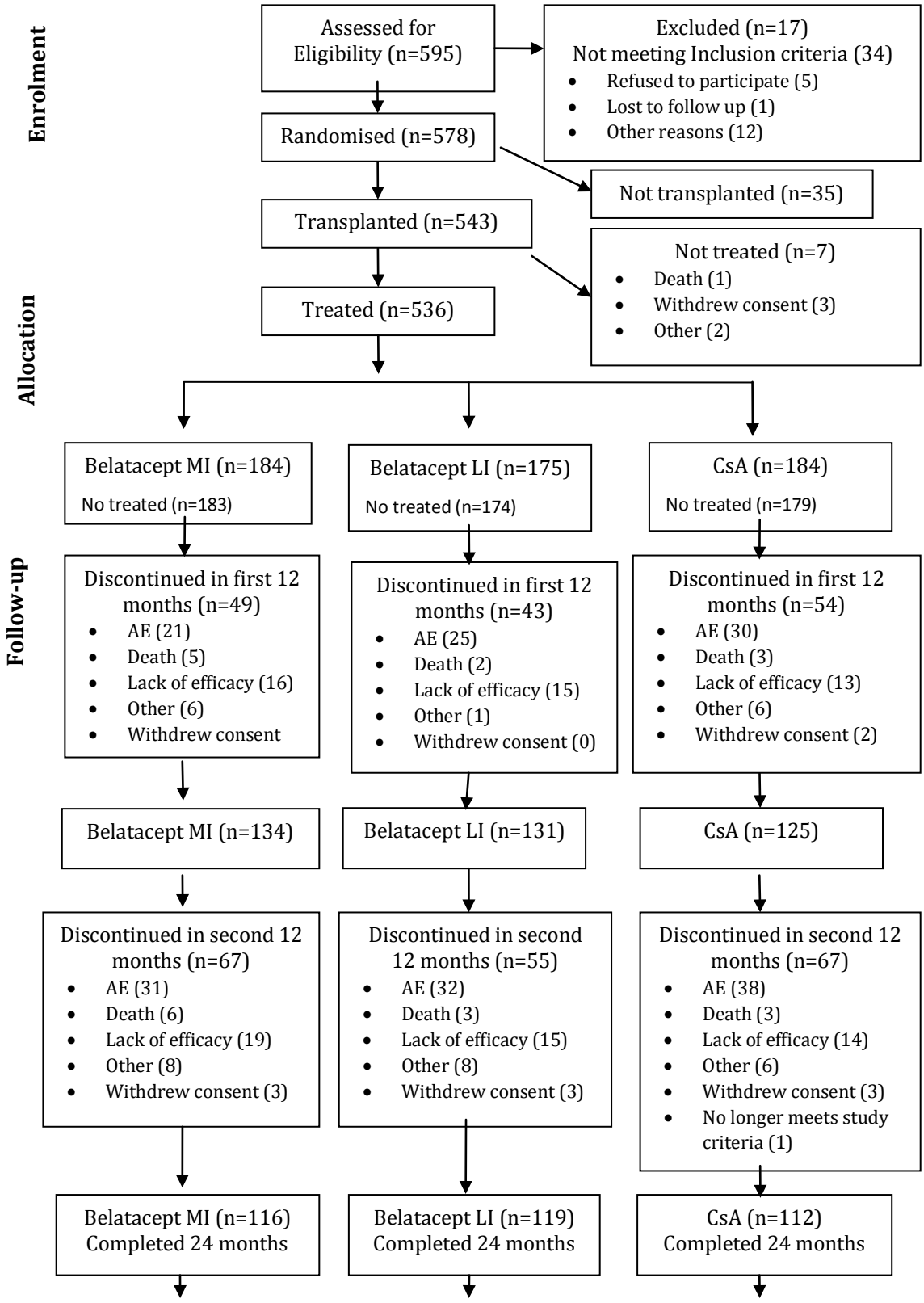
Hypertension related endpoints: analyses were performed using a cumulative logit model with treatment groups as the covariate. Odds ratio between each of the belatacept treatment groups and CsA and the corresponding 97.3% CIs obtained by exponentiating the constructed 97.3% CIs for the treatment effect estimates were provided. Chi-square test (Wald Chi-square) was used to test the treatment differences between each belatacept treatment group and CsA group at the 0.027 significance level.

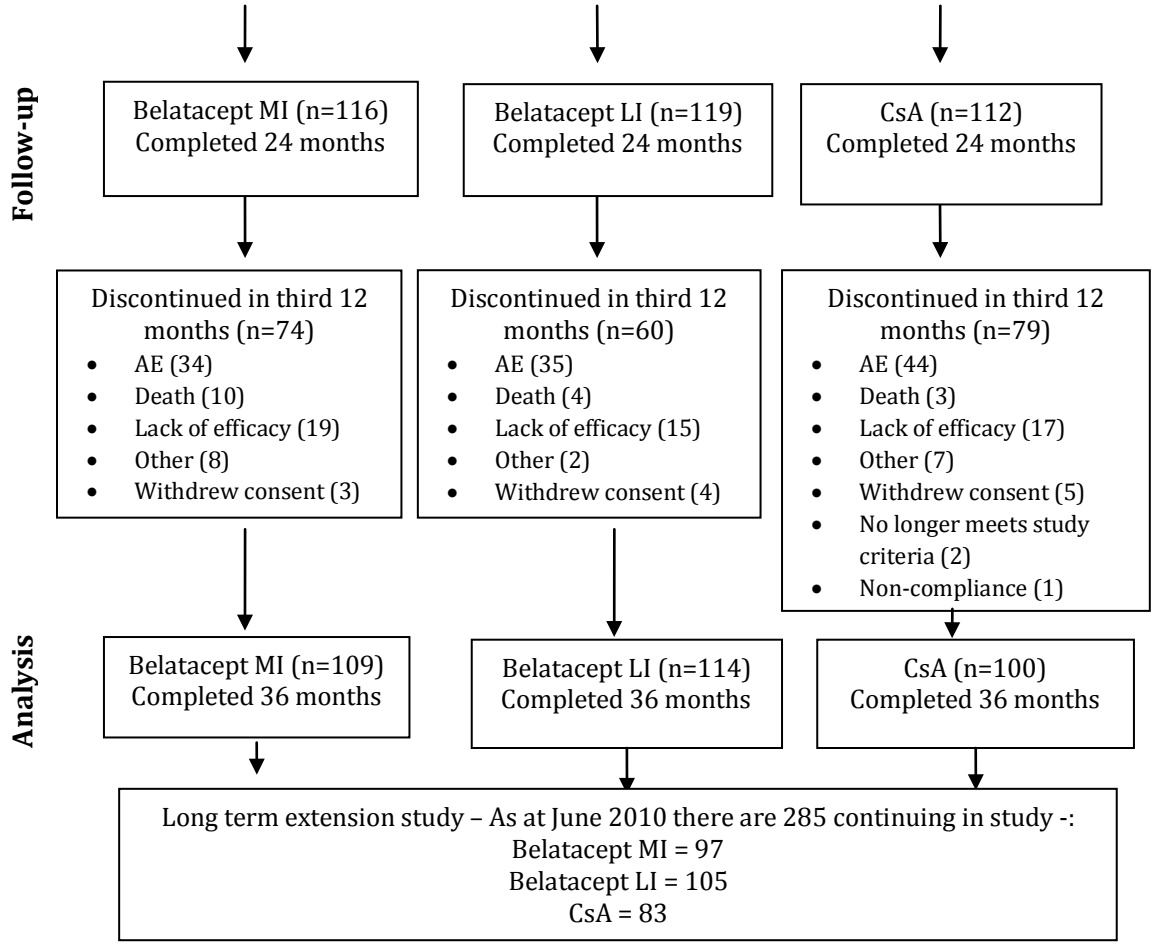
Dyslipidaemic related endpoints: the primary assessment was based on the change in non-HDL cholesterol from baseline to specified time points. Change from baseline in non-HDL cholesterol was analysed within the framework of an analysis of covariance (ANCOVA) model with factor for randomisation group (treatment) and baseline measurement to assess the difference between each of the belatacept treatment groups and CsA group. Each of the individual tests comparing a belatacept group to the CsA group was conducted at the 0.027 (two-sided).

Results

Participant flow

Figure 11. Participant flow. Figure continued across two pages.





Recruitment

The trial commenced with a staggered start worldwide with first subject first visit (FSFV) in March 2005 and last site commencing in Feb 2007. The last subject last visit (LSLV) was in May 2010 for the 36 month report. The database lock was in June 2010 and the 36 month report is dated Sept 2010.

Conduct of the study

Subjects receiving belatacept attended the clinic on treatment days to receive IV infusion of belatacept, however subjects receiving CsA were only required to attend clinic at visits Weeks 2, 4, 6 and 12 and then every 3 month interval. Thus, subjects on different treatments were seen at different time intervals by the investigators.

Overall 10 subjects had at least 1 relevant protocol deviation in the first 12 months that had the potential to affect the analysis of the primary efficacy endpoint and were excluded from the per protocol analysis but not the ITT analysis; 4 (2%) in the belatacept MI group, 5 (3%) in the belatacept LI group and 1 (0.5%) in the CsA group. The most common relevant protocol deviation in all groups was a donor and/or donor kidney not meeting any of the extended donor criteria.

There were no major amendments to the protocol which were likely to affect the efficacy or safety outcomes after the start of the study.

Baseline data

Baseline demographics of subjects who received a transplant were generally balanced among the treatment groups. The mean age of recipients was 56 years. Overall, 67% of subjects were male, 75% were White, and nearly half (49%) were from the EU. There were proportionately fewer females and more males in the belatacept LI group compared to the other 2 treatment groups and there was a trend to higher BMI in the CsA groups, compared to the belatacept groups.

Table 18. Baseline Demographics of Transplant Recipients: All Randomised and Transplanted Subjects (ITT). a The information is collected for US recipients only.

	Number (%) of Subjects			
Demographic Characteristic	**Belatacept MI N=184**	**Belatacept LI N=175**	**Cyclosporin N=184**	**Total N=543**
Age (Years)				
N	184	175	184	543
Mean (SD)	56.7 (12.6)	56.1 (12.4)	55.7 (12.2)	56.2 (12.4)
Median	59.0	58.0	57.0	58.0
Min – Max	21.0 – 80.0	21.0 – 79.0	24.0 – 79.0	21.0 – 80.0
Q1 – Q3	50.0 – 66.5	49.0 – 65.0	48.0 – 65.0	49.0 – 66.0
Age category, N (%)				
18-45	32 (17.4)	35 (20.0)	34 (18.5)	101 (18.6)
46-65	100 (54.3)	97 (55.4)	108 (58.7)	305 (56.2)
>65	52 (28.3)	43 (24.6)	42 (22.8)	137 (25.2)
Gender, N (%)				
Male	119 (64.7)	129 (73.7)	116 (63.0)	364 (67.0)
Female	65 (35.3)	46 (26.3)	68 (37.0)	179 (33.0)
Race, N (%)				

Number (%) of Subjects				
White	137 (74.5)	134 (76.6)	137 (74.5)	408 (75.1)
Black or African American	25 (13.6)	24 (13.7)	22 (12.0)	71 (13.1)
American Indian/Alaskan Native	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Asian	7 (3.8)	3 (1.7)	4 (2.2)	14 (2.6)
Other	14 (7.6)	13 (7.4)	21 (11.4)	48 (8.8)
Missing	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Ethnicity[a]				
US-Hispanic or Latino	5 (2.7)	7 (4.0)	8 (4.3)	20 (3.7)
US-Not Hispanic or Latino	45 (24.5)	34 (19.4)	38 (20.7)	117 (21.5)
Missing	134 (72.8)	134 (76.6)	138 (75.0)	406 (74.8)
Geographic Region				
North America	49 (26.6)	40 (22.9)	45 (24.5)	134 (24.7)
South America	45 (24.5)	47 (26.9)	50 (27.2)	142 (26.2)
Europe	89 (48.4)	86 (49.1)	89 (48.4)	264 (48.6)
ROW (Asia/Pacific)	1 (0.5)	1 (0.6)	0 (0.0)	2 (0.4)
Africa	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)

Table 19. Baseline Disease Characteristics of Transplant Recipients: All Randomized and Transplanted Subjects (ITT). Table continued across two pages.

Number (%) of Subjects				
Demographic Characteristic	**Belatacept – MI N=184**	**Belatacept – LI N=175**	**Cyclosporin N=184**	**Total N=543**
PRA %, (most recent) N	177	166	174	517
Mean (SD)	0.4 (1.8)	0.7 (2.6)	1.8 (9.6)	1.0 (5.9)
Median	0.0	0.0	0.0	0.0
MIN – MAX	0.0 – 17.0	0.0 – 20.0	0.0 – 93.0	0.0 – 93.0
Q1 – Q3	0.0 – 0.0	0.0 – 0.0	0.0 – 0.0	0.0 – 0.0
Categorised PRA (%), N (%)				
< 20%	177 (96.2)	165 (94.3)	168 (91.3)	510 (93.9)
>=20%	0 (0.0)	1 (0.6)	6 (3.3)	7 (1.3)
Missing	7 (3.8)	9 (5.1)	10 (5.4)	26 (4.8)
Highest PRA (%)				
N	174	160	170	504
Mean (SD)	3.7 (11.8)	3.3 (8.4)	4.4 (13.8)	3.8 (11.6)
Median	0.0	0.0	0.0	0.0
Min – Max	0.0 – 94.0	0.0 – 63.0 0.	0 – 98.0	0.0 – 98.0
Q1 – Q3	0.0 – 0.0	0.0 – 2.0	0.0 – 0.0	0.0 – 0.0
Categorized Highest PRA (%), N (%)				
< 20%	163 (88.6)	149 (85.1)	156 (84.8)	468 (86.2)
>=20%	11 (6.0)	11 (6.3)	14 (7.6)	36 (6.6)
Missing	10 (5.4)	15 (8.6)	14 (7.6)	39 (7.2)
Reported Cause of ESRD, N (%)				

Number (%) of Subjects				
Glomerulonephritis	41 (22.3)	46 (26.3)	33 (17.9)	120 (22.1)
Diabetes	26 (14.1)	19 (10.9)	36 (19.6)	81 (14.9)
Polycystic Kidneys	31 (16.8)	34 (19.4)	32 (17.4)	97 (17.9)
Hypertensive Nephrosclerosis	35 (19.0)	27 (15.4)	32 (17.4)	94 (17.3)
Renovascular And Other	4 (2.2)	4 (2.3)	2 (1.1)	10 (1.8)
Cong., Familial, and Met.	3 (1.6)	2 (1.1)	1 (0.5)	6 (1.1)
Tubular and Interstitial Diseases	12 (6.5)	7 (4.0)	11 (6.0)	30 (5.5)
Other	32 (17.4)	36 (20.6)	37 (20.1)	105 (19.3)
T-Cell Lymphocyte Cross Match				
Negative	184 (100)	175 (100)	183 (99.5)	542 (99.8)
Unknown	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Dialysis Prior To Transplant N (%)				
No	12 (6.5)	10 (5.7)	14 (7.6)	36 (6.6)
Yes	172 (93.5)	165 (94.3)	170 (92.4)	507 (93.4)
Urine Output within 24 Hrs Prior to Transplant				
N	135	122	133	390
Mean (SD)	535.3 (806)	371.0 (521)	408.7 (762)	440.7 (714)
Median	250.0	122.5	200.0	200.0
Min – Max	0.0 – 6800	0.0 – 2000	0.0 – 7200	0.0 – 7200
Q1 – Q3	0.0 – 800.0	0.0 – 500.0	0.0 – 500.0	0.0 – 550.0
Kidney Colour (After Re-Perfusion), N (%)				

Number (%) of Subjects				
Pink	162 (88.0)	153 (87.4)	158 (85.9)	473 (87.1)
Pale	6 (3.3)	2 (1.1)	2 (1.1)	10 (1.8)
Mottled	3 (1.6)	11 (6.3)	8 (4.3)	22 (4.1)
Missing	13 (7.1)	9 (5.1)	16 (8.7)	38 (7.0)
Specific Disease History of Hypertension, N (%)				
No	14 (7.6)	10 (5.7)	13 (7.1)	37 (6.8)
Yes	169 (91.8)	165 (94.3)	171 (92.9)	505 (93.0)
Unknown	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Specific Disease History of Dyslipidaemia, N (%)				
No	90 (48.9)	71 (40.6)	77 (41.8)	238 (43.8)
Yes	90 (48.9)	97 (55.4)	103 (56.0)	290 (53.4)
Unknown	4 (2.2)	7 (4.0)	4 (2.2)	15 (2.8)
Specific Disease History of Diabetes, N (%)				
No	146 (79.3)	146 (83.4)	131 (71.2)	423 (77.9)
Yes	38 (20.7)	28 (16.0)	53 (28.8)	119 (21.9)
Unknown	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Anti-Hypertensive Med., N (%)				
No	43 (23.4)	46 (26.3)	51 (27.7)	140 (25.8)
Yes	141 (76.6)	129 (73.7)	133 (72.3)	403 (74.2)
Lipid-Lowering Med., N (%)				
No	115 (62.5)	109 (62.3)	122 (66.3)	346 (63.7)

Number (%) of Subjects				
Yes	69 (37.5)	66 (37.7)	62 (33.7)	197 (36.3)
Anti-Diabetic Med., N (%)				
No	138 (75.0)	143 (81.7)	129 (70.1)	410 (75.5)
Yes	46 (25.0)	32 (18.3)	55 (29.9)	133 (24.5)

Table 20. Baseline Disease Characteristics of Transplant Donors: All Randomized and Transplanted Subjects (ITT).

Number (%) of Subjects				
Demographic Characteristic	**Belatacept – MI N=184**	**Belatacept – LI N=175**	**Cyclosporine N=184**	**Total N=543**
Primary Cause of Death: N (%)				
Trauma	31 (16.8)	23 (13.1)	30 (16.3)	84 (15.5)
Anoxia	9 (4.9)	9 (5.1)	17 (9.2)	35 (6.4)
CVA	125 (67.9)	126 (72.0)	128 (69.6)	379 (69.8)
Myocardial Infarction	2 (1.1)	6 (3.4)	2 (1.1)	10 (1.8)
Other	16 8.7)	11 (6.3)	7 (3.8)	34 (6.3)
Missing	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Extended Condition: N (%)				
Yes	181 (98.4)	172 (98.3)	183 (99.5)	536 (98.7)
Age ≥ 60	94 (51.1)	79 (45.1)	93 (50.5)	266 (49.0)
Age Of 50-59 With Complications	34 (18.5)	43 (24.6)	40 (21.7)	117 (21.5)
Anticipated CIT ≥ 24 Hrs	71 (38.6)	76 (43.4)	80 (43.5)	227 (41.8)
Donor with Cardiac Death	18 (9.8)	19 (10.9)	18 (9.8)	55 (10.1)
No	3 (1.6)	3 (1.7)	1 (0.5)	7 (1.3)
Cold Ischemic Time (Hour)				

Number (%) of Subjects				
N	183	174	184	541
Mean (SD)	19.6 (8.5)	21.2 (8.0)	19.4 (7.4)	20.0 (8.0)
Median	18.7	20.4	19.0	19.5
Min – Max	0.0 – 43.3	5.8 – 44.2	4.5 – 42.7	0.0 – 44.2
Q1 – Q3	13.8 – 24.7	15.8 – 26.2	14.0 – 24.6	14.4 – 25.0
Most Recent SCr Prior to Organ Retrieval (mg/dL)				
< 0.5	8 (4.3)	10 (5.7)	9 (4.9)	27 (5.0)
0.5 - <1	86 (46.7)	75 (42.9)	78 (42.4)	239 (44.0)
1 - < 1.5	52 (28.3)	47 (26.9)	48 (26.1)	147 (27.1)
1.5 - <2	16 (8.7)	17 (9.7)	27 (14.7)	60 (11.0)
>=	2 16 (8.7)	19 (10.9)	18 (9.8)	53 (9.8)
Missing	6 (3.3)	7 (4.0)	4 (2.2))	17 (3.1)

Table 21. Pre-Transplant Histocompatibility, Viral Serology and Transplant Characteristics Between Recipients and Donors: All Randomized and Transplanted Subjects (ITT). Table continued across two pages.

Number (%) of Subjects				
Demographic Characteristic	**Belatacept – MI N=184**	**Belatacept – LI N=175**	**Cyclosporin N=184**	**Total N=543**
No of HLA –A mismatches, N (%)				
0	30 (16.3)	33 (18.9)	27 (14.7)	90 (16.6)
1	92 (50.0)	70 (40.0)	76 (41.3)	238 (43.8)
2	62 (33.7)	72 (41.1)	80 (43.5)	214 (39.4)
Missing	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
No of HLA –B mismatches, N (%)				
0	20 (10.9)	17 (9.7)	18 (9.8)	55 (10.1)

Number (%) of Subjects				
1	76 (41.3)	79 (45.1)	77 (41.8)	232 (42.7)
2	88 (47.8)	79 (45.1)	88 (47.8)	255 (47.0)
Missing	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
No of HLA –DR mismatches, N (%)				
0	54 (29.3)	53 (30.3)	53 (28.8)	160 (29.5)
1	87 (47.3)	90 (51.4)	86 (46.7)	263 (48.4)
2	43 (23.4)	32 (18.3)	44 (23.9)	119 (21.9)
Missing	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Total No. Of HLA-mismatches N (%)				
0	9 (4.9)	6 (3.4)	6 (3.3)	21 (3.9)
1	7 (3.8)	9 (5.1)	12 (6.5)	28 (5.2)
2	21 (11.4)	29 (16.6)	22 (12.0)	72 (13.3)
3	53 (28.8)	44 (25.1)	36 (19.6)	133 (24.5)
4	48 (26.1)	42 (24.0)	51 (27.7)	141 (26.0)
5	35 (19.0)	32 (18.3)	41 (22.3)	108 (19.9)
6	11 (6.0)	13 (7.4)	15 (8.2)	39 (7.2)
Missing	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Viral Serology: CMV A, N (%)				
D+/R+	110 (59.8)	106 (60.6)	103 (56.0)	319 (58.7)
D+/R-	19 (10.3)	22 (12.6)	25 (13.6)	66 (12.2)
D+/U	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.4)
D-/R+	30 (16.3)	24 (13.7)	23 (12.5)	77 (14.2)
D-/R-	21 (11.4)	18 (10.3)	27 (14.7)	66 (12.2)
D-/U	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
U/R+	4 (2.2)	3 (1.7)	5 (2.7)	12 (2.2)
U/R-	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)

Number (%) of Subjects				
U/U	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Viral Serology: Epstein-Barr virus (EBV) A, N (%)				
D+/R+	74 (40.2)	65 (37.1)	65 (35.3)	204 (37.6)
D+/R-	5 (2.7)	5 (2.9)	2 (1.1)	12 (2.2)
D+/U	2 (1.1)	1 (0.6)	2 (1.1)	5 (0.9)
D-/R+	11 (6.0)	10 (5.7)	9 (4.9)	30 (5.5)
D-/R-	2 (1.1)	3 (1.7)	1 (0.5)	6 (1.1)
D-/U	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
U/R+	70 (38.0)	70 (40.0)	79 (42.9)	219 (40.3)
U/R-	6 (3.3)	10 (5.7)	13 (7.1)	29 (5.3)
U/U	14 (7.6)	11 (6.3)	13 (7.1)	38 (7.0)

Numbers analysed

- ITT population = 543 – all randomised and transplanted – Belatacept MI 184, Belatacept LI 175, CsA 184
- Completed 12 months of treatment: 390 subjects (MI 73%, LI 75%, CsA 70%)
- Completed 24 months of treatment: 34 subjects (MI 63%, LI 68%, CsA 63%)
- Completed 36 months of treatment: 323 subjects (MI 60%, LI 66%, CsA 56%)
- Entered long term extension study: 301 subjects (MI 103/183, LI 113/174, CsA 85/179)

Results/outcomes

Only results for ITT are presented; the results for per protocol dataset are similar.

Table 22. Summary of Key Efficacy Outcomes. Table continued across two pages.

	Belatacept MI	Belatacept LI	Cyclosporin
	N = 184	**N = 175**	**N = 184**
Subject and Graft Survival (n, %)			
Month 12[a]	**159 (86.4)**	**155 (88.6)**	**157 (85.3)**
Difference from CsA (97.3% CI)	1.1 (-7.1, 9.3)	3.2 (-4.8, 11.3)	-
Graft Loss (n, %)	17 (9.2%)	16 (9.1%)	20 (10.9%)
Death (n, %)	8 (4.3%)	5 (2.9%)	8 (4.3%)
Imputed as Graft Loss or Death	2 (1.1%)	0	2 (1.1%)
Month 24[a]	**152 (82.6)**	**147 (84.0)**	**152 (82.6)**
Difference from CsA (97.3% CI)	0 (-8.8, 8.8)	1.4 (-7.5, 10.2)	-
Graft Loss (n, %)	18 (9.8)	20 (11.4)	22 (12.0)
Death (n, %)	13 (7.1)	11 (6.3)	12 (6.5)
Imputed as Graft Loss or Death 3	(1.6)	0	2 (1.1)
Month 36	**148 (80.4)**	**144 (82.3)**	**147 (79.9)**
Difference from CsA (97.3% CI)	0.5 (-8.7, 9.8)	2.4 (-6.9, 11.6)	-
Graft Loss (n, %)	18 (9.8)	21 (12.0)	23 (12.5)
Death (n, %)	22 (12.0)	15 (8.6)	17 (9.2)
Imputed as Graft Loss or Death	0	0	1 (0.5)
Mean (SD) measured GFR with Imputation[b] (mL/min/1.73 m2)			
Month 12[c]	**52.1 (21.9)**	**49.5 (25.8)**	**45.2 (21.1)**
Estimated diff. From CsA (97.3% CI)	6.9 (1.1, 12.7)	4.3 (-1.5, 10.1)	-
P-Value	0.0089	0.0995	-
Month 24[c]	**51.5 (22.2)**	**49.7 (23.7)**	**45.0 (27.2)**
Estimated diff. From CsA (97.3% CI)	6.6 (0, 13.1)	4.7 (-1.8, 11.3)	-
P-Value	0.0276	0.1080	-
Month 36 (not performed per protocol)	**-**	**-**	**-**
Mean (SD) calculated GFR with Imputation[d] (mL/min/1.73 m2)			
Month 12[e]	**44.4 (22.8)**	**44.5 (21.8)**	**36.5 (21.1)**

	Belatacept MI	Belatacept LI	Cyclosporin
Difference from CsA (97.3% CI)	7.8 (2.4, 13.2)	8.0 (2.5, 13.4)	-
Month 24[e]	**44.4 (26.7)**	**42.8 (24.1)**	**34.9 (21.6)**
Difference from CsA (97.3% CI)	9.5 (3.4, 15.6)	8.0 (1.9, 14.0)	-
Month 36	**42.7 (27.6)**	**42.2 (25.2)**	**31.5 (22.1)**
Difference from CsA (97.3% CI)	11.2 (4.7, 17.7)	10.7 (4.3, 17.2)	–
Acute Rejection (n, %)[f]			
Month 12[g]	**32 (17.4)**	**31 (17.7)**	**26 (14.1)**
Difference from CsA (97.3% CI)[2]	3.5 (-5.2, 11.8)	3.4 (-5.0, 12.3)	-
Month 24[g]	**32 (17.4)**	**32 (18.3)**	**28 (15.2)**
Difference from CsA (97.3% CI)	2.2 (-6.4, 10.8)	3.1 (-5.7, 12.0)	-
Month 36	**33 (17.9)**	**33 (18.9)**	**29 (15.8)**
Difference from CsA (97.3% CI)	2.2 (-6.6, 10.9)	3.1 (-5.8, 12.1)	-

a Table S.5.1D in Month 24 CSR.

b Imputation Method: No imputation for subjects with graft loss or death, however, if a value was available, it was used in the analysis. For other missing data, measured GFR at other time-points or calculated GFR at the same time point that was used to impute the missing values at Months 12 or 24.

c Table S.5.2E in Month 24 CSR.

d For missing data due to graft loss or death, calculated GFR after graft loss or death was imputed as 0 (primary analysis) by Month 36.

e Table S.5.2.1M in Month 24 CSR.

f Acute Rejection is defined as central biopsy proven rejection that was either (1) clinically suspected by protocol defined reasons or (2) clinically suspected by other reasons and treated.

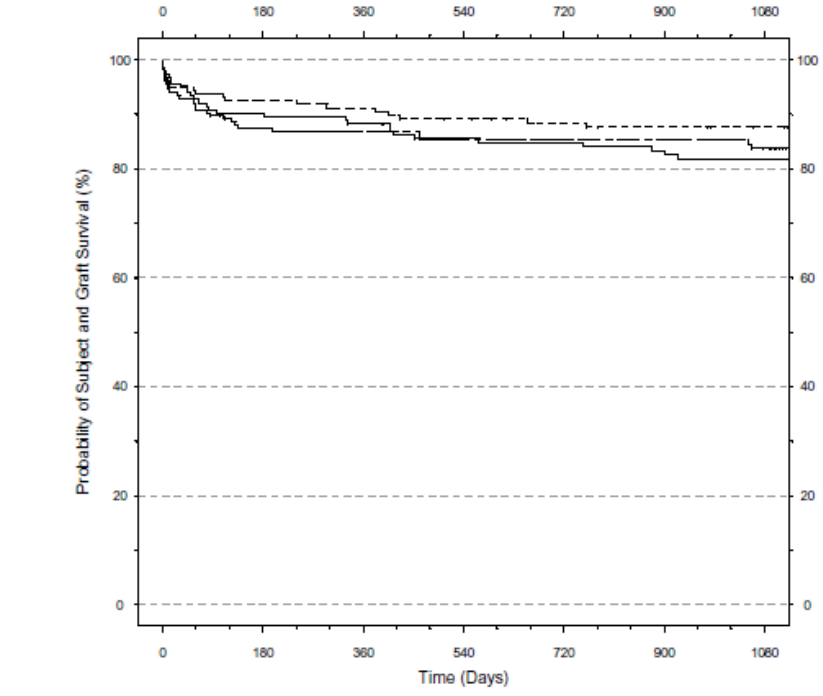
g Table S.5.1A in Month 24 CSR.

Abbreviations: CI – confidence interval, CsA – cyclosporin, GFR – glomerular filtration rate, LI – less intensive, MI – more intensive, SD – standard deviation

Death and graft loss

Comparable rates of death (12%, 9% and 9%) and graft loss (10%, 12% and 13%) from transplantation up to Month 36 were observed across the treatment groups (belatacept MI, LI and CsA, respectively).

Figure 12. Kaplan-Meier estimates of subject and graft survival. All randomised and transplanted subjects. On-treatment analysis.



For subject with event, the time to event is defined as minimum of event date and lastdose date (transplant date for not-treated subject) +56
For subject without event, the time to event is defined as last follow up date for on-treat subject, lastdose +56 for off-treat subject, and transplant +56 for not-treated subject.

Renal function

The difference in renal function, as assessed by calculated GFR, between belatacept and CsA seen at Month 12 and 24 was maintained; at Month 36 differences in calculated GFR were approximately 11 mL/min/1.73 m^2 higher in both belatacept groups compared with CsA. Measured GFR was not obtained at Month 36 according to the protocol.

The annual rate of change in calculated GFR from Months 3 to 36 was -0.9, -0.6, and -1.9 mL/min/1.73 m^2/yearr in the belatacept MI, LI and CsA groups, respectively.

Chronic kidney disease stage based on calculated GFR at Month 36 showed greater proportions of subjects with Stage 1 and 2 and fewer subjects with Stage 4 and 5 in the belatacept groups compared with CsA.

Subjects receiving belatacept experienced a delay in the time to progression to advanced renal dysfunction (CKD Stage 4 or 5), graft loss or death as compared with subjects treated with CsA. By 3 years after transplantation, approximately 50% of patients in the CsA group and 30% of subjects in the belatacept groups had reached this endpoint.

Acute rejection

One additional subject in each group experienced AR after Month 24. Up to Month 36, AR occurred in 18% (MI), 19% (LI), and 16% (CsA). Most events of AR occurred by Month 6. The proportion of subjects with AR classified as Banff Grade IIb or III was higher in the belatacept

MI group (9%) compared with the belatacept LI group (5%) and the CsA group (3%). After Month 36, there was no additional case of AR.

Through Month 36, there were comparable rates of the composite endpoint of BPAR, death, graft loss, and lost to follow-up between groups in both the ITT population and in the subgroup of recipients with Epstein-Barr virus (EBV) positive serostatus at baseline.

Impact of AR by month 24 on outcomes up to month 36

The overall rate of death by Month 36: in subjects with AR was 9% (3 subjects) in belatacept MI; 16% (5 subjects) in belatacept LI; and 18% (5 subjects) in CsA versu in subjects without AR 13% (19 subjects) in belatacept MI, 7% (10 subjects) in belatacept LI, and 8% (8 subjects) in CsA.

The overall rate of graft loss by Month 36: in subjects with AR was 9% (3 subjects) in belatacept MI; 16% (5 subjects) in belatacept LI; 21% (6 subjects) in CsA versus in subjects without AR 10% (15 subjects) in belatacept MI, 11% (16 subjects) in belatacept LI and 11% (17 subjects) in CsA.

Renal function (calculated GFR as observed or with imputation) at Month 36 was lower in subjects with AR than without AR in all treatment groups.

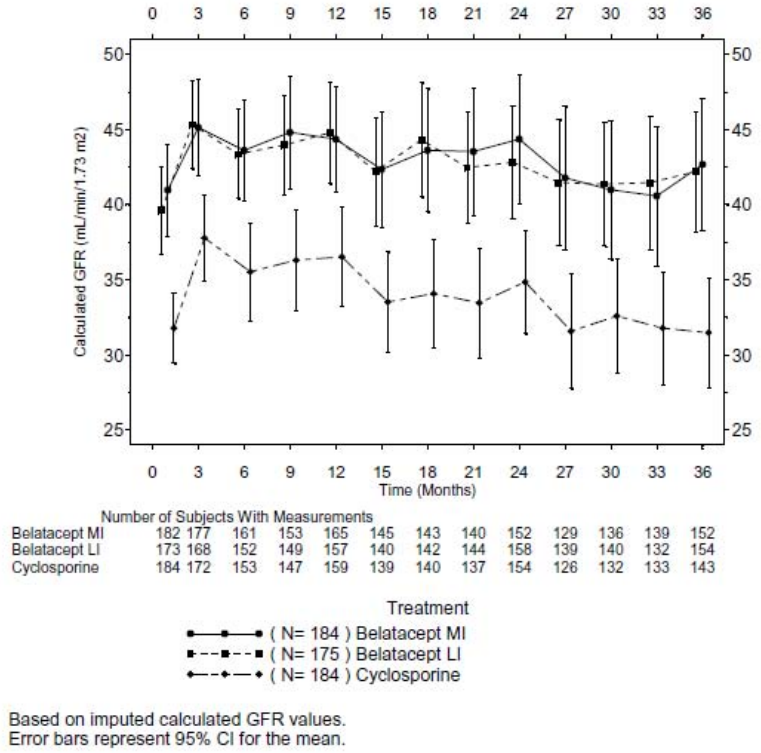
Metabolic effects

At Month 36, total cholesterol, non-HDL cholesterol and triglycerides were similar between the belatacept and CsA groups. Of note, about 50% of ITT population did not have lipid measurements at Month 36.

Diastolic and systolic blood pressure averaged 2 and 6 mmHg lower, respectively, in both belatacept groups compared with CsA. The use of anti-hypertensive medication was numerically lower in belatacept MI and was significantly lower in LI subjects compared with CsA.

The statistically significant differences between the belatacept MI and CsA groups in NODM observed at Month 12 were not observed at Month 36. No statistically significant differences were observed between the belatacept LI and CsA groups throughout the study.

Figure 13. Summary of calculated GFR with imputation post transplantation. All randomised and transplanted.



Study IM103100

Open label, randomised, controlled, multiple-dose and active controlled 12 month study of efficacy and safety of 2 partially blinded belatacept regimens (more intensive MI and less intensive LI) versus cyclosporin (CsA) as part of a quadruple drug regimen with MMF, corticosteroids and basiliximab in renal transplant recipients (12 month analysis)

Methods

Objectives

Primary objective

- To assess the efficacy (prophylaxis of clinically suspected and biopsy proven acute rejection (CSBPAR) at 6 months of belatacept versus CsA, when used in combination with MMF, corticosteroids and basiliximab, using a non-inferiority design. Acute rejection is based on interpretation of biopsy samples by a central pathologist using the revised Banff 97 criteria.

Secondary objectives

- Assess the incidence of CSBPAR at 6 months or patient death or graft loss (defined as functional or physical loss; for functional ≥ 56 consecutive days of dialysis was needed) at 1 year in subjects treated with belatacept compared with subjects treated with CsA
- Assess the efficacy (incidence of CSBPAR or presumed acute rejection) at 6 months and 1 year in the belatacept versus the CsA group
- Compare renal function (using iohexol clearance) in subjects treated with belatacept to that in subjects treated with CsA at 1 and 6 months and at 1 year
- Compare parameters of hypertension in subjects treated with belatacept to that in subjects treated with CsA

- Assess differences in serum cholesterol and triglycerides in subjects treated with belatacept compared to subjects treated with CsA
- Assess the overall safety in subjects treated with belatacept compared to subjects treated with CsA

Tertiary objectives:

- Assess patient death or graft loss at 1 year in subjects treated with belatacept compared with subjects treated with CsA
- Assess differences in the severity of acute rejection episodes in subjects treated with belatacept compared with subjects treated with CsA
- Assess differences in the incidence of PTDM in subjects treated with belatacept compared to subjects treated with CsA
- Assess the PK and immunogenicity of belatacept

Study design

The study was conducted at 41 sites worldwide. Not all sites are identified in the appendix to study report but the protocol identifies sites in USA, Canada, Austria, UK, Germany, Spain, France, Italy and Belgium.

Study participants

Inclusion criteria:

Recipients of first renal transplants. First 3 cohorts; 54 subjects

At the apparent direction of the US FDA the initial 3 cohorts of subjects (total of 36 belatacept and 18 CsA subjects) included only subjects at lower risk of acute rejection. The study results were then reviewed by a company DMC and the FDA and when approved by both groups the study then enrolled patients receiving both first and subsequent transplants but such that the total number of "higher risk subjects" was limited to approximately 10% of the total number of subjects. Higher risk was defined as:

- Those who had previously received a renal transplant and were receiving a subsequent transplant
- Those having a history of panel reactive antibodies (PRA) >20%, and
- Those considered by the investigators to be at relatively higher risk for acute rejection.

Recipient of a kidney from a cadaveric or living donor; except when the donor and recipient were human leukocyte antigen (HLA)-identical

Male and female subjects ≥ 18 years of age. Women of child bearing potential must have negative urine pregnancy test within 72 hrs of start of study and agree to a medically acceptable form of contraception throughout the study.

Willing to participate and provided signed, written informed consent.

Exclusion criteria:

- After first 3 cohorts (54 subjects).
- HLA identical donor-recipient pairs.
- Cold ischemia time > 36 hours (donor kidney).

- Evidence of infection with hepatitis C antibody-positive and polymerase chain reaction-positive subjects., hepatitis B surface antigen-positive subjects and subjects with human immunodeficiency virus.
- Subjects with a positive protein derivative tuberculosis test (within 1 year of enrolment), unless previously vaccinated with BCG or those with a history of adequate chemoprophylaxis.
- Subjects with any active infection that would normally exclude transplantation.
- Multiple organ transplant recipients.
- Donor age > 60 or < 6 years whose hearts weren't beating.
- Recipients with underlying renal disease of (due to risk of rapid disease recurrence in the allograft): focal segmental glomerulonephritis, Type I or II membranoproliferative glomerulonephritis, or haemolytic uremic syndrome / thrombotic thrombocytopenic purpure syndrome.
- Subjects with a positive T-cell lymphocytoxic crossmatch using donor lymphocytes and recipient serum.
- Subjects with a history of true allergy to IV iodinated X-ray contrast agents.
- Subjects whose life expectancy was severely limited by disease state of other underlying medical condition.
- Subjects with a history of cancer (other than non-melanoma skin cancers cured by local resection) within the last 5 years.
- Mammogram with any clinically significant abnormality requiring further investigations or biopsies.
- History of substance abuse (drug or alcohol) or psychotic disorders that were not compatible with adequate study follow-up.
- Subjects with a currently functioning non-renal transplant.
- Subjects previously treated with basiliximab for any reason.
- Subjects with active peptic ulcer disease, chronic diarrhoea or gastrointestinal malabsorption.
- Subjects with laboratory values that were Common Toxicity Criteria (CTC) Grade II or greater with the following allowances:
  - Haematology
    - Haemoglobin (Hb) may not have been <8 g/dL
    - Platelets may not have been <100,000/mm^3
    - Total white cell count (WCC) may not have been <3000/mm^3
  - Chemistry
    - All SCr and BUN values
    - All blood sugars
  - Urinalysis
    - All urinalysis results

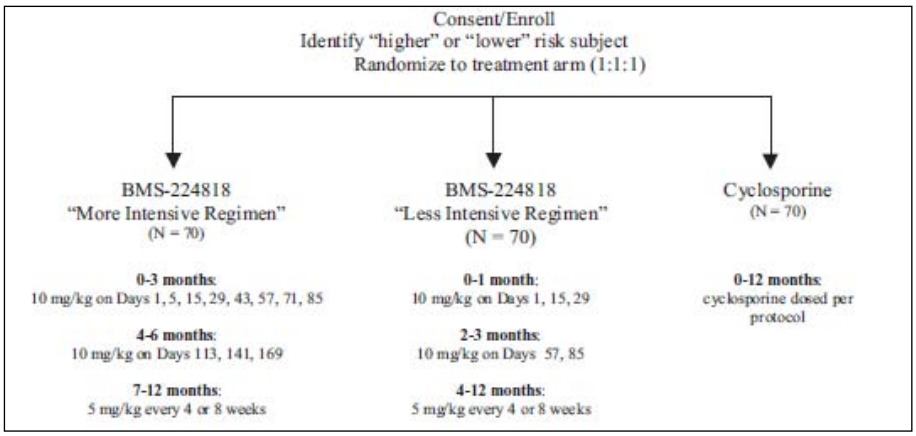
Subjects previously received any investigational drug within 30 days before the Day 1 visit.

Treatments

Belatacept MI regimen: subjects were dosed to achieve projected trough serum concentrations of approximately 20 µg/mL through to Day 99 and approximately 5 µg/mL through to Day 183 (10 mg/kg on Days 1, 5, 15, 29, 43, 57, 71, 85, 113, 141 and 169). After Day 169, subjects were reallocated and dosed to achieve projected through serum concentrations of either approximately 2 or 0.25 µg/mL (5 mg/kg every 4 or 8 weeks starting on Day 197).

Belatacept LI regimen: subjects were dosed to achieve trough serum concentrations of approximately 20 µg/mL through to Day 29 and approximately 5 µg/mL through to Day 99 (10 mg/kg on Days 1, 15, 29, 57 and 85). After Day 85 these subjects were reallocated and dosed to achieve projected trough serum concentrations of either approximately 2 or 0.25 µg/mL (5 mg/kg every 4 or 8 weeks starting on Day 113).

Figure 14. Treatments



The subjects dosed with belatacept every 8 weeks received placebo (dextrose 5% in water for injection) infusions on scheduled treatment days between infusions of active drug in active drug in order to blind treatment schedule assignment.

Cyclosporine: Oral CsA from commercial stock was administered in 2 divided doses daily. The initial dose was 7 ± 3 mg/kg. In the first month, the target serum trough level was 150-400 ng/mL and after the first month the target serum trough level was 150-300 ng/mL.

Background immunosuppressive therapy

Induction therapy (2 doses) of basiliximab IV.

Daily corticosteroids (protocol provided dosing regimen as follows).

- Day 1 (day of transplant): methylprednisolone (as sodium succinate) 500mg IV
- Day 2: methylprednisolone 250mg IV
- Day 3: prednisone (UK only prednisolone) 100mg PO
- Day 4: prednisone (UK only prednisolone) 50mg PO
- Day 5 to Day 30: prednisone (UK only prednisolone) 25 mg PO daily
- Day 31 to Day 44: prednisone (UK only prednisolone) 22.5 mg PO daily
- Day 45 to Day 58: prednisone (UK only prednisolone) 20 mg PO daily
- Day 59 to Day 72: prednisone (UK only prednisolone) 17.5 mg PO daily

- Day 73 to Day 86: prednisone (UK only prednisolone) 15 mg PO daily
- Day 87 to Day 100: prednisone (UK only prednisolone) 12.5 mg PO daily
- Day 101 to Day 114: prednisone (UK only prednisolone) 10 mg PO daily
- After Day 114: prednisolone (UK only prednisolone) dose may be decreased by 2.5mg every other month but not to less than 5 mg per day

Initial treatment with MMF (2g/day) orally, unless the investigator decided based upon the clinical situation to administer ≥1 doses IV. The first doses were administered in 2-3 divided doses approximately every 8-12 hours beginning as soon as the subject was able to tolerate medications by mouth.

Anti-infective therapy: All subjects received sulfamethoxazole/trimethoprim to prevent urinary tract infections (UTI) and *P. carinii* and gancyclovir or valacyclovir to prevent infections due to CMV and herpes simplex.

Study duration

The total study duration was 12 months. At the end of 12 months subjects were given option of entering long term extension study originally planned as 3 years but then extended to 7 years and then extended until the product is marketed or discontinued.

Outcomes/endpoints

Efficacy

Primary endpoint

The number of subjects who experienced any episode of acute rejection (that is, CSBPAR) by 6 months posttransplant.

Secondary endpoints

Key secondary endpoints included the following:

- The proportion of subjects with CSBPAR by Months 6, 9 and 12
- The proportion of subjects with
  - BPAR,
  - BPAR or treated acute rejection,
  - acute rejection or presumed acute rejection by Months 3, 6, 9, and 12
- Subject and graft survival by Month 12
- The proportion of subjects who had CAN by Months 3, 6 and 12
- Renal function as measured by GFR at Months 1, 6 and 12. SCr and calculated GFR using the MDRD formula at Months 1, 3, 6, 9 and 12
- Hypertension as measured by the prevalence of subjects with hypertension and the proportion of subjects using anti-hypertensive medications at Months 6 and 12 and SBP, DBP and mean arterial pressure (MAP) by treatment group at Months 1, 3, 6, 9 and 12
- Lipid profile as measured by the proportion of subjects using lipid-lowering medications at Months 6 and 12 and lipid parameters (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides) at Month 1, 3, 6, 9 and 12
- The incidence of PTDM by Months 1, 3, 6, 9 and 12

Sample size

The primary objective was to estimate the differences in the incidence of acute rejection by 6 months between each belatacept regimen and the CsA regimen using point estimates and 95% CI. Sample size was calculated based on the true acute rejection rate by 6 months in the CsA arm, estimated to be 15% and the assumption that the belatacept arms would have the same rate as the CsA arm. Adjusting for a drop-out rate of 10%, it was determined that a sample size of 63 subjects in each treatment group would afford 85% power based on simulation to ascertain that the upper bound of the 95% two-sided CIs (each belatacept regimen versus the CsA regimen) for the treatment difference would not be > 20%. If the upper bound of the treatment difference was < 20% then belatacept would have been considered as not worse than CsA in terms of the primary efficacy endpoint.

Randomisation

Subjects were randomised in a 1:1:1 ratio. No information is provided on how randomisation was done.

Blinding (masking)

Study medication was administered in an open label, partially blinded fashion so that study personnel and subjects know medication they were receiving, for example belatacept (IV infusion) or CsA (oral). The assigned dosing group of belatacept (MI or LI regimen) and the subsequent assignment to the maintenance dosing schedule (every 4 weeks or 8 weeks) were blinded both to subject and site personnel. Those subjects assigned to belatacept every 8 weeks received placebo (dextrose 5% in water for injection [D5W] infusions on scheduled treatment days between infusions of active drug in order to blind treatment schedule assignment. At the study site, only the pharmacist had the unblinded information in order to prepare the infusions. The prepared drug was then delivered to the study personnel so that neither study personnel nor subjects were aware of the contents of the infusions. No subjects were unblinded in the first 12 months of the study.

Statistical methods

Acute rejection

Acute rejection point estimates and 95% CI.

Subject and graft survival

Subject and graft survival*:* the proportion of subjects who survived with a functioning graft by Month 12 was summarised using point estimate, 95% CI within each treatment arms and 95% CI between each belatacept arm and CsA arm. Kaplan-Meier (KM) estimates of the cumulative subject and graft survival rates were also summarised by Month 12.

CAN

CAN: point estimates and 95% CI; within treatment arm and between belatacept arm and CsA arm.

Renalfunction

Renal Function: measured GFR at Months 1, 6, and 12, SCr and calculated GFR using the MDRD formula were summarised descriptively.

Other endpoints

Other endpoints*:* point estimates and 95% CI.

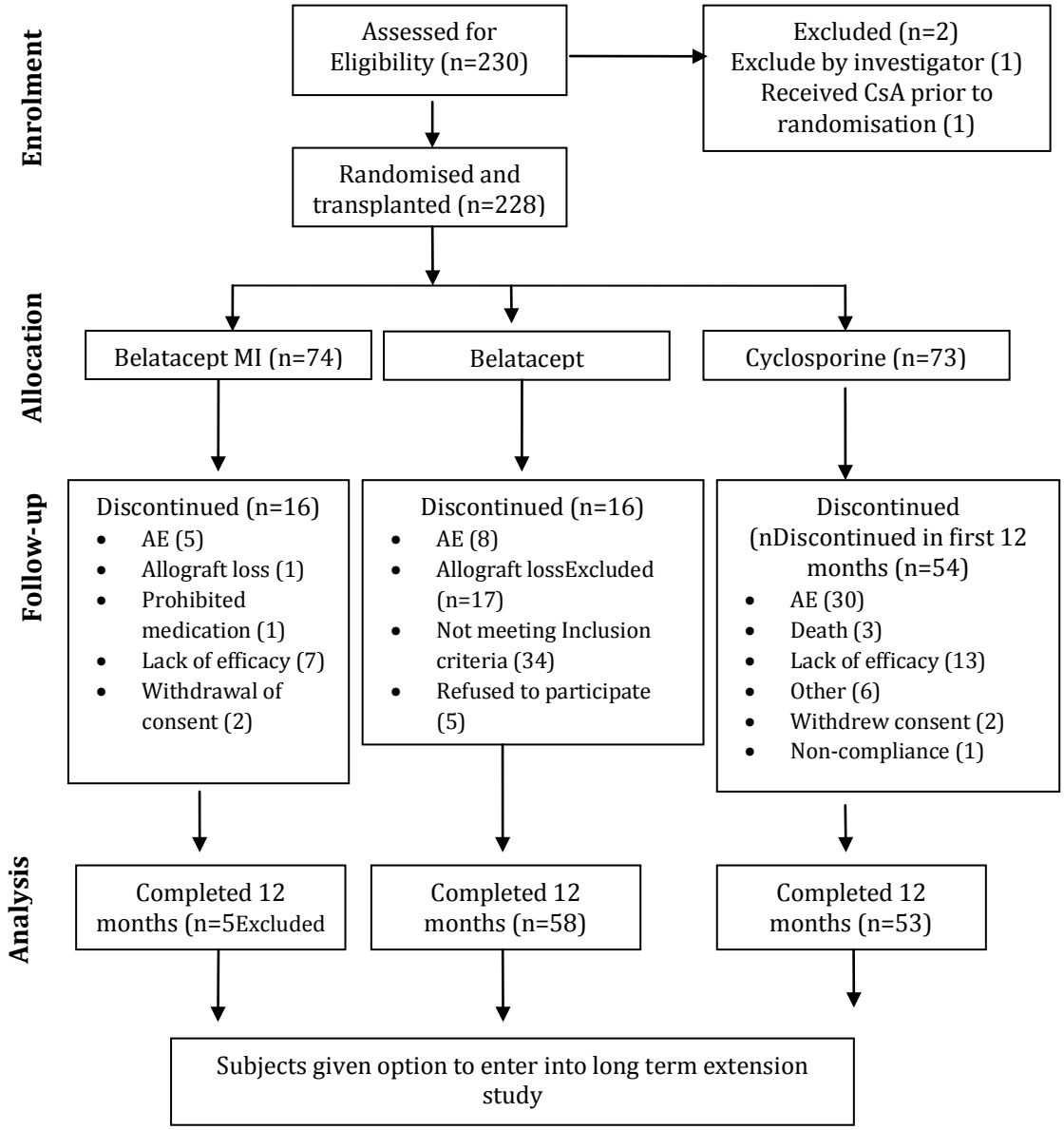
Safety

Safety*:* the study report states that no statistical tests were used for any safety parameter. This approach was stated to be adopted to recognise the lack of power and the potential for misleading interpretation of non-significant results.

Results

The following figure summarises the participant flow*.*

Figure 15. Participant flow



Recruitment

Study started in March 2001 and is described as still ongoing at time of writing the clinical study report (October 2006). At the end of 12 months treatment the patients were re-consented and

enrolled into a long term extension study which commenced in March 2002 and is described as ongoing at time of writing the clinical study report (October 2007).

Conduct of the study

The study commenced on Day 1: day of transplantation and first dose of study medication. Patients were hospitalised for transplantation and all study parameters were clearly defined in the protocol. There were no significant amendments to the protocol and the overall incidence of significant protocol deviations was low and similar among the treatment groups and there were no protocol deviations which had a significant impact on the efficacy or safety outcomes of the study. No subject was unblinded during the first 12 months of the study.

Baseline data

The demographic characteristics were generally balanced among the treatment groups. The majority of subjects in each group were White males.

The majority of donors were White males and the mean age of donors was 41 years.

Table 23. Selected Demographic Characteristics of Transplant Recipients

(Intent-To-Treat Analysis)

Baseline Characteristic	Belatacept-MI (N=74)	Belatacept-LI (N=71)	CsA (N=73)	Total (N=218)
Age(Years)				
N	74	71	73	218
Mean (SD)	46.5 (10.8)	42.1 (11.6)	46.1 (10.9)	44.9 (11.2)
Median	45.5	43.0	46.0	45.0
Min-Max	(23.0 - 70.0)	(18.0 - 71.0)	(23.0 - 66.0)	(18.0 - 71.0)
Q1-Q3	(39.0 - 55.0)	(34.0 - 50.0)	(38.0 - 56.0)	(37.0 - 54.0)
Age Category, N (%)				
18 - 45	37 (50.0)	42 (59.2)	36 (49.3)	115 (52.8)
46 - 60	31 (41.9)	26 (36.6)	33 (45.2)	90 (41.3)
>60	6 (8.1)	3 (4.2)	4 (5.5)	13 (6.0)
Gender, N (%)				
Male	54 (73.0)	48 (67.6)	49 (67.1)	151 (69.3)

Baseline Characteristic	Belatacept-MI (N=74)	Belatacept-LI (N=71)	CsA (N=73)	Total (N=218)
Female	20 (27.0)	23 (32.4)	24 (32.9)	67 (30.7)
Race, N (%)				
White	64 (86.5)	57 (80.3)	59 (80.8)	180 (82.6)
Black	6 (8.1)	6 (8.5)	6 (8.2)	18 (8.3)
Asian/Pac. Island.	3 (4.1)	4 (5.6)	5 (6.8)	12 (5.5)
Hispanic	1 (1.4)	4 (5.6)	3 (4.1)	8 (3.7)
Population : All randomized and transplanted subjects Belatacept-MI: Belatacept more intensive and Belatacept-LI: Belatacept less intensive				

Table 24. Pre-Transplant Histocompatibility, Viral Serology and Baseline Disease Characteristics of Transplant Recipients (Intent-To-Treat Analysis)

Baseline Characteristic	Belatacept-MI (N=74)	Belatacept-LI (N=71)	CsA (N=73)	Total (N=218)
Categorized, Most Recent PRA, N (%)				
< 20%	73 (98.6)	69 (97.2)	71 (97.3)	213 (97.7)
≥ 20%	1 (1.4)	2 (2.8)	1 (1.4)	4 (1.8)
Categorized, Highest PRA, N (%)				
< 20%	65 (87.8)	62 (87.3)	64 (87.7)	191 (87.6)
≥20%	6 (8.1)	5 (7.0)	4 (5.5)	15 (6.9)
Cause of ESRD, N (%)				
Glomerulonephritis	22 (29.7)	20 (28.2)	14 (19.2)	56 (25.7)
Diabetes	5 (6.8)	6 (8.5)	10 (13.7)	21 (9.6)
Hypertension	7 (9.5)	8 (11.3)	3 (4.1)	18 (8.3)

Baseline Characteristic	Belatacept-MI (N=74)	Belatacept-LI (N=71)	CsA (N=73)	Total (N=218)
Retran./Graft Fail	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.5)
Polycystic Kidneys	13 (17.6)	12 (16.9)	10 (13.7)	35 (16.1)
Other	27 (36.5)	24 (33.8)	36 (49.3)	87 (39.9)
Total # of HLA Mismatches, N (%)				
0	1 (1.4)	5 (7.0)	3 (4.1)	9 (4.1)
1	8 (10.8)	4 (5.6)	2 (2.7)	14 (6.4)
2	16 (21.6)	16 (22.5)	21 (28.8)	53 (24.3)
3	17 (23.0)	17 (23.9)	18 (24.7)	52 (23.9)
4	12 (16.2)	12 (16.9)	10 (13.7)	34 (15.6)
5	13 (17.6)	12 (16.9)	10 (13.7)	35 (16.1)
6	6 (8.1)	5 (7.0)	9 (12.3)	20 (9.2)
No. of Previous Transplants, N (%)				
0	73 (98.6)	67 (94.4)	71 (97.3)	211 (96.8)
1	0 (0.0)	3 (4.2)	1 (1.4)	4 (1.8)
>1	1 (1.4)	1 (1.4)	1 (1.4)	3 (1.4)
Type of Transplant, N (%)				
Living-related	15 (20.3)	12 (16.9)	8 (11.0)	35 (16.1)
Living-unrelated	8 (10.8)	7 (9.9)	8 (11.0)	23 (10.6)
Cadaveric	51 (68.9)	52 (73.2)	57 (78.1)	160 (73.4)

Baseline Characteristic	Belatacept-MI (N=74)	Belatacept-LI (N=71)	CsA (N=73)	Total (N=218)
Cold Ischemia Time (Hr)				
N	51	51	57	159
Mean (SD)	20.4 (7.0)	20.1 (8.0)	17.9 (7.3)	19.4 (7.5)
Median	20.1	19.9	16.7	19.0
Min-Max	(4.8 - 35.4)	(3.0 - 37.7)	(5.0 - 36.8)	(3.0 - 37.7)
Q1-Q3	(15.6 - 24.0)	(14.3 - 24.7)	(13.1 - 22.3)	(14.2 - 23.9)
Anti-Hypertensive, N (%)				
No	18 (24.3)	15 (21.1)	14 (19.2)	47 (21.6)
Yes	56 (75.7)	56 (78.9)	59 (80.8)	171 (78.4)
Lipid-Lowering, N (%)				
No	53 (71.6)	61 (85.9)	55 (75.3)	169 (77.5)
Yes	21 (28.4)	10 (14.1)	18 (24.7)	49 (22.5)
Anti-Diabetic, N (%)				
No	69 (93.2)	66 (93.0)	62 (84.9)	197 (90.4)
Yes	5 (6.8)	5 (7.0)	11 (15.1)	21 (9.6)
Viral Serology: CMV, N (%)				
D+/R+	22 (29.7)	25 (35.2)	24 (32.9)	71 (32.6)
D+/R-	11 (14.9)	16 (22.5)	16 (21.9)	43 (19.7)
D-/R+	20 (27.0)	15 (21.1)	12 (16.4)	47 (21.6)

Baseline Characteristic	Belatacept-MI (N=74)	Belatacept-LI (N=71)	CsA (N=73)	Total (N=218)
D-/R-	17 (23.0)	13 (18.3)	19 (26.0)	49 (22.5)
Not Done	4 (5.4)	2 (2.8)	2 (2.7)	8 (3.7)
Viral Serology: EBV, N (%)				
D+/R+	21 (28.4)	23 (32.4)	26 (35.6)	70 (32.1)
D+/R-	0 (0.0)	2 (2.8)	0 (0.0)	2 (0.9)
D-/R+	6 (8.1)	4 (5.6)	2 (2.7)	12 (5.5)
D-/R-	3 (4.1)	0 (0.0)	1 (1.4)	4 (1.8)
Not Done	44 (59.5)	42 (59.2)	44 (60.3)	130 (59.6)

Population : All randomized and transplanted subjects

Belatacept-MI: Belatacept more intensive and Belatacept-LI: Belatacept less intensive Note: "not done" means that there were no values for the donor, the recipient, or both individuals.

Numbers analysed

Intent-to-treat (ITT) dataset: included all randomised subjects who received a renal transplant.

Per-protocol (PP) dataset: included all randomised and transplanted subjects who did not violate the terms of the protocol that might have affected the efficacy outcome, as determined by the medical monitor.

As-treated dataset: included all randomised subjects who received a renal transplant and at least 1 dose of study medication.

Outcomes and estimation

Primary efficacy endpoint

The primary endpoint, acute rejection at 6 months, occurred infrequently and with similar frequency in all treatment groups. Both belatacept treatment arms (MI and LI) fulfilled the prespecified criteria for non-inferiority to CsA. The results are shown in Table 25.

Table 25. Summary of Acute Rejection up to Month 6 (Intent-To-Treat Analysis)

	Belatacept More Intensive (N = 74)	Belatacept Less Intensive (N = 71)	CsA (N = 73)
Up to Month 6			
Total Number of Subjects in the Population	74	71	73
Number of Subjects with Events (%)	5 (6.8%)	4 (5.6%)	6 (8.2%)
Mild Acute (IA)	2 (2.7%)	0 (0.0%)	1 (1.4%)
Mild Acute (IB)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Moderate Acute (IIA)	2 (2.7%)	3 (4.2%)	2 (2.7%)
Moderate Acute (IIB)	1 (1.4%)	1 (1.4%)	2 (2.7%)
Severe Acute (III)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asymptotic 95% Confidence Interval (%)	1.0 - 12.5	0.3 - 11.0	1.9 - 14.5
Difference in Event Rates (Belatacept - CsA) With Asymptotic 95% Confidence Interval (%)	-1.5 (-10.0,7.0)	-2.6 (-10.9, 5.7)	---

Population : All randomized and transplanted subjects

NOTE: For subjects who have more than one rejection, the most severe one is presented.

Acute Rejection is defined as Clinically suspected and Biopsy Proven rejection

Clinically-suspected is defined as increase in the serum creatinine from baseline >= 0.5 mg/dL.

Biopsy-proven acute rejection was assessed by the central pathologist.

Secondary endpoints

Acute rejection

The results for acute rejection at 12 months were similar to that seen at 6 months.

Table 26. Summary of Acute Rejection up to Year 1 (Intent-To-Treat Analysis)

	Belatacept More Intensive (N = 74)	Belatacept Less Intensive (N = 71)	CsA (N = 73)
Up to Year 1			
Total Number of Subjects in the Population	74	71	73
Number of Subjects with Events (%)	5 (6.8%)	4 (5.6%)	6 (8.2%)
Mild Acute (IA)	2 (2.7%)	0 (0.0%)	1 (1.4%)
Mild Acute (IB)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Moderate Acute (IIA)	2 (2.7%)	3 (4.2%)	2 (2.7%)
Moderate Acute (IIB)	1 (1.4%)	1 (1.4%)	2 (2.7%)
Severe Acute (III)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asymptotic 95% Confidence Interval (%)	1.0 - 12.5	0.3 - 11.0	1.9 - 14.5
Difference in Event Rates (Belatacept - CsA) With Asymptotic 95% Confidence Interval (%)	-1.5 (-10.0, 7.0)	-2.6 (-10.9, 5.7)	---

Biopsy proven acute rejection

Table 27. Summary of Biopsy-Proven Acute Rejection up to Year 1 (Intent-To-Treat Analysis)

	Belatacept More Intensive (N = 74)	Belatacept Less Intensive (N = 71)	CsA (N = 73)
Up to Year 1			
Total Number of Subjects in the Population	74	71	73
Number of Subjects with Events (%)	14 (18.9%)	21 (29.6%)	13 (17.8%)
Mild Acute (IA)	3 (4.1%)	4 (5.6%)	3 (4.1%)
Mild Acute (IB)	1 (1.4%)	4 (5.6%)	1 (1.4%)
Moderate Acute (IIA)	5 (6.8%)	8 (11.3%)	7 (9.6%)
Moderate Acute (IIB)	5 (6.8%)	5 (7.0%)	2 (2.7%)

	Belatacept More Intensive (N = 74)	Belatacept Less Intensive (N = 71)	CsA (N = 73)
Severe Acute (III)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asymptotic 95% Confidence Interval (%)	10.0 - 27.8	19.0 - 40.2	9.0 - 26.6
Difference in Event Rates (Belatacept - CsA) With Asymptotic 95% Confidence Interval (%)	1.1 (-11.4, 13.6)	11.8 (-2.0, 25.5)	---

Population : All randomized and transplanted subjects

NOTE: For subjects who have more than one rejection, the most severe one is presented.

Biopsy-proven acute rejection was assessed by the central pathologist.

Figure 16. Kaplan-Meier for Biopsy proven Acute Rejection through Month 12. ITT Population.

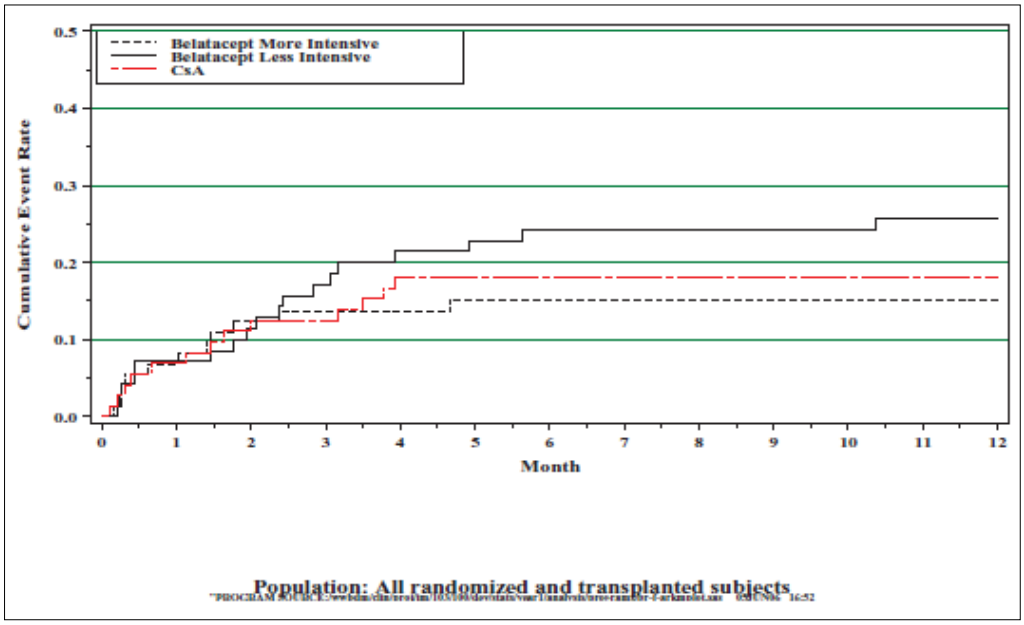


Table 28. Biopsy-proven acute rejection by belatacept maintenance treatment schedule

	MI every 4 weeks	MI Every 8 weeks	LI Every 4 weeks	LI Every 8 weeks
Month 6	1/31 (3%)	2/29 (7%)	7/31(23%)	5/31 (16%)
Month 12	2/31(7%)	4/29 (14%)	7/31 (23%)	9/31 (29%)

Death and graft survival

Table 29. Summary of Death or Graft Loss up to Year 1. (Intent-To-Treat Analysis)

	Belatacept More Intensive (N = 74)	Belatacept Less Intensive (N = 71)	CsA (N = 73)
Up to Year 1			
Total Number of Subjects in the Population	74	71	73
Number of Subjects with Events (%)	4 (5.4%)	1 (1.4%)	6 (8.2%)
Graft Loss (%)	3 (4.1%)	1 (1.4%)	3 (4.1%)
Death (%)	1 (1.4%)	0 (0.0%)	4 (5.5%)
Asymptotic 95% Confidence Interval (%)	0.3 - 10.6	0.0 - 4.1	1.9 - 14.5
Difference in Event Rates (Belatacept - CsA) With Asymptotic 95% Confidence Interval (%)	-2.8 (-11.0, 5.3)	-6.8 (-13.7, 0.1)	---

Renal function.

Table 30. Summary of Iohexol Clearance Rate (mL/min/1.73 m2) up to Year 1. (Intent-To-Treat Analysis)

	Belatacept More Intensive (N = 74)	Belatacept Less Intensive (N = 71)	CsA (N = 73)
Month 1 n	53	51	48
Mean (Std)	59.7 (17.3)	60.2 (14.4)	54.0 (19.3)

	Belatacept More Intensive (N = 74)	Belatacept Less Intensive (N = 71)	CsA (N = 73)
Median	58.3	60.5	52.5
Q25 - Q75	46.2 - 71.4	52.9 - 68.8	43.2 - 64.5
Min - Max	28.6 - 102.0	17.8 - 103.4	14.7 - 110.6
Month 6 n	41	41	31
Mean (Std)	62.2 (25.6)	64.5 (19.5)	56.0 (19.5)
Median	61.0	63.2	54.4
Q25 - Q75	52.1 - 70.3	52.0 - 71.5	45.0 - 68.6
Min - Max	30.9 - 186.3	24.8 - 145.3	11.4 - 96.9
Month 12 n	32	37	27
Mean (Std)	66.3 (20.7)	62.1 (15.9)	53.5 (16.4)
Median	66.9	60.8	49.3
Q25 - Q75	53.5 - 79.5	50.9 - 69.5	45.4 - 64.4
Min - Max	1.6 - 100.4	28.0 - 109.3	19.2 - 89.6

Table 31. Summary of Serum Creatinine (mg/dL) up to Year 1. (Intent-To-Treat Analysis)

	Belatacept More Intensive (N = 74)	Belatacept Less Intensive (N = 71)	CsA (N = 73)
Day 8 n	62	62	60
Mean (Std)	2.8 (2.3)	2.9 (2.4)	2.9 (2.7)
Median	1.9	1.8	1.8
Q25 - Q75	1.3 - 3.2	1.4 - 3.9	1.3 - 3.4
Min - Max	0.6 - 11.2	0.6 - 10.8	0.6 - 12.5
Month 1 n	68	69	65
Mean (Std)	1.3 (0.5)	1.3 (0.5)	1.6 (1.0)
Median	1.2	1.2	1.3

	Belatacept More Intensive (N = 74)	Belatacept Less Intensive (N = 71)	CsA (N = 73)
Q25 - Q75	1.0 - 1.4	1.0 - 1.5	1.0 - 1.6
Min - Max	0.7 - 2.8	0.7 - 4.0	0.6 - 6.1
Month 3 n	62	63	58
Mean (Std)	1.3 (0.6)	1.3 (0.5)	1.4 (0.8)
Median	1.2	1.2	1.2
Q25 - Q75	1.0 - 1.6	1.0 - 1.6	1.1 - 1.5
Min - Max	0.6 - 4.6	0.6 - 3.2	0.5 - 5.4
Month 6 n	62	66	54
Mean (Std)	1.2 (0.4)	1.2 (0.3)	1.4 (0.7)
Median	1.2	1.2	1.3
Q25 - Q75	1.0 - 1.5	1.0 - 1.4	1.1 - 1.5
Min - Max	0.6 - 2.9	0.6 - 1.9	0.5 - 3.9
Month 9 n	57	58	42
Mean (Std)	1.2 (0.5)	1.2 (0.4)	1.4 (0.8)
Median	1.1	1.1	1.2
Q25 - Q75	0.9 - 1.5	0.9 - 1.4	1.0 - 1.7
Min - Max	0.5 - 2.6	0.6 - 2.7	0.5 - 4.2
Month 12 n	60	59	50
Mean (Std)	1.2 (0.5)	1.2 (0.6)	1.4 (1.3)
Median	1.1	1.1	1.2
Q25 - Q75	0.9 - 1.4	0.9 - 1.4	0.9 - 1.4
Min - Max	0.7 - 3.0	0.6 - 4.4	0.5 - 9.6

Table 32. Summary of Calculated GFR (mL/min/1.73 m2) using Levey Formula up to Year 1. (Intent-To-Treat Analysis)

	Belatacept More Intensive (N = 74)	Belatacept Less Intensive (N = 71)	CsA (N = 73)
Day 8 n	62	62	60
Mean (Std)	41.8 (25.6)	37.9 (22.8)	39.9 (25.3)
Median	40.1	41.9	36.6
Q25 - Q75	19.1 - 57.0	16.6 - 52.7	17.9 - 58.6
Min - Max	5.1 - 104.8	4.5 - 101.3	4.5 - 101.5
Month 1 n	68	69	65
Mean (Std)	65.3 (21.4)	65.6 (20.6)	56.9 (20.9)
Median	61.8	66.8	58.6
Q25 - Q75	48.8 - 78.8	51.8 - 74.8	43.3 - 68.5
Min - Max	26.0 - 117.0	18.9 - 132.5	12.1 - 113.7
Month 3 n	62	63	58
Mean (Std)	66.1 (22.1)	67.8 (22.6)	63.4 (27.6)
Median	64.4	69.3	60.5
Q25 - Q75	50.9 - 77.9	50.1 - 78.1	49.2 - 73.8
Min - Max	13.1 - 123.9	24.6 - 122.0	9.2 - 174.5
Month 6 n	62	65	54
Mean (Std)	70.1 (21.1)	69.9 (20.0)	63.3 (26.5)
Median	67.2	68.5	62.9
Q25 - Q75	54.2 - 83.6	56.0 - 80.3	46.2 - 79.3
Min - Max	17.6 - 118.3	29.5 - 126.1	13.6 - 147.0
Month 9 n	57	58	41
Mean (Std)	72.4 (24.7)	72.0 (22.5)	63.9 (30.2)
Median	72.2	69.8	61.5

	Belatacept More Intensive (N = 74)	Belatacept Less Intensive (N = 71)	CsA (N = 73)
Q25 - Q75	55.1 - 86.1	55.3 - 91.5	43.9 - 79.1
Min - Max	21.4 - 135.5	26.1 - 122.6	13.5 - 135.8
Month 12 n	60	59	50
Mean (Std)	72.4 (22.5)	73.2 (22.5)	68.0 (28.1)
Median	72.1	72.3	67.5
Q25 - Q75	57.0 - 88.8	57.3 - 89.2	51.0 - 79.0
Min - Max	18.6 - 118.0	16.7 - 116.4 0	5.5 - 136.

Summary of efficacy results

- Similar acute rejection was seen at 6 months and 12 months in each treatment arms. The prespecified criteria for non-inferiority to CsA was met by both belatacept treatment arms.
- None of the subjects experienced severe (Grade III rejections). Few subjects in any treatment group experienced > 1 episode of BPAR
- By Month 12, the incidence of CAN was lower in both belatacept groups than in the CsA group. The incidence of CAN was higher in the belatacept MI group than in the LI group
- By Month 12, 5 deaths had been reported (1 and 4 in the belatacept MI and CsA groups, respectively). Seven graft losses were reported (3 each in the belatacept MI and CsA groups and 1 in the belatacept LI group)
- At Month 6 and 12 the mean iohexol clearance was greater in both belatacept groups than in the CsA group
- At Months 6 and 12, mean total cholesterol and triglyceride values were numerically lower than both belatacept groups than in the CsA group
- The overall incidence of PTDM was low and similar among the treatment groups
- At Month 6, the prevalence of hypertension as similar in the belatacept MI and CsA groups and numerically lower in the belatacept LI group. At Month 12, the prevalence of hypertension was numerically lower in both belatacept groups than in the CsA group.

IM103100 long term extension study (LTE)

The primary objective of the long term extension study was to assess the ongoing safety and tolerability of belatacept but additional efficacy and immunogenicity data was also collected.

Overall 128 subjects entered the LTE phase; 102 in the combined belatacept group and 26 in the CsA group. Two belatacept subjects were not treated with the study drug after consenting to enrol.

The sample size was not re-calculated and no statistical analysis was done with all results simply summarised descriptively. As the study consists of subjects who have self selected from

those who did not discontinue from the first year of the study they tended to have better renal function. In addition there was differential enrolment from the belatacept and CsA group with more subjects in the CsA group deciding not to enrol in the LTE. This resulted in a very small control group which limits the ability to make comparisons across treatment groups. Therefore only key data from this study is presented.

It is noted that the date of the LTE study report is July 2008 with a data cut-off of Oct 2007. It is disappointing that a more recent update was not provided.

Safety data from this study are discussed under *Safety* below.

Results

Acute rejection

Two cases of acute rejection (CSBPAR) were reported, both in the belatacept group (1 each in the MI-8 week and LI-8 week groups). A total of 6 cases (6%) of BPAR, including the 2 cases of CSBPAR confirmed by the central pathologist were reported; all occurred in the combined belatacept group. All of these cases were mild or moderate in severity.

Deaths and graft survival

Five deaths were reported: 3 in the combined belatacept group (2 died with a functioning graft) and 2 in the CsA group (both died with a functioning graft). Two subjects experienced graft loss; both occurred in the combined belatacept group.

Renal function

Table 33. Creatinine clearance

	Combined belatacept group	CsA group.
Mean calculated creatinine clearance (Cockcroft-Gault formula)		
12 months	88.3 mL/min/m^2	83.2 mL/min/m^2
60 months	86.4 mL/min/m^2	66.8 mL/min/m^2
mean calculated creatinine GFR (MDRD formula)		
12 months	75.8 mL/min/m^2	74.4 mL/min/m^2
60 months	77.2 mL/min/m^2	59.3 mL/min/m^2

The prevalence of CAN (all cases in the LTE phase) was 32 cases (31%) in the combined belatacept group and 11 cases (42%) in the CsA group. The incidence of CAN (all new cases reported in the LTE phase) was 25 cases (25%) in the combined belatacept group and 9 cases (35%) in the CsA group.

Conclusions

Very few conclusions can be drawn from this study but within the limitations of the study the results are consistent with the results seen from the 3 year data in the Phase III studies.

Clinical studies in special populations

All three efficacy studies were conducted in renal transplant recipients. No other special populations were studied that are relevant to this application.

Analysis performed across trials (pooled analyses)

Pooled core studies

A post hoc analysis was provided of select long term efficacy and safety parameters from the pivotal studies; IM103008, IM103027 and IM103100. This analysis was done to provide additional efficacy analysis to the individual 36 month clinical study reports. The pooled study report is dated November 2010.

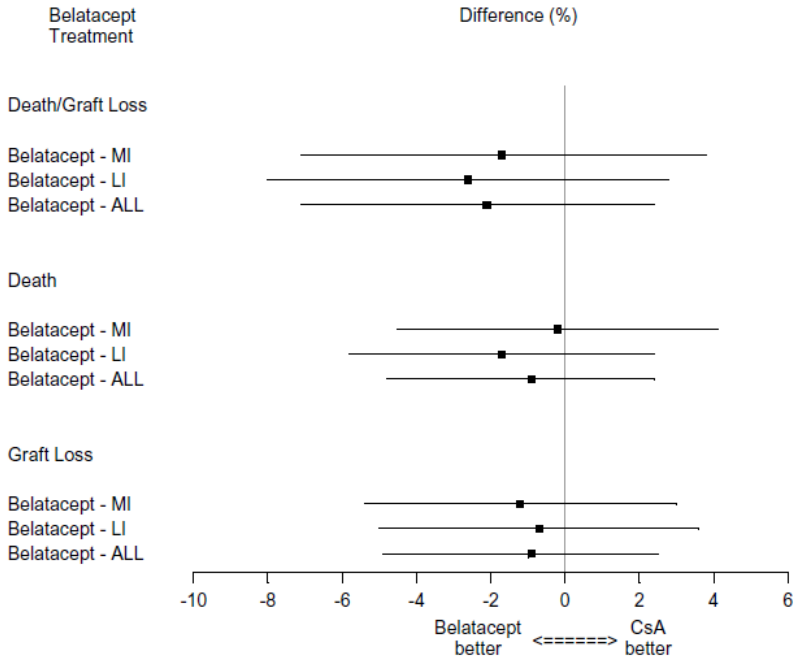
Each of the 3 studies was a randomised, partially blinded, parallel group, multicentre trial that evaluated 2 belatacept treatment regimens (more intensive MI and less intensive LI) versus a cyclosporin based regimen in de novo renal transplant recipients. In each study, subjects also received basiliximab induction and maintenance therapy with mycophenolate Mofetil and corticosteroids. The Phase III studies (IM103008 and IM103027) were designed as 36 month studies with the primary endpoint assessed at 12 months. The Phase II study (IM103100) was designed as a 12 month study with the primary endpoint assessed at 6 months. Subjects from all 3 core studies could elect to continue in their respective studies for long-term follow up.

Death and graft loss

The proportion of subjects treated with the LI regimen that experienced either death or graft loss was similar to CsA, with the lower bounds of the 97.3% CI indicating that subjects treated with belatacept had no more than 8% more events than those given CsA. The LI regimen was no more than 5% worse on the endpoint of graft loss.

The proportion of subjects who died was also comparable and ruled out that belatacept was more than 6% worse than CsA with regard to overall mortality. In each assessment, the point estimates for subject and graft survival favoured belatacept, and the results were similar when the MI and LI groups were pooled to increase the total number of events in the analysis.

Figure 17. Summary of difference of death or graft loss up to Month 36. Subjects pooled by randomised treatment group across studies IM103008 and IM10327.



Post transplant Diabetes Mellitus (PTDM)

The frequency of PTDM (defined as use of an anti-diabetic agent for >30 days or ≥ 2 fasting plasma glucose values > 126 mg/dL in a subject not diabetic at baseline), was lower in the belatacept LI than CsA group at Month 12 (4.6% versus 9.6%; p=0.018). The difference between treatment groups was not statistically significant at Month 36 (7.9% versus 10.4%). Consistent results were seen in the pooled belatacept MI group and in individual studies.

Dyslipidaemia

Compared to CsA, belatacept treatment had a favourable impact on non-high density lipoprotein (HDL) cholesterol. Mean non-HDL cholesterol increased from baseline to Month 12 and 36 in all treatment groups. In the pooled analysis, these adjusted increases were statistically significantly smaller (p<0.001) in the belatacept groups compared with CsA.

Supportive studies

Study IM103100 is variously described in the submission as pivotal or as supportive. It is included above as a pivotal trial.

There were a number of studies included which were Phase II studies in renal transplant but do not contribute significantly to the efficacy results. They are summarised in tabular form in the introduction to the clinical section. They were included in the submission primarily for contributing to safety.

Evaluator's overall conclusions on clinical efficacy

Key issues with the efficacy data include:

- same primary outcomes in the pivotal trials
  - composite of patient and graft survival at 12 months

  - the composite endpoint of renal function
    - GFR < 60 mL/min/1.73m^2 at Month 12
    - GFR decrease ≤ 10 mL/min/1.73m^2 from Month 3 to Month 12
    - GFR measured by the cold iothalamate method
- Acute rejection not consistent endpoint in pivotal trials
  - Co-primary endpoint in IM103008
  - Secondary endpoint in IM103027
  - Sole primary endpoint in IM103100
- Non-inferiority margin different in 2 pivotal trials. Is 20% NI margin acceptable for acute rejection compared to 10% NI margin for subject and graft survival?
- Are the endpoints in this submission consistent with that provided by other immunosuppressive agents?
- Problem of increased AR rate in belatacept in compared to CsA. More higher grade AR with belatacept
- Are endpoints and numbers found in trial sufficiently sensitive to see true differences?
- Better overall GFR with belatacept. Is this benefit of belatacept or absence of toxicity of CsA?

Overall the survival rate of subjects with a functioning graft was similar in the belatacept MI (95% and 86%) and LI (97% and 89%) groups and CsA (93% and 85%) group for study IM103008 and IM103027, respectively This met the pre-specified 10% non-inferiority margin. The lower margin of the 97.3% CIs for the difference between belatacept LI and CsA was 2% in Study IM103008 and 5% in Study 103027. The rates of the individual components were similar across treatment groups within each study.

While there is a consistently increased acute rejection rate with belatacept at 12 months this does not appear to translate to an impact on subject or graft loss. The question arises as to whether the trials were sensitive enough to detect a difference.

The non-inferiority margin of 20% for acute rejection is argued in the statistical analysis plan as justified by the sponsor on the basis of an assumption (based on published historical data) of an expected rate of AR of 53% for immunosuppressive regimens which did not rely on CNI. This was compared to the rate of AR of approximately 15% for CsA based regimens. It was therefore estimated that compared to placebo, the addition of CsA in a regimen with MMF would reduce the rate of AR by approximately 38%. A margin of 20% then represents a retention of around 50% of the activity of CsA over placebo for the prevention of AR. Review of past studies in renal transplantation for MMF treatment arms with a background of CsA the BPAR rate by 6 months was approximately 18-20% in the MMF treatment arms. Comparing the various trials there was a calculation that the lower 95% confidence bound for the point estimate gives the smallest effect size of 20%. The sponsor argues that the 20% non-inferiority margin preserves around 50% of the estimated CsA effect and is not greater than the estimated smallest effect size of CsA used with similar background therapy. This appears to be an acceptable justification but while it is sufficient to justify an effect over placebo it may not be sensitive enough to demonstrate an effect over current standard multidrug therapy.

Belatacept treatment resulted in a statistically significant improvement in renal function over CsA as assessed by both measured and calculated GFR. The differences were seen as early as 4 weeks after transplantation and were maintained for over 3 years after transplantation in

recipients of both SCD and ECD. Since CsA is known to be nephrotoxic this would appear to be the result of lack of toxicity from CsA rather than a direct benefit of belatacept.

This improvement in renal function did not appear to lead to improved graft or subject survival.

The pivotal studies conducted over 3 years have demonstrated that belatacept combined with background immunosuppressive regimen of basiliximab induction and maintenance therapy with MMF and corticosteroids has a comparable efficacy as judged by subject and graft loss and renal function to a treatment regimen of CsA and the same background therapy.

Safety

Study IM103008

Other data collected in this study have been summarised above under *Efficacy*.

Study safety assessments

All randomised subjects who received a renal transplant were evaluated for safety (Intent-to-Treat [ITT] dataset).

Safety assessment included: adverse events (AEs), clinically significant changes in vital signs, physical examination, laboratory tests abnormalities and electrocardiogram (ECG) abnormalities.

All women ≥ 40 years of age, or women of any age with first degree relative with a history of breast cancer or who had other risks of breast cancer had a mammogram at baseline and an annual mammogram.

Safety events of clinical interest (established from Phase II studies) were:

- All malignancies
- Post transplantation lymphoproliferative disorder (PTLD)
- Infections
- Chronic heart failure and pulmonary oedema
- Thrombotic/embolic episodes
- Proteinuria (2+ proteinuria on 2 consecutive visits (from central laboratory only)
- Cardiovascular events that included non-fatal myocardial infarction, stroke, and revascularisation (surgical or percutaneous) procedures
- Autoimmune events
- Infusional events: acute peri-infusional events (up to 1 hour after infusion) and peri-infusional events (up to 24 hours after infusion)

Safety

No statistical testing of any group differences was done. Results are summarised descriptively.

Table 34. Summary of Subjects with Adverse Events Reported after Randomization up to Month 36: All Randomised and Transplanted Subjects (ITT)

Randomisation up to Month 36:	Belatacept – MI (N=219)	Belatacept – LI (N=226)	Cyclosporine (N=221)
Deaths	7 (3.2)	5 (2.2)	11 (5.0)
SAEs	133 (60.7)	131 (58.0)	150 (67.9)
Related SAEs	62 (28.3)	50 (22.1)	68 (30.8)
Discontinued due to SAEs	13 (5.9)	14 (6.2)	18 (8.1)
AEs	218 (99.5)	225 (99.6)	219 (99.1)
Related AEs	141 (64.4)	150 (66.4)	180 (81.4)
Discontinued due to AEs	16 (7.3)	16 (7.1)	31 (14.0)

Overall safety summary

Deaths and SAEs were reported with similar frequency across all treatment groups in the first 12 months but by Month 36 were slightly lower in both belatacept groups than CsA

The overall proportion of subjects with infections was comparable. The annual incidence rates of viral and fungal infections decreased over time in all three treatment groups.

A total of 7 subjects developed TB by Month 36: 4 (MI), 2 (LI) and 1 (CsA). One MI and 2 LI subjects developed TB after Month 24. All patients were enrolled in India.

The proportion of subjects in all 3 treatment groups with thrombotic/embolic events, pulmonary oedema, heart failure and proteinuria by Month 36 were comparable; few events occurred post Month 12.

By Month 36, few subjects reported autoimmune events: 1%, 1%, and 3% in the belatacept MI, LI, and CsA groups, respectively.

By Month 36, 3, 2, 1 subjects in the belatacept MI, LI and CsA groups had post transplant lymphoproliferative disorder (PTLD); 2 PTLD events occurred between Month 12 and Month 18. No PTLD events were reported after Month 18 in this study

Treatment related AEs (TEAEs) reported

Table 35. TEAEs

Time	Belatacept MI N=219	Belatacept LI N=226	CsA N=221
By end Month 12	53%	54%	74%
By end Month 24	61%	62%	79%

Time	Belatacept MI N=219	Belatacept LI N=226	CsA N=221
By end Month 36	65%	66%	81%

Malignancies

Table 36. Malignancies

	Belatacept MI N=219	Belatacept LI N=226	CsA N=221
By end Month 12	2%	2%	1%
By end Month 24	6%	3%	4%
By end Month 36	8%	4%	5%

PTLD

Table 37. PTLD

	Belatacept MI N=219	Belatacept LI N=226	CsA N=221
By end Month 12	1	2	1
By end Month 24	3	2	1
By end Month 36	3	2	1
Post 36 months	3	2	1

Infections

Overall the proportions of subjects with infections (all and viral) were comparable between the treatment groups. The most common infections in all treatment groups were urinary tract infections, influenza and nasopharyngitis. Infections led to discontinuation of study therapy in 3%, 2% and 1% of subjects (belatacept MI, LI and CsA, respectively).

Viral infections which led to death occurred in 3 subjects; one due to polyoma-associated nephropathy, one due to West Nile virus infection and one due to CMV infection. Incidence rates of polyoma virus infection were similar between the treatment groups.

Autoimmune events

By 36 months the number of autoimmune events was low and comparable between treatment groups. In each treatment group, all autoimmune disorders were reported by 1 subject each, with the exception of hyperthyroidism which was reported by 2 subjects in the CsA group. One event of demyelination (belatacept MI) and one of psoriasis (belatacept LI) were considered by the investigator to be treatment related. None of the autoimmune events led to discontinuation.

Peri-infusional events

By 36 months, AEs of acute infusional events were reported in approximately 4% of subjects (8 in MI and 10 in LI). The most common acute infusional events were hypertension and infusion site extravasation in the MI group and hypertension and hypotension in the LI group.

Clinical laboratory monitoring

Full laboratory monitoring of haematology and biochemistry was conducted throughout the study and overall there no unexpected marked abnormalities and the proportion of marked abnormalities was balanced between the treatment groups.

Table 38. Incidence Rates of the Most Common Serious Adverse Events Reported after Randomisation up to Month 36: All Randomized and Transplanted Subjects (ITT)

	Treatment Group								
	Belatacept – MI (N=219)			Belatacept – LI (N=226)			Cyclosporine (N=221)		
System Organ Class Preferred Term	Subjects with Event (%)	Exposure – (patient years)	Incidence Rate*	Subjects with Event (%)	Exposure (patient – years)	Incidence Rate*	Subjects with Event (%)	Exposure (patient – years)	Incidence Rate*
Total Subjects with SAE	133 (60.7)			131 (58.0)			150 (67.9)		
Infections and Infestations	62 (28.3)	420.4	14.7	73 (32.3)	444.9	16.4	73 (33.0)	381.0	19.2
Urinary Tract Infection	13 (5.9)	492.6	2.6	16 (7.1)	520.6	3.1	25 (11.3)	458.1	5.5
Cytomegalovirus Infection	12 (5.5)	499.6	2.4	12 (5.3)	527.6	2.3	7 (3.2)	490.6	1.4
Gastroenteritis	6 (2.7)	513.1	1.2	3 (1.3)	544.0	0.6	4 (1.8)	499.2	0.8
Pyelonephritis	5 (2.3)	516.2	1.0	7 (3.1)	538.0	1.3	4 (1.8)	498.1	0.8
Pyelonephritis acute	5 (2.3)	510.6	1.0	2 (0.9)	546.3	0.4	2 (0.9)	502.2	0.4
Pneumonia	3 (1.4)	518.5	0.6	7 (3.1)	544.9	1.3	10 (4.5)	493.5	2.0

	Treatment Group								
Renal and Urinary Disorders	29 (13.2)	460.3	6.3	25 (11.1)	502.6	5.0	42 (19.0)	439.9	9.5
Renal Impairment	4 (1.8)	510.8	0.8	6 (2.7)	540.6	1.1	3 (1.4)	502.5	0.6
Renal Failure Acute	4 (1.8)	512.5	0.8	3 (1.3)	546.0	0.5	8 (3.6)	492.5	1.6
Gastrointestinal Disorders	27 (12.3)	482.4	5.6	18 (8.0)	524.4	3.4	26 (11.8)	469.3	5.5
Diarrhoea	4 (1.8)	518.2	0.8	7 (3.1)	538.7	1.3	9 (4.1)	494.7	1.8
Abdominal Pain	3 (1.4)	515.6	0.6	1 (0.4)	545.9	0.2	5 (2.3)	496.0	1.0
Injury, Poisoning and Procedural Complications	25 (11.4)	477.7	5.2	27 (11.9)	492.3	5.5	37 (16.7)	440.7	8.4
Graft Dysfunction	4 (1.8)	512.4	0.8	7 (3.1)	530.7	1.3	12 (5.4)	479.2	2.5
Therapeutic agent Toxicity	0	519.3	0.0	0	548.9	0.0	7 (3.2)	491.8	1.4
Neoplasms benign,	19 (8.7)	497.1	3.8	9 (4.0)	541.1	1.7	12 (5.4)	486.9	2.5

	Treatment Group								
malignant and unspecified (incl cysts and polyps)									
Basal cell carcinoma	5 (2.3)	510.5	1.0	3 (1.3)	548.4	0.5	4 (1.8)	499.0	0.8
General disorders and administration site conditions	18 (8.2)	492.0	3.7	16 (7.1)	529.1	3.0	18 (8.1)	473.5	3.8
Pyrexia	12 (5.5)	500.2	2.4	10 (4.4)	532.6	1.9	11 (5.0)	481.3	2.3
Blood and lymphatic system disorders	15 (6.8)	494.8	3.0	8 (3.5)	533.2	1.5	12 (5.4)	490.2	2.4
Anaemia	5 (2.3)	507.6	1.0	2 (0.9)	545.4	0.4	5 (2.3)	500.9	1.0
Leucopoenia	5 (2.3)	511.3	1.0	1 (0.4)	547.5	0.2	4 (1.8)	497.9	0.8
Cardiac disorders	13 (5.9)	503.5	2.6	10 (4.4)	534.0	1.9	14 (6.3)	487.2	2.9
Cardiac arrest	2 (0.9)	519.0	0.4	2 (0.9)	548.7	0.4	5 (2.3)	499.2	1.0
Investigations	11 (5.0)	500.6	2.2	14 (6.2)	520.8	2.7	15 (6.8)	474.7	3.2

	Treatment Group								
Blood creatinine increased	4 (1.8)	513.3	0.8	10 (4.4)	525.7	1.9	12 (5.4)	480.4	2.5
Vascular disorders	11 (5.0)	497.8	2.2	13 (5.8)	532.0	2.4	22 (10.0)	469.6	4.7
Lymphocele	2 (0.9)	516.2	0.4	2 (0.9)	543.9	0.4	8 (3.6)	488.9	1.6
Endocrine disorders	2 (0.9)	515.4	0.4	2 (0.9)	543.6	0.4	5 (2.3)	494.5	1.0
Hyper-parathyroidism	2 (0.9)	515.4	0.4	2 (0.9)	543.6	0.4	5 (2.3)	494.5	1.0

The exposure (patient-years) of a subject is calculated from randomization date to the event date, or the last dose date+56,or Month 36, whichever is the earliest.

Incidence >= 2 percent is based on preferred term in any treatment group.

* Incidence Rate = Per 100 person-years

MedDRA Version: 13.0

Study IM103027

This study is also discussed under *Efficacy* above.

Safety analysis

There was no statistical testing of group differences with respect to frequencies of all AEs or laboratory abnormalities or changes in clinical laboratory tests from baseline.

No statistical analysis of safety was undertaken by the company. All results are presented only in descriptive terms. Differences between the groups are claimed by the company but the significance of these differences is uncertain.

Table 39. Summary of Subjects with Adverse Events Reported After Randomization up to Month 36. All Randomized and Transplanted Subjects (ITT)

	Belatacept – MI (N=184)	Belatacept – LI (N=175)	Cyclosporin (N=184)
Randomization up to Month 36:	**N (%)**	**N (%)**	**N (%)**
Deaths	18 (9.8)	8 (4.6)	10 (5.4)
SAEs	149 (81.0)	139 (79.4)	146 (79.3)
Related SAEs	60 (32.6)	51 (29.1)	58 (31.5)
Discontinued due to SAEs	31 (16.8)	31 (17.7)	28 (15.2)
AEs	182 (98.9)	174 (99.4)	184 (100)
Related AEs	115 (62.5)	106 (60.6)	141 (76.6)
Discontinued due to AEs	34 (18.5)	36 (20.6)	44 (23.9)
Events of Clinical Interest			
Malignancies	16 (8.7%)	15 (8.6%)	19 (10.3%)
PTLD (up to database lock)	2 (1.1%)	4 (2.3%)	0*
Tuberculosis	2 (1.1%)	4 (2.3%)	0
Fungal Infections	45 (24.5%)	24 (13.7%)	43 (23.4%)
Viral Infections	73 (39.7%)	68 (38.9%)	70 (38.0%)
CMV infections	32 (17.4%)	27 (15.4%)	31 (16.8%)
Polyoma virus infections	12 (6.5%)	7 (4.0%)	9 (4.9%)

	Belatacept – MI (N=184)	Belatacept – LI (N=175)	Cyclosporin (N=184)
Herpes infections	32 (17.4%)	29 (16.6%)	25 (13.6%)
Autoimmune Events	6 (3.3%)	5 (2.9%)	3 (1.6%)
Pulmonary Oedema	6 (3.3%)	8 (4.6%)	7 (3.8%)
Heart Failure	14 (7.6%)	7 (4.0%)	7 (3.8%)
Thrombotic and Embolic Events	25 (13.6%)	27 (15.4%)	24 (13.0%)

Population: All Randomized and Transplanted Subjects

* One case of PTLD was reported in a CsA-treated subject after database lock.

Deaths

Table 40. Deaths

Time	Belatacept MI N=184		Belatacept LI N=175		CsA N=184	
	n	**%**	**n**	**%**	**n**	**%**
Up to 12 months	8	4	4	4	8	4
Up to 24 months	13	7	11	6	12	7
Up to 36 months	22	12	15	9	17	9

The rate of death appears higher in the Belatacept MI group and comparable between the Belatacept LI and CsA group.

The most common cause of death in all 3 treatment groups was infection (5-7 per group). Of the AEs which resulted in death the causes in those where there was more than 1 were: sudden death (3), sepsis (2), CVA (2) in the belatacept MI group and septic shock (4), cardiopulmonary arrest (2) and CVA (2) in the CsA group.

Serious adverse events (SAEs)

The rates of SAEs were comparable across the treatment groups. The most common SAEs in all treatment groups were infections and included urinary infections and CMV.

Table 41. Incidence Rates of the Most Common Serious Adverse Events Reported after Randomization up to Month 36: All Randomized and Transplanted Subjects (ITT). Table continued across three pages.

	Belatacept – MI (N=184)			Belatacept – LI (N=175)			Cyclosporin (N=184)		
System Organ Class Preferred Term	**Subjects with Event (%)**	**Exposure (patient-years)**	**Incidence Rate***	**Subjects with Event (%)**	**Exposure (patient-years)**	**Incidence Rate***	**Subjects with Event (%)**	**Exposure (patient-years)**	**Incidence Rate***
Total subjects with SAE	149 (81.0)			139 (79.4)			146 (79.3)		
Infections and infestations	**89 (48.4)**	**232.5**	**38.3**	**71 (40.6)**	**270.7**	**26.2**	**84 (45.7)**	**254.3**	**33.0**
Urinary tract infection	19 (10.3)	352.4	5.4	22 (12.6)	352.3	6.2	18 (9.8)	357.5	5.0
Cytomegalovirus infection	17 (9.2)	360.6	4.7	16 (9.1)	363.0	4.4	12 (6.5)	360.1	3.3
Pyelonephritis	10 (5.4)	370.2	2.7	1 (0.6)	386.0	0.3	9 (4.9)	366.4	2.5
Pneumonia	9 (4.9)	374.7	2.4	4 (2.3)	385.5	1.0	6 (3.3)	373.3	1.6
Gastroenteritis	7 (3.8)	377.0	1.9	2 (1.1)	384.7	0.5	3 (1.6)	374.3	0.8
Herpes zoster	6 (3.3)	377.7	1.6	2 (1.1)	385.2	0.5	1 (0.5)	376.8	0.3
Sepsis	5 (2.7)	382.8	1.3	3 (1.7)	383.5	0.8	5 (2.7)	374.2	1.3
Urosepsis	3 (1.6)	384.5	0.8	5 (2.9)	383.3	1.3	5 (2.7)	370.8	1.3

	Belatacept – MI (N=184)			Belatacept – LI (N=175)			Cyclosporin (N=184)		
Pyelonephritis acute	3 (1.6)	380.1	0.8	0	388.7	0.0	4 (2.2)	367.9	1.1
Septic shock	1 (0.5)	385.4	0.3	1 (0.6)	388.6	0.3	4 (2.2)	378.1	1.1
Escherichia urinary tract Infection	1 (0.5)	383.3	0.3	0	388.7	0.0	4 (2.2)	370.3	1.1
Renal and urinary disorders	**43 (23.4)**	**330.2**	**13.0**	**36 (20.6)**	**320.8**	**11.2**	**49 (26.6)**	**308.1**	**15.9**
Renal failure acute	7 (3.8)	379.0	1.8	4 (2.3)	382.0	1.0	8 (4.3)	370.0	2.2
Renal vein thrombosis	6 (3.3)	385.1	1.6	1 (0.6)	388.6	0.3	0	378.7	0.0
Ureteric stenosis	4 (2.2)	380.1	1.1	3 (1.7)	382.9	0.8	4 (2.2)	374.4	1.1
Renal artery stenosis	2 (1.1)	382.3	0.5	5 (2.9)	375.5	1.3	6 (3.3)	369.8	1.6
Renal impairment	2 (1.1)	383.9	0.5	3 (1.7)	384.0	0.8	7 (3.8)	374.0	1.9
Urinary fistula	1 (0.5)	385.3	0.3	0	388.7	0.0	6 (3.3)	365.9	1.6
Injury,	**36 (19.6)**	**328.4**	**11.0**	**39 (22.3)**	**334.0**	**11.7**	**53 (28.8)**	**313.0**	**16.9**

	Belatacept – MI (N=184)			Belatacept – LI (N=175)			Cyclosporin (N=184)		
poisoning and Procedural complications									
Graft dysfunction	8 (4.3)	368.9	2.2	6 (3.4)	374.9	1.6	11 (6.0)	364.2	3.0
Graft loss	4 (2.2)	385.5	1.0	4 (2.3)	388.2	1.0	6 (3.3)	377.8	1.6
Complications of Transplanted kidney	3 (1.6)	382.6	0.8	7 (4.0)	382.2	1.8	7 (3.8)	372.1	1.9
Wound dehiscence	1 (0.5)	384.0	0.	3 5 (2.9)	382.7	1.3	2 (1.1)	374.0	0.5
Gastrointestinal disorders	**29 (15.8)**	**343.9**	**8.4**	**22 (12.6)**	**353.1**	**6.2**	**28 (15.2)**	**339.6**	**8.2**
Diarrhoea	14 (7.6)	371.3	3.8	7 (4.0)	375.3	1.9	4 (2.2)	375.8	1.1
Vomiting	2 (1.1)	383.2	0.5	2 (1.1)	383.1	0.5	5 (2.7)	371.6	1.3
Cardiac disorders	**26 (14.1)**	**353.8**	**7.3**	**15 (8.6)**	**364.8**	**4.1**	**24 (13.0)**	**351.8**	**6.8**
Atrial fibrillation	7 (3.8)	376.5	1.9	5 (2.9)	383.1	1.3	2 (1.1)	373.5	0.5
Cardiac failure	5 (2.7)	382.3	1.3	2 (1.1)	384.1	0.5	3 (1.6)	372.7	0.8

	Belatacept – MI (N=184)			Belatacept – LI (N=175)			Cyclosporin (N=184)		
congestive									
Myocardial infarction	5 (2.7)	381.5	1.3	1 (0.6)	387.6	0.3	2 (1.1)	378.0	0.5
Angina pectoris	1 (0.5)	384.9	0.3	1 (0.6)	387.8	0.3	4 (2.2)	372.7	1.1
Cardiac arrest	1 (0.5)	385.9	0. 3	0	388.7	0.0	4 (2.2)	373.9	1.1
General disorders and Administration site Conditions	**22 (12.0)**	**357.2**	**6.2**	**15 (8.6)**	**360.4**	**4.2**	**22 (12.0)**	**348.0**	**6.3**
Pyrexia	13 (7.1)	365.7	3.6	9 (5.1)	372.6	2.4	11 (6.0)	360.8	3.0
Chest pain	4 (2.2)	380.9	1.1	1 (0.6)	386.0	0.3	3 (1.6)	377.3	0.8
Respiratory, thoracic and Mediastinal disorders	**19 (10.3)**	**368.9**	**5.2**	**12 (6.9)**	**366.6**	**3.3**	**12 (6.5)**	**365.1**	**3.3**
Dyspnoea	1 (0.5)	383.5	0.3	4 (2.3)	380.8	1.1	2 (1.1)	377.6	0.5
Pulmonary embolism	1 (0.5)	385.9	0.3	1 (0.6)	385.9	0.3	4 (2.2)	373.7	1.1
Blood and lymphatic system	**18 (9.8)**	**358.6**	**5.0**	**14 (8.0)**	**360.9**	**3.9**	**14 (7.6)**	**362.7**	**3.9**

	Belatacept – MI (N=184)			Belatacept – LI (N=175)			Cyclosporin (N=184)		
Disorders									
Leucopoenia	8 (4.3)	376.3	2.1	2 (1.1)	385.5	0.5	5 (2.7)	373.9	1.3
Anaemia	6 (3.3)	376.1	1.6	6 (3.4)	375.6	1.6	5 (2.7)	372.2	1.3
Vascular disorders	**17 (9.2)**	**361.5**	**4.7**	**27 (15.4)**	**337.2**	**8.0**	**27 (14.7)**	**339.1**	**8.0**
Deep vein thrombosis	4 (2.2)	377.8	1.1	4 (2.3)	382.9	1.0	2 (1.1)	374.9	0.5
Lymphocele	2 (1.1)	380.3	0.5	5 (2.9)	374.3	1.3	10 (5.4)	360.0	2.8
Metabolism and nutrition Disorders	**16 (8.7)**	**366.8**	**4.4**	**17 (9.7)**	**358.4**	**4.7**	**14 (7.6)**	**354.5**	**3.9**
Dehydration	6 (3.3)	377.3	1.6	5 (2.9)	377.8	1.3	4 (2.2)	371.3	1.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**16 (8.7)**	**372.2**	**4.3**	**15 (8.6)**	**371.8**	**4.0**	**16 (8.7)**	**363.1**	**4.4**
Basal cell carcinoma	5 (2.7)	382.1	1.3	2 (1.1)	384.8	0.5	6 (3.3)	371.8	1.6
Squamous cell carcinoma	5 (2.7)	378.9	1.3	1 (0.6)	387.4	0.3	4 (2.2)	374.2	1.1

	Belatacept – MI (N=184)			Belatacept – LI (N=175)			Cyclosporin (N=184)		
(skin)									
Investigations	**9 (4.9)**	**370.9**	**2.4**	**15 (8.6)**	**361.2**	**4.2**	**21 (11.4)**	**342.3**	**6.1**
Blood creatinine increased	8 (4.3)	373.4	2.1	10 (5.7)	364.3	2.7	16 (8.7)	353.7	4.5

The exposure (patient-years) of a subject is calculated from randomization to the event date, or the last dose date+56, or Month 36, whichever is the earliest.
Incidence ≥2 percent is based on preferred term in any treatment group. * incidence rate = per 100 person-years
MedDRA version: 13.0

Overall adverse events

By Month 12 (and up to Month 36) 99% to 100% of subjects had reported AEs in all treatment groups. The most common (≥ 25%) AEs in all 3 treatment groups were anaemia, graft dysfunction, urinary tract infection, diarrhoea, constipation, peripheral oedema, pyrexia and hypertension. Other AEs (≥ 25%) included nausea and leucopoenia in the belatacept MI and CsA groups and vomiting in the belatacept LI group.

Malignancies

The incidence rates of malignancies (all malignancies, malignancies excluding non-melanoma skin cancer and non-melanoma skin cancer) were comparable across the treatment groups and remained low over time, with the exception of PTLD.

PTLD

Table 42. PTLD

Time	Belatacept MI N=184	Belatacept LI N=175	CsA N=184
	n	**n**	**n**
Up to 12 months	1	2	0
Up to 24 months	2	3	0
Up to 36 months	2	3	0
Up to database lock	2	4	0
After database lock	2	4	1

Infections

The overall proportion of subjects with infections (all and viral) was comparable between the treatment groups.

There was a higher frequency of polyoma virus in the belatacept MI group compared with both the belatacept LI and CsA group. One fatal case of PML occurred in the second year of the study (23 months after randomisation) in the Belatacept MI group.

The frequency of herpes zoster infections was higher in both belatacept groups compared to CsA group.

Thrombotic/embolic Events

The proportions of subjects in all 3 treatment groups with thrombotic/embolic events, pulmonary oedema, heart failure and proteinuria were comparable; few events were reported after 12 months.

Autoimmune events

Autoimmune events were low and comparable between the treatment groups; 6 (3%), 5 (3%) and 3 (2%) subjects in the belatacept MI, LI and CsA groups. All autoimmune disorders were reported by 1 subject each with the exception of hyperthyroidism, which was reported by 2 subjects in the CsA group. One subject in the belatacept MI group had

Guillain-Barre syndrome at Week 28 and the study drug was discontinued. None of the autoimmune events led to death.

Peri infusional events

The proportions of periinfusional events were comparable in the 2 belatacept groups; most of these events were not serious and considered by the investigator to be unrelated to the treatment and they did not lead to discontinuation.

Clinical laboratory monitoring

Full laboratory monitoring of haematology and biochemistry was conducted throughout the study and overall, the proportion of subjects with marked abnormalities was balanced across the 3 treatment groups. Up to 36 Months few subjects had clinically meaningful changes in most biochemistry values, including liver function tests alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Study IM103100

This study is also discussed above under *Efficacy above*.

Safety

The safety data below is presented for the Safety dataset which is the as treated population.

Table 43. Summary of Subjects with Adverse Events Reported During 12 Months Post-Transplant (As-Treated Population)

Number (%) of Subjects			
	Belatacept-MI (N=74)	**Belatacept-LI (N=71)**	**CsA (N=71)**
Deaths	0	0	2 (2.8)
SAEs	50 (67.6)	52 (73.2)	42 (59.2)
Related SAEs	21 (28.4)	23 (32.4)	21 (29.6)
Discontinued due to SAEs	13 (17.6)	14 (19.7)	10 (14.1)
AEs	73 (98.6)	69 (97.2)	68 (95.8)
Related AEs	43 (58.1)	40 (56.3)	50 (70.4)
Discontinued due to AEs	13 (17.6)	15 (21.1)	14 (19.7)

Deaths

There were 5 deaths overall. There were no deaths in the LI group. One death in the MI group occurred at Day 440 (after 12 month study completed) and was due to pneumonia considered not likely to be related to the study drug by investigator. There were 4 deaths in the CsA group; three considered unrelated to study drug by investigator (1 death at Day 320 due to cardiac arrest, 1 death at Day 230 due to unknown cause and 1 death at Day 3 due to pulmonary embolus). One death at Day 163 due to pneumonia (and subsequent cardiopulmonary arrest and myocardial infarction) was considered as possibly related to the study drug by the investigator.

Serious Adverse Events

Table 44. Summary of Most Frequent (at Least 2 Subjects in Any Group) Serious Adverse Events Related to the Study Medication During 12 Months Post-Transplant (As-Treated Population)

MedDRA System Organ Class Preferred term	Belatacept-MI (N=74) n (%)	Belatacept-LI (N=71) n (%)	CsA (N=71) n (%)
No. of Subjects with Related SAEs	21 (28.4)	23 (32.4)	21 (29.6)
General Disorders & Admin. Site Conditions	2 (2.7)	4 (5.6)	2 (2.8)
Pyrexia	1 (1.4)	4 (5.6)	2 (2.8)
Immune System Disorders	10 (13.5)	14 (19.7)	8 (11.3)
Transplant Rejection	8 (10.8)	11 (15.5)	7 (9.9)
Kidney Transplant Rejection	2 (2.7)	3 (4.2)	1 (1.4)
Infections & Infestations	7 (9.5)	4 (5.6)	9 (12.7)
Cytomegalovirus Infection	3 (4.1)	1 (1.4)	3 (4.2)
Urinary Tract Infection	1 (1.4)	0	2 (2.8)
Pneumonia	0	0	2 (2.8)
Injury, Poisoning & Procedural Complications	0	1 (1.4)	3 (4.2)
Therapeutic Agent Toxicity	0	0	2 (2.8)
Investigations	2 (2.7)	1 (1.4)	1 (1.4)
Blood Creatinine Increased	2 (2.7)	1 (1.4)	1 (1.4)
Neoplasms Benign, Malignant & Unspecified (incl. Cysts & Polyps)	2 (2.7)	0	1 (1.4)
Lymphoproliferative Disorder[a]	2 (2.7)	0	0
Renal & Urinary Disorders	0	1 (1.4)	3 (4.2)
Respiratory, Thoracic & Mediastinal Disorders	2 (2.7)	0	1 (1.4)

a In addition, 1 additional case of PTLD occurred after the cutoff date for the 12-month analysis (Subject IM103100-1-6 in the belatacept MI group on Day 396) that was considered not likely related to the study drug by the investigator.

MedDRA = Medical Dictionary for Regulatory Activities and SAE = serious adverse event.

The overall incidence of discontinuations due to SAEs was similar in both belatacept groups, and numerically lower in the CsA group. The most common cause was transplant rejection in all groups.

Malignancies - PTLD

Three subjects in the belatacept MI group developed PTLD; two of these cases developed it during the 12 months of the study and one case developed it after the cut-off date for the 12 month analysis.

Two subjects in the CsA group developed cancers; one case of metastatic thyroid cancer and one case of squamous cell carcinoma of skin.

Related adverse events

Table 45. Summary of Most Frequent (at Least 3 Subjects in Any Group) Adverse Events Related to the Study Medication During 12 Months Post-Transplant (As-Treated Population)

MedDRA System Organ Class Preferred term	Belatacept-MI (N=74) n (%)	Belatacept-LI (N=71) n (%)	CsA (N=71) n (%)
Blood & Lymphatic System Disorders	8 (10.8)	3 (4.2)	9 (12.7)
No. of Subjects with Related AEs	43 (58.1)	40 (56.3)	50 (70.4)
Leukopenia	4 (5.4)	1 (1.4)	2 (2.8)
Anemia	2 (2.7)	0	5 (7.0)
Cardiac Disorders	3 (4.1)	0	1 (1.4)
Endocrine Disorders	0	0	3 (4.2)
Hirsutism	0	0	3 (4.2)
Gastrointestinal Disorders	7 (9.5)	5 (7.0)	8 (11.3)
Diarrhoea	3 (4.1)	2 (2.8)	1 (1.4)
Vomiting	1 (1.4)	4 (5.6)	0
General Disorders & Admin. Site Conditions	7 (9.5)	9 (12.7)	8 (11.3)
Pyrexia	4 (5.4)	5 (7.0)	4 (5.6)
Hepatobiliary Disorders	2 (2.7)	2 (2.8)	3 (4.2)
Immune System Disorders	10 (13.5)	17 (23.9)	9 (12.7)
Transplant Rejection	8 (10.8)	13 (18.3)	8 (11.3)
Kidney Transplant Rejection	2 (2.7)	3 (4.2)	1 (1.4)
Infections & Infestations	20 (27.0)	12 (16.9)	19 (26.8)

MedDRA System Organ Class Preferred term	Belatacept-MI (N=74) n (%)	Belatacept-LI (N=71) n (%)	CsA (N=71) n (%)
Urinary Tract Infection	7 (9.5)	5 (7.0)	7 (9.9)
Cytomegalovirus Infection	5 (6.8)	3 (4.2)	8 (11.3)
Herpes Simplex	3 (4.1)	1 (1.4)	0
Oral Candidiasis	3 (4.1)	2 (2.8)	1 (1.4)
Nasopharyngitis	0	1 (1.4)	3 (4.2)
Injury, Poisoning & Procedural Complications	2 (2.7)	2 (2.8)	9 (12.7)
Therapeutic Agent Toxicity	0	0	3 (4.2)

Clinical laboratory monitoring

The changes in laboratory values of haematology, biochemistry and urinalysis were generally reflective of the significant changes in the physiological state of subjects who have undergone renal transplantation. The changes were consistent with the expected changes of decrease in creatinine and an increase in haematocrit which was seen in all groups.

No clinically meaningful differences in haematology values were observed between the treatment groups in haematology with the exception of a higher incidence of subjects with abnormally low haemoglobin in the belatacept MI group than in the other groups (18% MI versus 10% LI and 13% CsA)

No clinically meaningful differences in biochemistry values were observed between the treatment groups.

Vital signs and physical findings

In general, mean SBP, DBP and MAP values remained stable or decreased slightly over time in all treatment groups.

IM103100 Long term extension study (LTE)

This study is also discussed above under *Efficacy*.

Safety

The overall incidence of AEs was 90% in the combined belatacept group and 92% in the CsA group. The incidence of discontinuations of study medication due to AEs was 9% in the belatacept group and 4% in the CsA group. The incidence of SAEs was 46% in the belatacept group and 54% in the CsA group.

Fifteen subjects developed malignancies; 12 (12%) in the belatacept group and 3 (12%) in the CsA group. One subject developed PTLD in the CsA group.

The incidence of serious infections was 16% in the belatacept group and 27% in the CsA groups. The most common serious infections were urinary tract infections in both treatment groups.

Analysis performed across trials (pooled analyses)

Pooled core studies

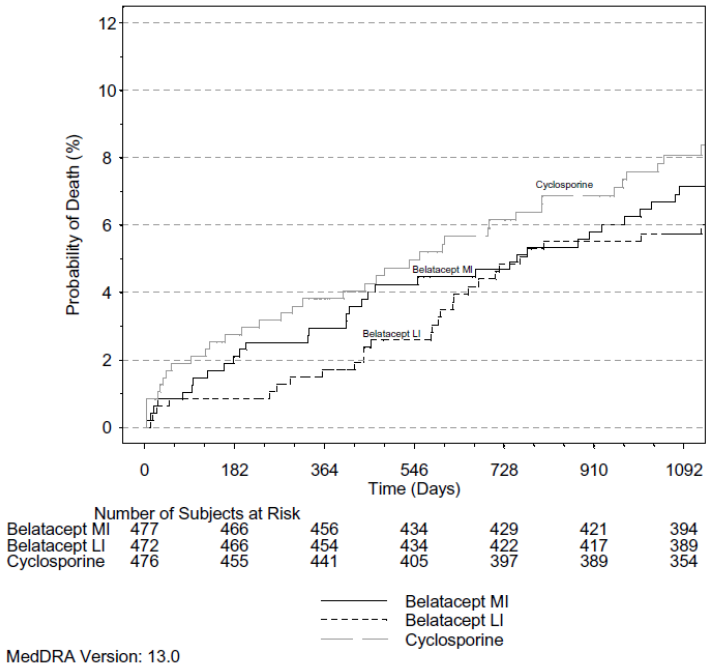
Safety

Nearly all subjects in the core studies experienced one or more AEs. The most common (>10%) AEs reported were fairly similarly distributed across the 3 treatment groups. The most frequently reported AEs in the belatacept treated subjects by Month 12 and up to Month 36 were anaemia, peripheral oedema, constipation, diarrhoea and urinary tract infection.

In the pooled analysis from the 3 studies, the frequency of AEs considered by the investigator as treatment related at 36 months was similar in the belatacept LI (64%) and the MI (65%) groups and lower than in the CsA group (78%). The differences noted were mostly due to higher frequencies of dyslipidaemia, increased blood creatinine, hypertension, tremor and hirsutism/hypertrichosis in the CsA group.

Deaths

Figure 18. Kaplan-Meier estimates of Time to Onset of Death up to Year 3. Pooled core studies -008, -027 and -100.



MedDRA Version: 13.0
All randomized and transplanted subjects from Studies -008 and -027
All randomized, transplanted and treated subjects from Study -100
The overall exposure (duration) of a subject is calculated from randomization date (027or 008 study) or transplant date and time (100 study) to the event date, or the last follow up date, or database lock date whichever is the earliest.

Malignancies

Up to Month 36 the frequencies of all malignancies was lower in the belatacept LI group compared with the belatacept MI and CsA groups.

Table 46. Malignant Neoplasms (Pooled Core Studies)

	Number of Subjects (%)					
	Up to Month 12			**Up to Month 36**		
	Belatacept			**Belatacept**		
	MI N =477	**LI N =472**	**CsA N =476**	**MI N =477**	**LI N =472**	**CsA N =476**
Any malignant neoplasm[a]	16 (3.4)	9 (1.9)	16 (3.4)	41 (8.6)	27 (5.7)	34 (7.1)
Non-melanoma skin cancer	5 (1.0)	1 (0.2)	7 (1.5)	20 (4.2)	7 (1.5)	17 (3.6)
Malignant neoplasms excluding non-melanoma skin cancers	11 (2.3)	8 (1.7)	9 (1.9)	21 (4.4)	20 (4.2)	17 (3.6)
PTLD	4 (0.8)	4 (0.8)	1 (0.2)	8 (1.7)	5 (1.1)	1 (0.2)
Malignant neoplasms excluding non-melanoma skin cancers and PTLD	7 (1.5)	4 (0.8)	8 (1.7)	13 (2.7)	15 (3.2)	16 (3.4)
a Subjects counted once in the all malignant neoplasm row could be counted in more than 1 row appearing below it.						

PTLD

A total of 15 subjects with PTLD were reported at the time of the Month 24 database lock across the 3 core studies. Two (2) additional cases of PTLD were reported after the Month 24 database lock, both in Study IM103027. One subject in the belatacept LI group had CNS PTLD and died. One other subject in the CsA group had non-CNS PTLD and died; this event was reported after the 36 month database lock. Both cases occurred approximately 4 years after transplantation.

Table 47. Post Transplant Lymphoproliferative Disorder (Pooled Core Studies)

	Number of Subjects (%)		
	MI N =477	**LI N =472**	**CsA N = 476**
Cumulative up to Month 24 database lock	8 (1.7)	5 (1.1)	2 (0.4)
Cumulative up to Month 36	8 (1.7)	5 (1.1)	1 (0.2)
Cumulative up to Month 36 database lock	8 (1.7)	6 (1.3)	3 (0.6)[a]
a 1 PTLD case in the CsA group was reported after the 36 month database lock.			

Infections

Table 48. Infections Up to Month 36 (Pooled Core Studies)

	Number of Subjects (%)					
	Up to Month 12			Up to Month 36		
	Belatacept MI N =477	Belatacept LI N =472	CsA N =476	Belatacept MI N =477	Belatacept LI N =472	CsA N =476
Infections and Infestations	337 (70.7)	339 (71.8)	351 (73.7)	378 (79.2)	387 (82.0)	384 (80.7)
Serious Infections	128 (26.8)	110 (23.3)	130 (27.3)	171 (35.8)	158 (33.5)	180 (37.8)
Viral infections	126 (26.4)	118 (25.0)	132 (27.7)	185 (38.8)	184 (39.0)	172 (36.1)
CMV	53 (11.1)	56 (11.9)	65 (13.7)	66 (13.8)	65 (13.8)	70 (14.7)
Polyoma virus	23 (4.8)	11 (2.3)	23 (4.8)	30 (6.3)	18 (3.8)	27 (5.7)
Herpes	38 (8.0)	31 (6.6)	29 (6.1)	74 (15.5)	67 (14.2)	51 (10.7)
Fungal infections	66 (13.8)	52 (11.0)	72 (15.1)	109 (22.9)	79 (16.7)	98 (20.6)
Tuberculosis	2 (0.4)	2 (0.4)	1 (0.2)	6 (1.3)	6 (1.3)	1 (0.2)

Infusional events

The proportion of subjects in the pooled population who had acute infusion related events (within 1 hr of infusion) was 26% in the MI group and 21% in the LI group. The most frequently reported acute events were: hypotension and hypertension. The proportion of subjects who had post infusion events occurring within 24 hours of infusion was 50% in the MI group and 51% in the LI group. The most frequently reported events were: hypertension, nausea and hypotension.

Autoimmune events

The frequency of autoimmune events were similar in the treatment groups in the pooled population up to Month 36; belatacept MI 1.7%, belatacept LI 1.7% and CsA 1.9%. The most common autoimmune disorder reported in the belatacept treated subjects was psoriasis (2 subjects each in the MI and LI groups). The most common autoimmune disorder in the CsA treated subjects was hyperthyroidism (4 subjects).

Safety outcomes of acute rejection

To examine the impact of treatment for AR on safety, the rates of infection and neoplasm across subgroups of subjects who did and did not experience AR were examined in the pooled population up to Month 36.

Table 49. Infections and Neoplasms up to Database Lock Stratified by Acute Rejection Status Up to Month 36 (IM103008 and IM103027 Pooled)

	Number (%) of Subjects					
	Belatacept MI		Belatacept LI		CsA	
	AR N = 86	No AR N = 317	AR N = 72	No AR N = 329	AR N = 50	No AR N = 355
Overall Infections	64 (74.4)	257 (81.1)	60 (83.3)	269 (81.8)	41 (82.0)	286 (80.6)
Serious Infection	28 (32.6)	123 (38.8)	28 (38.9)	116 (35.3)	23 (46.0)	134 (37.7)
Viral Infections	36 (41.9)	121 (38.2)	26 (36.1)	128 (38.9)	17 (34.0)	134 (37.7)
Neoplasms (benign/ malignant/unspecified)	6 (7.0)	53 (16.7)	11 (15.3)	42 (12.8)	7 (14.0)	51 (14.4)
Malignancies	3 (3.5)	31 (9.8)	8 (11.1)	17 (5.2)	4 (8.0)	27 (7.6)

Immunogenicity results

A comprehensive assessment of immunogenicity was conducted in all studies using belatacept and the results are presented in an integrated report at end of 2 years and end of 3 years. The data presented in the 3 year report represents a median of 3.3 years of exposure with a subset of subjects exposed for approximately 7 years.

The comprehensive immunogenicity assessment included the prevalence and incidence rates of seropositive subjects, antibody specificity, neutralising activity, titre, persistence of immunogenicity and timing of seroconversion. In addition, the impact of seroconversion on PK (clearance and trough concentrations), efficacy (mainly through graft loss and acute rejection) and safety (including acute infusional events, peri-infusional events and autoimmune events) was systematically evaluated.

Assays

Immunogenicity was evaluated using an electrochemiluminescence (ECL) assay. This assay was validated with respect to meet current standards for sensitivity and specificity in order to ensure detection of clinically relevant antibodies that could impact safety and/or efficacy. The assay was determined to be sufficiently sensitive based on a polyclonal monkey surrogate positive control, consistently providing anti-drug antibody detection at 12.5 ng/mL in normal human serum and naive dialysis patient serum. The assay was able to detect antibodies to belatacept in serum containing belatacept concentrations up to 10 µg/mL. All samples were evaluated initially in a screening assay. Positive samples were subjected to a confirmatory assay, which determined antibody binding and titre to specific regions of the belatacept molecule. Samples positive to the modified CRLA4 region were further analysed for neutralising antibody (NAb).

Seroconversion rates

Cumulative antibody prevalence was 5.3% during treatment and 6.5% following discontinuation of belatacept for ≥56 days. Incidence rates among the pivotal studies were consistent at approximately 2/100 patient years. The overall incidence did not increase

with prolonged exposure. In the subjects who seroconverted, titres of anti-belatacept antibodies were most often low (<20). It is noted by the company that given the high sensitivity of the assay and its design to meet a 5% false positive rate at screening, that many of the suspected anti-belatacept positive samples had not only low titres but also that the titres did not increase over the baseline pre-dose titres. Anti-belatacept antibodies were often transient and continued treatment with belatacept did not necessarily cause anti-belatacept antibodies to persist. Antibody titres did not increase upon continued treatment with belatacept.

These results, particularly during the long maintenance phase of the studies, suggest that the immunogenicity profile of belatacept is consistent with the presence of low antibody titres and/or the fact that belatacept does not act as a sensitising agent in the renal transplant recipients.

Effect on pharmacokinetics

There was no difference in clearance among the seropositive, indeterminate and seropositive subject cohorts. There was also no impact on clearance in seropositive subjects with specificity to the modified CTLA4 region as well as those having neutralising antibodies.

There was no apparent effect of development of anti-belatacept antibodies on serum levels of belatacept when assessment was done by subject trough serum belatacept according to antibody status over time.

Effect on Efficacy

In order to assess the impact of immunogenicity on efficacy the relationship between seroconversion and graft loss/death, and acute rejection was assessed for subjects who were seropositive. The most conservative approach was taken by including all 65 seropositive subjects identified in the pivotal studies. A total of 55 of these subjects were seropositive while on treatment and 10 were seropositive during the post-treatment follow-up (that is, ≥ 65 days after the last dose of belatacept).

Of the total 65 seropositive subjects, 6 subjects experienced graft loss (2 subjects also died); 4 during the first 2 years of the study and 2 during Year 3. Four of the 6 subjects who experienced graft loss/death did so early after transplantation (2 subjects on Day 1, 1 subject on Day 3 and 1 subject on Day 8). Because the early onset of graft loss occurred before humoral immunity could develop and because graft failure was linked to other causes, it was considered unlikely that these 4 events were due to the presence of anti-belatacept antibodies.

The 2 subjects who experienced graft loss during Year 3 presented with anti-CLTA4 antibody titres that were low and not determined to have neutralising activity. Based on the clinical presentations, the timing of the seroconversion and the low titres of anti-CTLA4 antibodies, it was considered unlikely that the event of graft loss was related to seroconversion.

Of the 65 seropositive subjects, 10 experienced AR. In all cases, antibody titres were low (<20) and presence of anti-belatacept antibodies did not seem associated with the AR event. For 3 of the 10 subjects, on treatment titres did not exceed baseline antibody titres. Five out of ten (5/10) with AR were seronegative at the time of the event and seroconverted only at a much later timepoint (4/5 only seroconverted after discontinuation of therapy). Only 2 subjects were seropositive at the time of the AR with an antibody titre of 20 which exceeded their baseline titre. Both subjects continued treatment with belatacept without progression of immunogenicity (that is, subsequent samples negative or no increase) and the AR events were not exacerbated by continued dosing with belatacept.

Effect on safety

Safety in relation to acute and per-infusional events and autoimmune events were analysed in the 65 seropositive subjects.

Acute and peri-infusional events

A total of 8 seropositive subjects experienced 9 acute infusional events. One subject developed an SAE of hypotension on Day 1 (also experienced intra-operative haemorrhage) and discontinued treatment (that is, received only 1 dose of belatacept). The subject was seropositive on Day 58 (CTLA4-specific, titre of 20). All other events were mild to moderate in intensity and did not lead to discontinuation. These events included dizziness (3 subjects), hypotension (1), pruritis (1), injection site extravasation (1), pyrexia (1) and hypertension (1). None of the subjects who continued therapy experienced worsening or recurrence of the event. It is also noted that the timing of the seropositive sample was not associated with the occurrence of the AE in almost all subject (most were months or years between the event and the finding of the seropositive sample).

A total of 11 subjects experienced peri-infusional events. All events were mild or moderate and none led to discontinuation. The majority of subjects (8/11) had transient immunogenicity (only seropositive at 1 or 2 timepoints) and all but 3 had titres ≥ 20. Only in a few cases did the detection of seropositive samples coincide with the occurrence of the AE and in all but 2 subjects, the AE did not recur in spite of continued treatment with belatacept. In the 2 subjects with recurring AEs the second AE occurred much later (not at time of next infusion but at least 100 days later) and did not worsen (recurring event still mild).

In summary, there did not appear to be an association between the occurrence of acute or peri-infusional events and the detection of anti-belatacept antibodies.

Autoimmune events

Of the 65 seropositive subjects in the core clinical program, 38 subjects had anti-CTLA4 antibodies. Of these, a total of 3 subjects developed an autoimmune event. Two of these events (keratoconjunctivitis sicca and Guillain Barre) occurred before development of antibodies and one event (psoriasis) occurred 4 years after the occurrence of a single seropositive finding. Based on the timing of the seroconversion, the low titre, and the lack of neutralising activity, the autoimmune events did not appear associated with the occurrence of anti-CTLA4 antibodies.

Summary of safety data

The summary of clinical safety is taken primarily from the sponsor's Clinical Overview which is dated December 2010 and the Pooled Study report dated November 2010. These contain more up to date information than the 3 year individual study reports.

Patient exposure

Safety assessment is based on populations described in Table 50 below.

Table 50. Safety population

Study	Belatacept MI	Belatacept LI	CsA	Total
IM103008	219	226	221	666
IM103027	184	175	184	543

Study	Belatacept MI	Belatacept LI	CsA	Total
IM103100	74	71	71	216
Total	477	472	476	1425

Pooled median exposure	1203 days	1205 days	1148 days
At least 12 month	366 (77%)	369 (78%)	350 (75%)
At least 36 months	311 (65%)	329 (70%)	264 (57%)

Eighty-one subjects have received belatacept for 5 years and 75 have been treated for more than 7 years (most of subjects exposed for 7 years come from Study 103100.

Adverse events

Up to Month 12 nearly all subjects experienced one or more AEs. The most common (>10%) were similarly distributed across the 3 treatment groups with the highest frequency in the peri-operative period, suggesting that many of these events may be associated with postoperative morbidity rather than study treatment.

Up to Month 36 the most common AEs (>20%) in subjects treated with a belatacept regimen were anaemia, peripheral oedema, constipation, diarrhoea, urinary tract infection, hypertension, pyrexia, nausea, graft dysfunction, cough, vomiting, leucopoenia, hypophosphataemia and headache.

Up to Month 36 the frequency of AEs that were considered by the investigator to be treatment-related was lower in the belatacept groups (64.8% MI and 63.6%LI) compared with the CsA group (78.2%). This was mostly due to higher frequencies of dyslipidaemia, increased blood creatinine and hypertension.

The sponsor presented a list of adverse reactions rather than adverse events. In line with the Australian policy of listing adverse events the evaluator has edited the tabulations provided by the company of all adverse events reported in the pooled long term data from core studies to provide a list of the AEs which occurred in ≥1% in the subjects.

A line listing of adverse reactions that fall below the cut-off of 1% by System Organ Classes (SOC) using the Council for International Organizations of Medical Sciences (CIOMS) frequencies (usually uncommon, rare) is taken from the sponsor's list.

Table 51. Adverse reactions by SOC. Table continued across 15 pages.

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
	N	%	N	%	N	%
Total subjects with an event	473	99.2	470	99.6	472	99.2
Infections and infestations	378	79.2	387	82.0	384	80.7

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Urinary tract infection	161	33.8	172	36.4	170	35.7
Upper respiratory tract infection	81	17.0	73	15.5	75	15.8
Nasopharyngitis	76	15.9	69	14.6	82	17.2
Cytomegalovirus infection	57	11.9	57	12.1	61	12.8
Bronchitis	46	9.6	52	11.0	32	6.7
Influenza	42	8.8	48	10.2	35	7.4
Gastroenteritis	36	7.5	31	6.6	31	6.5
Herpes zoster	36	7.5	23	4.9	23	4.8
Sinusitis	24	5.0	33	7.0	34	7.1
Oral herpes	23	4.8	33	7.0	17	3.6
Oral candidiasis	34	7.1	20	4.2	30	6.3
Pharyngitis	17	3.6	28	5.9	14	2.9
Pneumonia	19	4.0	22	4.7	29	6.1
Pyelonephritis	23	4.8	11	2.3	19	4.0
Onychomycosis	18	3.8	13	2.8	11	2.3
Bk virus infection	17	3.6	12	2.5	16	3.4
Respiratory tract infection	12	2.5	17	3.6	12	2.5
Candidiasis	15	3.1	10	2.1	10	2.1
Rhinitis	12	2.5	11	2.3	15	3.2
Cellulitis	12	2.5	10	2.1	9	1.9
Fungal infection	13	2.7	9	1.9	14	2.9
Escherichia urinary tract infection	10	2.1	11	2.3	19	4.0
Wound infection	13	2.7	8	1.7	13	2.7
Tinea versicolour	7	1.5	13	2.8	22	4.6
Fungal skin infection	11	2.3	8	1.7	5	1.1
Gastroenteritis viral	9	1.9	10	2.1	9	1.9
Urinary tract infection bacterial	7	1.5	12	2.5	10	2.1

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Sepsis	9	1.9	6	1.3	14	2.9
Ear infection	8	1.7	6	1.3	8	1.7
Herpes simplex	8	1.7	6	1.3	5	1.1
Postoperative wound infection	9	1.9	5	1.1	10	2.1
Pyelonephritis acute	11	2.3	3	0.6	12	2.5
Urosepsis	6	1.3	8	1.7	9	1.9
Localised infection	4	0.8	9	1.9	6	1.3
Lower respiratory tract infection	7	1.5	6	1.3	8	1.7
Vaginal infection	6	1.3	7	1.5	3	0.6
Folliculitis	5	1.0	7	1.5	6	1.3
Urinary tract infection enterococcal	5	1.0	7	1.5	4	0.8
Asymptomatic bacteriuria	5	1.0	6	1.3	6	1.3
Body tinea	7	1.5	4	0.8	3	0.6
Cystitis	5	1.0	6	1.3	4	0.8
Herpes virus infection	6	1.3	5	1.1	5	1.1
Bacteraemia	7	1.5	3	0.6	9	1.9
Bacteriuria	4	0.8	6	1.3	4	0.8
Oesophageal candidiasis	5	1.0	4	0.8	3	0.6
Polyomavirus-associated nephropathy	6	1.3	3	0.6	6	1.3
Tinea pedis	7	1.5	2	0.4	3	0.6
Orchitis	3	0.6	5	1.1	1	0.2
Tooth abscess	5	1.0	3	0.6	3	0.6
Genital herpes	5	1.0	2	0.4	5	1.1
Subcutaneous abscess	6	1.3	1	0.2	0	
Lobar pneumonia	5	1.0	1	0.2	3	0.6
Osteomyelitis	5	1.0	1	0.2	1	0.2
Tooth infection	5	1.0	1	0.2	1	0.2

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Urinary tract infection pseudomonal	3	0.6	2	0.4	7	1.5
Abscess	3	0.6	1	0.2	5	1.1
Septic Shock	3	0.6	1	0.2	5	1.1
Viral Infection	2	0.4	2	0.4	6	1.3
Paronychia	1	0.2	2	0.4	5	1.1
Gastrointestinal disorders	**357**	**74.8**	**366**	**77.5**	**365**	**76.7**
Diarrhoea	196	41.1	179	37.9	164	34.5
Constipation	138	28.9	155	32.8	161	33.8
Nausea	126	26.4	116	24.6	129	27.1
Vomiting	84	17.6	105	22.2	95	20.0
Abdominal pain	65	13.6	82	17.4	74	15.5
Dyspepsia	38	8.0	38	8.1	39	8.2
Abdominal pain upper	34	7.1	39	8.3	48	10.1
Abdominal distension	28	5.9	23	4.9	27	5.7
Haemorrhoids	26	5.5	18	3.8	19	4.0
Flatulence	16	3.4	25	5.3	27	5.7
Abdominal pain lower	14	2.9	22	4.7	8	1.7
Aphthous stomatitis	14	2.9	22	4.7	10	2.1
Gastritis	18	3.8	18	3.8	18	3.8
Gastrooesophageal reflux disease	13	2.7	21	4.4	19	4.0
Abdominal discomfort	10	2.1	14	3.0	18	3.8
Mouth ulceration	13	2.7	5	1.1	5	1.1
Rectal haemorrhage	12	2.5	6	1.3	6	1.3
Toothache	9	1.9	8	1.7	4	0.8
Stomatitis	5	1.0	10	2.1	3	0.6
Oesophagitis	6	1.3	8	1.7	2	0.4
Haematochezia	5	1.0	8	1.7	4	0.8

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Dysphagia	6	1.3	4	0.8	3	0.6
Food poisoning	5	1.0	5	1.1	2	0.4
Gastrointestinal haemorrhage	8	1.7	2	0.4	5	1.1
Inguinal hernia	5	1.0	5	1.1	6	1.3
Gastrointestinal disorder	4	0.8	5	1.1	7	1.5
Gingivitis	6	1.3	3	0.6	6	1.3
Haemorrhoidal haemorrhage	4	0.8	5	1.1	3	0.6
Ileus paralytic	3	0.6	6	1.3	1	0.2
Odynophagia	3	0.6	6	1.3	5	1.1
Abdominal hernia	6	1.3	2	0.4	8	1.7
Hernial eventration	3	0.6	5	1.1	2	0.4
Hiatus hernia	1	0.2	7	1.5	4	0.8
Pancreatitis	6	1.3	2	0.4	1	0.2
Oral disorder	2	0.4	5	1.1	1	0.2
Umbilical hernia	3	0.6	3	0.6	8	1.7
Melaena	5	1.0	0		2	0.4
Dental caries	1	0.2	1	0.2	7	1.5
Gingival hyperplasia	2	0.4	0		24	5.0
Gingival bleeding	0		1	0.2	5	1.1
Gingival hypertrophy	1	0.2	0		18	3.8
Metabolism and nutrition disorders	356	74.6	355	75.2	367	77.1
Hypophosphataemia	82	17.2	101	21.4	67	14.1
Hypokalaemia	87	18.2	90	19.1	66	13.9
Dyslipidaemia	84	17.6	77	16.3	99	20.8
Hyperkalaemia	63	13.2	86	18.2	86	18.1
Hyperglycaemia	72	15.1	68	14.4	75	15.8
Hypercholesterolaemia	57	11.9	49	10.4	54	11.3

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Hypocalcaemia	46	9.6	54	11.4	46	9.7
Hyperlipidaemia	34	7.1	36	7.6	36	7.6
Hypercalcaemia	38	8.0	31	6.6	36	7.6
Hypomagnesaemia	36	7.5	33	7.0	49	10.3
Diabetes mellitus	28	5.9	30	6.4	40	8.4
Metabolic acidosis	27	5.7	26	5.5	29	6.1
Decreased appetite	22	4.6	27	5.7	23	4.8
Hyperphosphataemia	23	4.8	22	4.7	23	4.8
Dehydration	21	4.4	22	4.7	22	4.6
Acidosis	19	4.0	22	4.7	30	6.3
Hypoglycaemia	15	3.1	23	4.9	30	6.3
Hyperuricaemia	16	3.4	19	4.0	52	10.9
Hyponatraemia	16	3.4	16	3.4	23	4.8
Hypertriglyceridaemia	16	3.4	12	2.5	26	5.5
Fluid overload	14	2.9	11	2.3	11	2.3
Iron deficiency	11	2.3	11	2.3	9	1.9
Obesity	10	2.1	10	2.1	14	2.9
Hypovolaemia	8	1.7	11	2.3	9	1.9
Hypoalbuminaemia	8	1.7	8	1.7	8	1.7
Vitamin D deficiency	7	1.5	8	1.7	1	0.2
Fluid retention	5	1.0	9	1.9	11	2.3
Gout	5	1.0	9	1.9	10	2.1
Glucose tolerance impaired	4	0.8	3	0.6	6	1.3
Diabetic ketoacidosis	0		5	1.1	1	0.2
Diabetes mellitus inadequate control	3	0.6	1	0.2	6	1.3
Increased appetite	2	0.4	1	0.2	6	1.3
Overweight	3	0.6	0		6	1.3

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Injury, poisoning and procedural complications	318	66.7	314	66.5	346	72.7
Graft dysfunction	108	22.6	112	23.7	146	30.7
Procedural pain	87	18.2	94	19.9	89	18.7
Incision site pain	74	15.5	67	14.2	83	17.4
Complications of transplanted kidney	21	4.4	35	7.4	37	7.8
Chronic allograft nephropathy	22	4.6	16	3.4	40	8.4
Complications of transplant surgery	17	3.6	11	2.3	18	3.8
Wound dehiscence	12	2.5	15	3.2	14	2.9
Fall	16	3.4	9	1.9	15	3.2
Contusion	9	1.9	15	3.2	7	1.5
Graft complication	15	3.1	8	1.7	12	2.5
Post procedural haematoma	11	2.3	11	2.3	8	1.7
Arteriovenous fistula thrombosis	9	1.9	12	2.5	17	3.6
Wound	10	2.1	10	2.1	5	1.1
Wound secretion	13	2.7	6	1.3	9	1.9
Excoriation	10	2.1	7	1.5	2	0.4
Joint sprain	13	2.7	3	0.6	9	1.9
Skin laceration	11	2.3	5	1.1	5	1.1
Foot fracture	6	1.3	9	1.9	7	1.5
Wound complication	5	1.0	9	1.9	10	2.1
Incisional hernia	3	0.6	10	2.1	8	1.7
Incision site haematoma	5	1.0	7	1.5	4	0.8
Limb injury	6	1.3	6	1.3	5	1.1
Perirenal haematoma	5	1.0	7	1.5	4	0.8
Arteriovenous fistula site complication	2	0.4	8	1.7	2	0.4
Graft loss	5	1.0	5	1.1	9	1.9

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Post procedural haemorrhage	6	1.3	4	0.8	3	0.6
Anaemia postoperative	4	0.8	5	1.1	4	0.8
Post procedural discharge	5	1.0	4	0.8	10	2.1
Ankle fracture	1	0.2	7	1.5	2	0.4
Incision site complication	5	1.0	3	0.6	6	1.3
Road traffic accident	6	1.3	2	0.4	0	
Seroma	4	0.8	4	0.8	8	1.7
Vascular graft complication	5	1.0	3	0.6	2	0.4
Operative haemorrhage	5	1.0	2	0.4	3	0.6
Post procedural complication	5	1.0	2	0.4	0	
Rib fracture	2	0.4	5	1.1	2	0.4
Wound evisceration	2	0.4	5	1.1	3	0.6
Meniscus lesion	5	1.0	1	0.2	1	0.2
Drug toxicity	2	0.4	3	0.6	16	3.4
Wrist fracture	2	0.4	2	0.4	5	1.1
Therapeutic agent toxicity	0		0		39	8.2
General disorders and administration site conditions	**304**	**63.7**	**309**	**65.5**	**317**	**66.6**
Oedema peripheral	168	35.2	160	33.9	192	40.3
Pyrexia	127	26.6	136	28.8	120	25.2
Fatigue	48	10.1	45	9.5	49	10.3
Oedema	44	9.2	41	8.7	50	10.5
Chest pain	39	8.2	29	6.1	45	9.5
Asthenia	27	5.7	30	6.4	37	7.8
Pain	30	6.3	25	5.3	36	7.6
Chills	15	3.1	21	4.4	20	4.2
Malaise	11	2.3	11	2.3	8	1.7

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Generalised oedema	14	2.9	6	1.3	19	4.0
Influenza like illness	7	1.5	7	1.5	4	0.8
Chest discomfort	6	1.3	7	1.5	5	1.1
Impaired healing	5	1.0	6	1.3	7	1.5
Catheter site pain	5	1.0	3	0.6	7	1.5
Face oedema	5	1.0	3	0.6	11	2.3
Inflammation	3	0.6	5	1.1	2	0.4
Fibrosis	5	1.0	2	0.4	3	0.6
Localised oedema	3	0.6	3	0.6	6	1.3
Blood and lymphatic system disorders	**273**	**57.2**	**279**	**59.1**	**287**	**60.3**
Anaemia	184	38.6	191	40.5	199	41.8
Leukopenia	104	21.8	93	19.7	112	23.5
Thrombocytopenia	38	8.0	16	3.4	30	6.3
Neutropenia	24	5.0	27	5.7	25	5.3
Leukocytosis	25	5.2	24	5.1	11	2.3
Polycythaemia	20	4.2	24	5.1	18	3.8
Lymphopenia	16	3.4	14	3.0	11	2.3
Pancytopenia	4	0.8	4	0.8	9	1.9
Lymphadenopathy	6	1.3	1	0.2	1	0.2
Renal and urinary disorders	272	57.0	273	57.8	288	60.5
Haematuria	77	16.1	72	15.3	77	16.2
Proteinuria	66	13.8	73	15.5	50	10.5
Dysuria	48	10.1	48	10.2	45	9.5
Renal tubular necrosis	42	8.8	39	8.3	58	12.2
Renal impairment	19	4.0	25	5.3	38	8.0
Leukocyturia	18	3.8	22	4.7	20	4.2

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Hydronephrosis	21	4.4	8	1.7	22	4.6
Renal failure acute	14	2.9	12	2.5	21	4.4
Bladder spasm	8	1.7	14	3.0	14	2.9
Renal artery stenosis	10	2.1	12	2.5	12	2.5
Urinary incontinence	11	2.3	11	2.3	10	2.1
Urinary retention	11	2.3	8	1.7	20	4.2
Pollakiuria	13	2.7	5	1.1	5	1.1
Nocturia	11	2.3	4	0.8	11	2.3
Ureteric stenosis	7	1.5	7	1.5	13	2.7)
Vesicoureteric reflux	9	1.9	4	0.8	6	1.3
Nephropathy	5	1.0	7	1.5	11	2.3
Polyuria	4	0.8	8	1.7	4	0.8
Renal vein thrombosis	9	1.9	2	0.4	1	0.2
Glycosuria	4	0.8	6	1.3	2	0.4
Nephrolithiasis	4	0.8	4	0.8	6	1.3
Pyuria	2	0.4	6	1.3	1	0.2
Urethral pain	4	0.8	4	0.8	7	1.5
Kidney fibrosis	2	0.4	5	1.1	5	1.1
Renal failure	6	1.3	1	0.2	10	2.1
Renal tubular disorder	4	0.8	3	0.6	12	2.5
Oliguria	2	0.4	4	0.8	7	1.5
Perinephric effusion	6	1.3	0		10	2.1
Anuria	1	0.2	4	0.8	5	1.1
Bladder pain	3	0.6	2	0.4	5	1.1
Urinary fistula	5	1.0		0	7	1.5
Nephropathy toxic	1	0.2	1	0.2	7	1.5
Urinoma	0	0	2	0.4	5	1.1

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Vascular disorders	**233**	**48.8**	**247**	**52.3**	**264**	**55.5**
Hypertension	130	27.3	144	30.5	174	36.6
Hypotension	72	15.1	75	15.9	55	11.6
Haematoma	25	5.2	25	5.3	29	6.1
Lymphocele	14	2.9	20	4.2	41	8.6
Deep vein thrombosis	10	2.1	9	1.9	4	0.8
Orthostatic hypotension	10	2.1	6	1.3	12	2.5
Phlebitis	8	1.7	4	0.8	5	1.1
Hot flush	4	0.8	6	1.3	5	1.1
Thrombosis	3	0.6	6	1.3	4	0.8
Thrombophlebitis	6	1.3	2	0.4	1	0.2
Flushing	3	0.6	4	0.8	5	1.1
Venous thrombosis	1	0.2	5	1.1	1	0.2
Hypertensive crisis	3	0.6	1	0.2	14	2.9
Lymphorrhoea	0		4	0.8	5	1.1
Respiratory, thoracic and mediastinal disorders	**225**	**47.2**	**234**	**49.6**	**205**	**43.1**
Cough	104	21.8	110	23.3	84	17.6
Dyspnoea	46	9.6	55	11.7	69	14.5
Oropharyngeal pain	33	6.9	30	6.4	26	5.5
Dyspnoea exertional	22	4.6	16	3.4	19	4.0
Productive cough	15	3.1	18	3.8	14	2.9
Nasal congestion	16	3.4	14	3.0	10	2.1
Pulmonary oedema	12	2.5	10	2.1	8	1.7
Rhinorrhoea	6	1.3	15	3.2	14	2.9
Epistaxis	10	2.1	9	1.9	8	1.7
Sinus congestion	8	1.7	11	2.3	7	1.5

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Rales	9	1.9	9	1.9	9	1.9
Wheezing	10	2.1	8	1.7	4	0.8
Pleural effusion	7	1.5	10	2.1	7	1.5)
Acute pulmonary oedema	3	0.6	8	1.7	5	1.1
Respiratory tract congestion	4	0.8	7	1.5	6	1.3
Atelectasis	2	0.4	8	1.7	5	1.1
Lung disorder	3	0.6	7	1.5	4	0.8
Rhinitis allergic	4	0.8	5	1.1	0	
Dysphonia	3	0.6	5	1.1	2	0.4
Hiccups	6	1.3	2	0.4	3	0.6
Asthma	5	1.0	2	0.4	1	0.2
Haemoptysis	2	0.4	5	1.1	3	0.6
Pulmonary congestion	3	0.6	3	0.6	5	1.1
Hypoxia	2	0.4	3	0.6	5	1.1
Sleep apnoea syndrome	3	0.6	2	0.4	12	2.5
Pulmonary embolism	2	0.4	1	0.2	6	1.3
Investigations	**224**	**47.0**	**229**	**48.5**	**227**	**47.7**
Blood creatinine increased	69	14.5	69	14.6	98	20.6
Weight increased	42	8.8	33	7.0	30	6.3
C-reactive protein increased	21	4.4	23	4.9	18	3.8
Weight decreased	17	3.6	24	5.1	13	2.7
Urine output decreased	16	3.4	11	2.3	16	3.4
Alanine aminotransferase increased	15	3.1	10	2.1	7	1.5
Blood pressure increased	12	2.5	13	2.8	11	2.3
Hepatic enzyme increased	11	2.3	10	2.1	8	1.7
Liver function test abnormal	9	1.9	10	2.1	10	2.1
White blood cell count decreased	9	1.9	10	2.1	11	2.3

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Aspartate aminotransferase increased	7	1.5	9	1.9	3	0.6
Body temperature increased	6	1.3	10	2.1	4	0.8
Blood cholesterol increased	9	1.9	6	1.3	9	1.9
Blood glucose increased	9	1.9	6	1.3	4	0.8
Polyomavirus test positive	9	1.9	6	1.3	7	1.5
White blood cell count increased	5	1.0	10	2.1	12	2.5
Blood phosphorus decreased	9	1.9	5	1.1	4	0.8
Blood alkaline phosphatase increased	7	1.5	5	1.1	7	1.5
Cardiac murmur	6	1.3	6	1.3	6	1.3
Blood magnesium decreased	4	0.8	7	1.5	9	1.9
Blood potassium decreased	7	1.5	4	0.8	4	0.8
Haematocrit decreased	4	0.8	7	1.5	3	0.6
Blood creatine increased	5	1.0	5	1.1	10	2.1
Blood immunoglobulin G decreased	5	1.0	5	1.1	0	
Blood immunoglobulin m decreased	7	1.5	3	0.6	1	0.2
Blood parathyroid hormone increased	4	0.8	6	1.3	6	1.3
Gamma-glutamyltransferase increased	4	0.8	5	1.1	1	0.2
Blood potassium increased	2	0.4	6	1.3	4	0.8
Oxygen saturation decreased	6	1.3	2	0.4	3	0.6
Platelet count decreased	5	1.0	2	0.4	3	0.6
Blood bilirubin increased	1	0.2	5	1.1	6	1.3
Transaminases increased	1	0.2	5	1.1	3	0.6
Vitamin D decreased	0		5	1.1	2	0.4
Blood uric acid increased	1	0.2	3	0.6	5	1.1
Musculoskeletal and connective tissue disorders	**224**	**47.0**	**209**	**44.3**	**203**	**42.6**
Arthralgia	65	13.6	76	16.1	59	12.4

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Back pain	75	15.7	57	12.1	62	13.0
Pain in extremity	60	12.6	56	11.9	61	12.8
Muscle spasms	32	6.7	21	4.4	33	6.9
Myalgia	24	5.0	26	5.5	23	4.8
Musculoskeletal pain	18	3.8	20	4.2	11	2.3
Osteopenia	20	4.2	17	3.6	18	3.8
Osteoporosis	14	2.9	13	2.8	8	1.7
Osteoarthriti s	15	3.1	7	1.5	7	1.5
Flank pain	8	1.7	13	2.8	7	1.5
Joint swelling	9	1.9	12	2.5	8	1.7
Neck pain	11	2.3	8	1.7	7	1.5
Bone pain	6	1.3	10	2.1	10	2.1
Muscular weakness	7	1.5	9	1.9	17	3.6
Musculoskeletal chest pain	5	1.0	7	1.5	6	1.3
Groin pain	6	1.3	5	1.1	3	0.6
Arthritis	3	0.6	7	1.5	6	1.3
Bursitis	7	1.5	3	0.6	3	0.6
Spinal osteoarthritis	7	1.5	2	0.4	4	0.8
Tendonitis	4	0.8	3	0.6	6	1.3
Musculoskeletal stiffness	4	0.8	2	0.4	5	1.1
Nervous system disorders	**189**	**39.6**	**196**	**41.5**	**207**	**43.5**
Headache	91	19.1	95	20.1	80	16.8
Dizziness	47	9.9	39	8.3	44	9.2
Tremor	36	7.5	42	8.9	84	17.6
Hypoaesthesia	16	3.4	15	3.2	10	2.1
Paraesthesia	12	2.5	18	3.8	30	6.3
Sciatica	8	1.7	10	2.1	6	1.3

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Cerebrovascular accident	7	1.5	3	0.6	2	0.4
Lethargy	7	1.5	3	0.6	6	1.3
Neuropathy peripheral	4	0.8	6	1.3	6	1.3
Syncope	3	0.6	7	1.5	7	1.5
Somnolence	2	0.4	7	1.5	5	1.1
Migraine	3	0.6	5	1.1	2	0.4
Memory impairment	6	1.3	0		1	0.2
Burning sensation	1	0.2	3	0.6	10	2.1
Skin and subcutaneous tissue disorders	**193**	**40.5**	**178**	**37.7**	**189**	**39.7**
Acne	32	6.7	35	7.4	47	9.9
Pruritus	34	7.1	22	4.7	22	4.6
Alopecia	25	5.2	26	5.5	10	2.1
Skin lesion	25	5.2	21	4.4	14	2.9
Rash	24	5.0	21	4.4	27	5.7
Night sweats	14	2.9	16	3.4	10	2.1
Hyperhidrosis	15	3.1	14	3.0	3	0.6
Ecchymosis	18	3.8	4	0.8	17	3.6
Skin ulcer	16	3.4	5	1.1	7	1.5
Erythema	11	2.3	7	1.5	9	1.9
Dry skin	5	1.0	5	1.1	2	0.4
Skin exfoliation	9	1.9	1	0.2	5	1.1
Decubitus ulcer	4	0.8	4	0.8	5	1.1
Hirsutism	3	0.6	5	1.1	24	5.0
Hyperkeratosis	5	1.0	3	0.6	5	1.1
Rash papular	6	1.3	2	0.4	5	1.1
Skin discolouration	5	1.0	2	0.4	2	0.4

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Actinic keratosis	5	1.0	1	0.2	6	1.3
Hypertrichosis	5	1.0	0		19	4.0
Nail growth abnormal	1	0.2	1	0.2	5	1.1
Psychiatric disorders	**145**	**30.4**	**140**	**29.7**	**149**	**31.3**
Insomnia	80	16.8	80	16.9	89	18.7
Anxiety	53	11.1	47	10.0	48	10.1
Depression	33	6.9	27	5.7	31	6.5
Confusional state	7	1.5	9	1.9	7	1.5
Agitation	5	1.0	6	1.3	2	0.4
Hallucination	2	0.4	3	0.6	5	1.1
Restlessness	3	0.6	1	0.2	6	1.3
Cardiac disorders	**127**	**26.6**	**130**	**27.5**	**148**	**31.1**
Tachycardia	32	6.7	35	7.4	36	7.6
Atrial fibrillation	29	6.1	14	3.0	19	4.0
Bradycardia	19	4.0	12	2.5	18	3.8
Sinus bradycardia	9	1.9	13	2.8	15	3.2
Left ventricular hypertrophy	8	1.7	13	2.8	8	1.7
Palpitations	6	1.3	10	2.1	12	2.5
Angina pectoris	4	0.8	10	2.1	15	3.2
Cardiac failure	8	1.7	6	1.3	3	0.6
Cardiac failure congestive	10	2.1	4	0.8	7	1.5
Arrhythmia	5	1.0	6	1.3	8	1.7
Myocardial infarction	7	1.5	3	0.6	7	1.5
Sinus tachycardia	5	1.0	5	1.1	3	0.6
Atrioventricular block first degree	2	0.4	5	1.1	5	1.1
Coronary artery disease	1	0.2	5	1.1	3	0.6
Cardiac arrest	3	0.6	2	0.4	9	1.9

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Reproductive system and breast disorders	**89**	**18.7**	**83**	**17.6**	**79**	**16.6**
Erectile dysfunction	11	2.3	10	2.1	17	3.6
Benign prostatic hyperplasia	10	2.1	9	1.9	8	1.7
Scrotal oedema	8	1.7	7	1.5	3	0.6
Prostatitis	5	1.0	5	1.1	12	2.5
Epididymitis	5	1.0	4	0.8	3	0.6
Metrorrhagia	3	0.6	4	0.8	3	0.6
Scrotal swelling	5	1.0	1	0.2	3	0.6
Vaginal haemorrhage	6	1.3	0		2	0.4
Eye disorders	**89**	**18.7**	**78**	**16.5**	**71**	**14.9**
Conjunctivitis	20	4.2	11	2.3	13	2.7
Cataract	15	3.1	11	2.3	18	3.8
Visual acuity reduced	9	1.9	8	1.7	6	1.3
Vision blurred	8	1.7	6	1.3	11	2.3
Ocular hyperaemia	3	0.6	8	1.7	1	0.2
Conjunctival haemorrhage	7	1.5	3	0.6	3	0.6
Neoplasms benign, malignant and unspecified (incl cysts and Polyps)	**69**	**14.5**	**52**	**11.0**	**58**	**12.2**
Skin papilloma	15	3.1	9	1.9	16	3.4
Basal cell carcinoma	12	2.5	5	1.1	11	2.3
Squamous cell carcinoma of skin	9	1.9	2	0.4	7	1.5
Melanocytic naevus	6	1.3	4	0.8	2	0.4
Seborrhoeic keratosis	2	0.4	6	1.3	2	0.4
Immune system disorders	**49**	**10.3**	**53**	**11.2**	**33**	**6.9**
Transplant rejection	22	4.6	27	5.7	13	2.7
Seasonal allergy	13	2.7	13	2.8	5	1.1
Hypersensitivity	4	0.8	3	0.6	7	1.5

System Organ Class Preferred Term	Belatacept - MI N = 477		Belatacept - LI N = 472		Cyclosporin N = 476	
Ear and labyrinth disorders	**33**	**6.9**	**35**	**7.4**	**30**	**6.3**
Vertigo	6	1.3	13	2.8	8	1.7
Ear pain	5	1.0	10	2.1	4	0.8
Tinnitus	10	2.1	5	1.1	5	1.1
Hypoacusis	5	1.0	3	0.6	7	1.5
Endocrine disorders	**37**	**7.8**	**25**	**5.3**	**49**	**10.3**
Cushingoid	17	3.6	10	2.1	18	3.8
Hyperparathyroidism	13	2.7	8	1.7	16	3.4
Hypothyroidism	4	0.8	1	0.2	6	1.3
Hepatobiliary disorders	**27**	**5.7**	**31**	**6.6**	**36**	**7.6**
Cytolytic hepatitis	8	1.7	3	0.6	4	0.8
Cholelithiasis	3	0.6	5	1.1	11	2.3
Hepatic cyst	2	0.4	1	0.2	6	1.3
Congenital, familial and genetic disorders	7	1.5	10	2.1	11	2.3
Hydrocele	5	1.0	6	1.3	7	1.5

Based on 3 year database lock.

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

All randomized, transplanted and treated subjects from Study -100

Adverse events counting from randomization date for studies -008 and -027 and from transplant date and time for study -100

System Organ Classes (SOC) and Preferred Terms are sorted by decreasing frequencies in the all belatacept column within Each PT and SOC

MedDRA Version: 13.0

Uncommon and rare events

Uncommon (≥ 1/1,000 to < 1/100). Company did not provide any rare events.

Infections and infestations

Uncommon: progressive multifocal leukoencephalopathy, cerebral fungal infection, cytomegalovirus (CMV) colitis, polyomavirus associated nephropathy, genital herpes, staphylococcal infection.

Neoplasms, benign, malignant and unspecified

Uncommon: epstein-Barr virus associated lymphoproliferative disorder.

Blood and lymphatic system disorders

Uncommon: Monocytopenia.

Immune system disorders

Uncommon: blood immunoglobulin G decreased, blood immunoglobulin M decreased

Nervous system disorders

Uncommon: encephalitis, Guillain-Barre syndrome

Gastrointestinal disorders

Uncommon: gastrointestinal disorder

Renal and urinary disorders

Uncommon: renal artery thrombosis

Peri infusional AEs

The peri-infusional events are predominantly background events occurring as a consequence of the transplant surgery and natural history of the subject's condition and are not associated with the infusion of belatacept itself or the occurrence of anti-belatacept antibodies.

Serious adverse events and deaths

Deaths

Up to Month 12 and continuing to Month 36 the frequencies of all deaths and of AEs with outcomes of death were numerically lower in the LI group compared with the CsA or MI group (Table 52).

Table 52. Summary of Deaths (Pooled Core Studies)

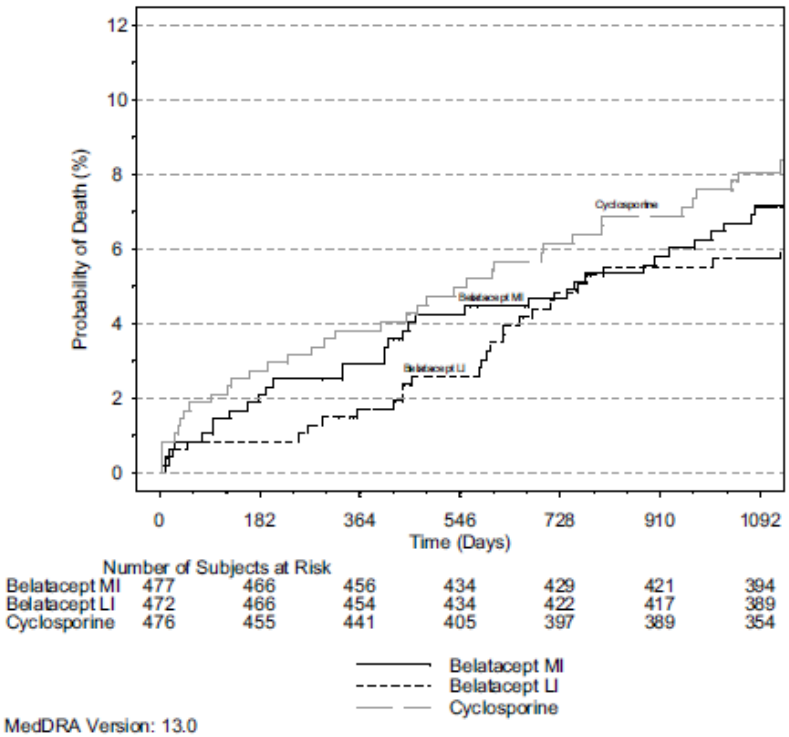
	Number of Subjects (%)					
	Up to Month 12			**Up to Month 36**		
	Belatacept			**Belatacept**		
	MI N =477	**LI N =472**	**CsA N =476**	**MI N =477**	**LI N =472**	**CsA N =476**
Total deaths	14 (2.9)	9 (1.9)	18 (3.8)	33 (6.9)	26 (5.5)	36 (7.6)
AE with outcome of	14 (2.9)	7 (1.5)	18 (3.8)	31 (6.5)	20 (4.2)	36 (7.6)

	Number of Subjects (%)					
death						
Unknown death reason	0	2 (0.4)	0	2 (0.4)	6 (1.3)	0

Review of the narratives for all deaths indicates that most deaths were due to infections, operative complications, cardiac disorders, respiratory disorders and neoplasms.

The time to onset of all deaths up to Month 36 is shown in the Kaplan-Meier plot shown in Figure 19 below.

Figure 19. Kaplan-Meier estimates of Time to onset of Death up to Year 3. Pooled Core studies.



MedDRA Version: 13.0
All randomized and transplanted subjects from Studies -008 and -027
All randomized, transplanted and treated subjects from Study -100
The overall exposure (duration) of a subject is calculated from randomization date (027or 008 study) or transplant date and time (100 study) to the event date, or the last follow up date, or database lock date whichever is the earliest.

Malignancies

Overall there was a lower frequency of all malignancies in the LI group, largely driven by a lower frequency of non-melanoma skin cancers (Table 53).

Table 53. Malignant Neoplasms (Pooled Core Studies)

	Number of Subjects (%)					
	Up to Month 12			**Up to Month 36**		
	Belatacept			**Belatacept**		
	MI	**LI**	**CsA**	**MI**	**LI**	**CsA**

	Number of Subjects (%)					
	N =477	**N =472**	**N =476**	**N =477**	**N =472**	**N =476**
Any malignant neoplasm[a]	16 (3.4)	9 (1.9)	16 (3.4)	41 (8.6)	27 (5.7)	34 (7.1)
Non-melanoma skin cancer	5 (1.0)	1 (0.2)	7 (1.5)	20 (4.2)	7 (1.5)	17 (3.6)
Malignant neoplasms excluding non-melanoma skin cancers	11 (2.3)	8 (1.7)	9 (1.9)	21 (4.4)	20 (4.2)	17 (3.6)
PTLD	4 (0.8)	4 (0.8)	1 (0.2)	8 (1.7)	6 (1.3)	3 (0.6)
Malignant neoplasms excluding non-melanoma skin cancers and PTLD	7 (1.5)	4 (0.8)	8 (1.7)	13 (2.7)	15 (3.2)	16 (3.4)

a Subjects counted once in the all malignant neoplasm row could be counted in more than 1 row appearing below it.

Other than CNS PTLD there were no other primary CNS neoplasms and no excess of other known virally mediated tumours, such as cervical cancer or Kaposi's sarcoma. Up to Month 36 there were a total of 6 cases of breast cancer all in women older than 40 years and all but one in women over 50 years. (4 cases in MI, 1 in LI and 1 in CsA groups).

PTLD

PTLD is a spectrum of disorders which range from a virally driven B cell proliferation presenting as a mononucleosis like disorder to a high grade malignant lymphoma. The overall incidence is reported to be about 1% in renal transplant recipients, which is 30 – 50 times greater than the general population. Transplant recipients who are seronegative for EBV are at high risk for infection if they receive organs from seropositive donors. A primary EBV infection places patients at risk for EBV related lymphoproliferative disease.

A total of 17 cases of PTLD were reported up to Month 36.

Table 54. Post Transplant Lymphoproliferative Disorder (Pooled Core Studies)

	Number of Subjects (%)		
	MI N =477	**LI N =472**	**CsA N = 476**
Cumulative up to Month 12	4 (0.8)	4 (0.8)	1 (0.2)
Cumulative up to June/July 2010	8 (1.7)	6 (1.3)	3 (0.6)

Number of Subjects (%)			
database lock			
Renal allograft	2	3	0
Fatal	1	1	0
Disseminated	0	0	3
Fatal	0	0	3
CNS PTLD	6	3	0
Fatal	3	3	0
Total fatal PTLD cases	4	4	3

A total of 9 of the 17 subjects with PTLD died during the studies. Of the 8 fatalities who received belatacept, 6 patients had PTLD with CNS involvement and the other 2 patients had renal PTLD. All 3 PTLD cases who received CsA were fatal.

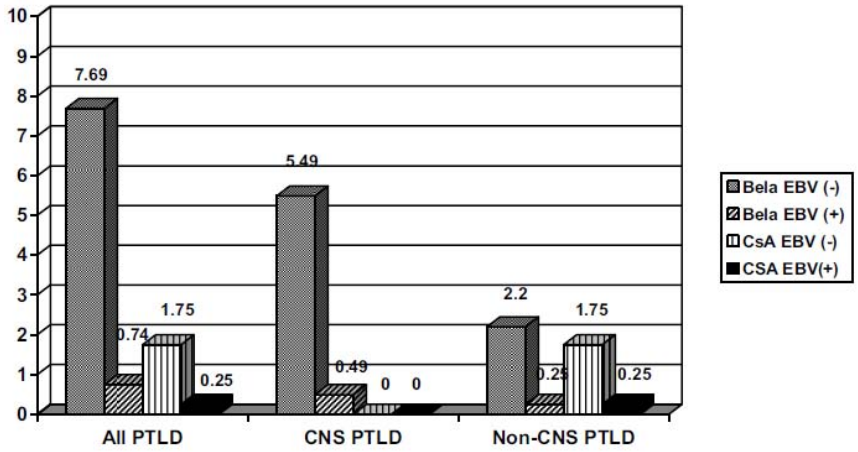
In the renal transplant studies, most cases of PTLD in the belatacept group (13/14) occurred in the first 18 months post transplant, with 1 case occurring 47 months post transplant.

In addition to the 14 cases reported in the renal transplant recipients 2 additional cases of PTLD were reported in a Phase II liver transplant study (IM103045) in subjects receiving basiliximab + belatacept MI + MMF + corticosteroids and belatacept LI + MMF + corticosteroids. It has been reported that liver transplant recipients are at higher risk of developing PTLD than renal transplant recipients.

In addition the company analysed the data with respect to EBV status as it is known to be the strongest risk factor for renal transplant recipients (but not for liver transplant recipients).

While EBV-negative subjects comprised approximately 11% of the study population across treatment groups, 50% of the cases of PTLD occurred in the EBV-negative subjects, EBV-positive patients treated with belatacept also appeared to be at a somewhat higher risk of PTLD than corresponding patients treated with CsA.

Figure 20. Percent of subjects with PTLD by treatment group and EBV serostatus.



All PTLD*: Bela EBV (-) 7/91, Bela EBV (+) 6/810; CsA EBV (-) 1/ 57; CsA EBV(+) 1/399
CNS PTLD: Bela EBV (-) 5/91, Bela EBV (+) 4/810; CsA EBV (-) 0/57; CsA EBV(+) 0/399
Non-CNS PTLD: Bela EBV (-) 2/91, Bela EBV (+) 2/810; CsA EBV (-) 1/57; CsA EBV(+) 1/399

* 1/48 subject in the belatacept MI group with non-CNS PTLD had baseline EBV status unknown; 1/20 subject in the CsA group with non-CNS PTLD had baseline EBV status unknown.

Infections

Up to 36 months the most common infections (>10% in any group) were urinary tract infections, upper respiratory tract infections, nasopharyngitis, CMV infections, bronchitis and influenza.

The overall frequency of serious infections up to Month 36 was lower in the LI group compared to the MI and CsA groups. The most common (≥ 2%) serious infections were urinary tract infections, CMV infection, pyelonephritis, gastroenteritis and pneumonia.

The cumulative frequency of TB (total 13 cases) was higher in both belatacept groups than the CsA group. Nearly all of the cases of TB were reported in subjects who currently or previously resided in countries with high prevalence of TB. Ten subjects lived in endemic areas (4 Brazil and 6 India) and 3 lived in France (1 previously lived in Mali).

The cumulative frequency of CNS infections up to Month 36 was low and similar in the LI group (2, 0.4%) and the CsA group (1, 0.2%) compared with the MI group (8 (1.7%).

Of the 8 subjects in the MI group with CNS infections, 3 had cryptococcal meningitis (one with reactivation of a previous primary Chagas infection), and 1 each had West Nile viral infection, cerebral aspergillosis, cerebral fungal infection, PML and herpes zoster (facial nerve). The 2 subjects in the LI group had cryptococcal meningitis and one subject in the CsA group had encephalitis meningococcal.

Table 55. Infections Up to Month 36 (Pooled Core Studies)

	Number of Subjects (%)					
	Up to Month 12			Up to Month 36		
	Belatacept MI N =477	Belatacept LI N =472	CsA N =476	Belatacept MI N =477	Belatacept LI N =472	CsA N =476
Infections and Infestati	337 (70.7)	339 (71.8)	351 (73.7)	378 (79.2)	387 (82.0)	384 (80.7)

	Number of Subjects (%)					
ons						
Serious Infections	128 (26.8)	110 (23.3)	130 (27.3)	171 (35.8)	158 (33.5)	180 (37.8)
Viral infections	126 (26.4)	118 (25.0)	132 (27.7)	185 (38.8)	184 (39.0)	172 (36.1)
CMV	53 (11.1)	56 (11.9)	65 (13.7)	66 (13.8)	65 (13.8)	70 (14.7)
Polyoma virus	23 (4.8)	11 (2.3)	23 (4.8)	30 (6.3)	18 (3.8)	27 (5.7)
Herpes	38 (8.0)	31 (6.6)	29 (6.1)	74 (15.5)	67 (14.2)	51 (10.7)
Fungal infections	66 (13.8)	52 (11.0)	72 (15.1)	109 (22.9)	79 (16.7)	98 (20.6)
Tuberculosis	2 (0.4)	2 (0.4)	1 (0.2)	7 (1.5)*	6 (1.3)	1 (0.2)
*One of the cases in the MI group was confirmed after the 36 database lock						

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML), also known as progressive multifocal leukoencephalitis, is a rare and usually fatal viral disease that is characterized by progressive damage or inflammation of the white matter of the brain at multiple locations. It is caused by the reactivation of a common virus in the central nervous system of immune-compromised individuals. Polyomavirus JC (often called JC virus) is carried by a majority of people and is harmless except among those with lowered immune defences.

Two cases of PML, both fatal, have been reported in belatacept MI treated subjects up to database lock; 1 renal transplant recipient and 1 liver transplant recipients. Both subjects received the MI regimen as well as concomitant immunosuppressive regimen The MI regimen in the liver transplant study was more intensive than that used in the renal transplant studies.

One case of PMF, confirmed by the identification of JC virus by PCR in cerebrospinal fluid and an MRI which revealed evidence of demyelination, resulted in the death of a 63 year old women in the ECD renal transplant study. The patient had been treated for approximately 2 years. The second confirmed case was reported in a 52 year old man in an ongoing liver transplant study. This subject was received an augmented MI regimen + MMF (at higher than recommended dose) and corticosteroids for approximately 6 months.

No cases of PML have been reported with the belatacept LI regimen.

Laboratory findings

Overall belatacept was not associated with clinically significant adverse effects on haematology and chemistry laboratory parameters. Up to 36 months, hypophosphataemia was more frequently reported in belatacept treated subjects; 17% MI, 21% LI and 13%

CsA. The majority of these AEs occurred between 0 and 3 months and none were serious or resulted in discontinuation. Evaluation of the central laboratory values, the mean and median blood phosphorus levels were similar in the three treatment groups at each specified time point up to Month 36.

Proteinuria, defined in the studies as 2+ on a urine dipstick assessment on 2 consecutive visits, was reported in 3-5% more subjects receiving belatacept than CsA up to Month 36. Review of the urine protein by visit indicates an excess of subjects with urine protein 2+ or greater at Month 1 but the urine protein profile at Months 3, 6 and 12 was similar in the belatacept and CsA groups. CsA is known to have an antiproteinuric effect and so this result was not unexpected.

Belatacept was associated with reductions in serum levels of IgG, IgM and IgA in all treatment groups. There was no association between low immunoglobulin levels and the incidence of serious infections.

Safety in special populations

No special populations other than renal transplant have been studied.

Immunological events

Up to Month 36 in the core studies the frequency of autoimmune AEs was similar in the three treatment groups; 8, (1.7%) MI; 8, (1.7%) LI and 9 (1.9%) CsA. The most common autoimmune disorders in belatacept treated subjects was psoriasis (2 subjects each in the MI and LI groups). The most common autoimmune disorder in CsA treated subjects was hyperthyroidism (4 subjects).

Three autoimmune events in the belatacept groups were reported as serious: sarcoidosis (LI), Guillain Barre syndrome (MI) and panuveitis (MI).

Overall the incidence of autoimmune disorders is low and similar between the treatments and suggests that belatacept does not predispose subjects to an increased risk of development of autoimmune events.

Safety related to drug-drug interactions and other interactions

No particular safety issues were seen in the one interaction study (with MMF) that was done.

Discontinuation due to edverse events

Up to month 12 the frequency of AEs leading to discontinuation in the pivotal studies was slightly lower in the MI (9.9%) and LI (11.4%) groups compared to the CsA (13.9%) group.

This trend was also seen up to Month 36 months; MI (13.8%), LI (15.0%) and CsA (18.7%).

Most AEs leading to discontinuation were reported for only 1 subject. AEs leading to discontinuations in > 1% of belatacept subjects in either treatment groups were: transplant rejection, CMV infection, renal vein thrombosis and complications of transplanted kidney.

Post marketing experience

Product is not marketed in any country and so there is no post marketing experience.

Evaluator's overall conclusions on clinical safety

Key features of the safety assessment:

- More AR with belatacept and higher grade
- Better overall GFR with belatacept. Is this a benefit of belatacept or absence of toxicity of CsA?
- Incidence of PTLD, especially CNS, higher with belatacept.

PML occurred with belatacept.

- Slightly better cardiovascular profile.
- Similar metabolic profile.

Of the two belatacept dosing regimens evaluated in the core studies, the belatacept LI regimen demonstrated a more favourable safety profile. Up to Month 36, the frequency of death was lower in the LI group (5.5%) compared with the MI group (6.9%). The frequency of serious infections, serious fungal infections, malignant neoplasms, CNS PTLD, polyoma virus, CNS infections and fungal infections were also less frequent in the LI group compared with the MI group. No cases of PML have been reported with the LI regimen. The sponsor is only seeking approval for the LI dose regimen which is appropriate.

Clinical summary and conclusions

Clinical aspects

Pharmacokinetics

Belatacept has a consistent and predictable PK profile that is similar in healthy subjects and renal transplant recipients. It exhibits linear PK, a low volume of distribution consistent with restriction to the extracellular space and an apparent terminal elimination half-life in serum of approximately 8-10 days.

A population PK analysis was conducted using 13,648 samples included from 984 subjects of whom 60 were from Phase I studies in healthy subjects and 924 were from the Phase II and III studies in renal transplant recipients. The overall mean variability (day to day range) for belatacept (MI and LI) was C_{max} 15% (14-16%); C_{avg} 23% (14-27%) and C_{min} 47% (19-57%). The PK of belatacept was not impacted by gender, race, age, renal function, hepatic function, diabetes, concomitant dialysis or subject type (healthy versus renal transplant recipient).

Data from the Phase III studies demonstrate that exposure to belatacept during the peri-transplant period was approximately 2 fold higher for the MI regimen compared to the LI regimen, consistent with the 2 fold higher total dose for the MI regimen during the 2-6 month period. Exposure to belatacept then tapered to similar values during the maintenance phase (beyond Month 6) when the dose and frequency of administration were identical for the 2 regimens.

Overall the targeted C_{min} levels of 20 and 5 μg/mL for the initial period and 2 μg/mL for the maintenance period were attained in approximately 80% and 90% of the patients, respectively when intended for each dose regimen. In the long term extension of the Phase II study, belatacept C_{min} was consistently maintained up to 5 years posttransplantation.

Pharmacodynamics

The pharmacodynamic effects of belatacept are consistent with its specific role in blocking the interactions of CD28 with CD80/86. *In vitro* belatacept inhibits T cell proliferation and the production of cytokines IL-2, interferon-γ, IL-4 and TNFα.

Receptor occupancy was ≥ 85% in the first month for both the MI and LI regimens when both dose and exposures were similar. During the 2-6 month post transplantation period when the dose and exposure of belatacept were greater for the MI than the LI regimen, CD86 receptor occupancy tended to be numerically higher for the MI regimen than the LI regimen: (2-3 months: MI 85%, LI 72%; 4-6 months: MI 72%, LI 59%). After 6 months, when dosing was similar for both regimens, the receptor occupancy remains ≥59%.

Data from the Phase III studies suggest that belatacept may inhibit the development of antibodies directed against donor human leukocyte antigens (HLA).

Immunogenicity

Belatacept treatment resulted in a low seroconversion rate; antibody prevalence in the pivotal trials (4 week dosing) was 5.3% during treatment and 6.5% following discontinuation of belatacept for ≥56 days. Incidence rate was consistent at approximately 2/100 patient years.

Where immunogenicity was detected, it was mostly transient and with very low titres. Continued dosing with belatacept did not lead to an increase in titres. Measurement made during the maintenance phase of treatment provide the most sensitive index of an anti-belatacept antibody response because persistent, high affinity IgG1 anti-drug antibodies should have been detected during the maintenance phase if a clinically meaningful immune mediate response were to occur. Overall the profile of anti-belatacept immunogenicity, as assessed with a sensitive ECL assay, is not consistent with that of a significantly immunogenic protein.

Evaluation of the relationship between immunogenicity and clinical parameters showed there was no impact of antibody development on PK, efficacy or safety.

Clinical efficacy

The efficacy data was based on the results of the pivotal trials; two Phase III trials and one Phase II trial. The sponsor states that cyclosporin was chosen as the comparator rather than tacrolimus because data on the effects of cyclosporin on subject and graft survival were available to inform the selection of the non-inferiority margin and because when the Phase III studies were commenced cyclosporin was approved in combination with the background immunosuppressive medications used in the Phase III trials, making it the standard therapy to use as comparator.

Dose-response studies and main clinical studies

Belatacept was studied in two dose regimens constructed using an integrated assessment of belatacept PK, pharmacodynamics and nonclinical and clinical efficacy and safety data. Both regimens were constructed to provide greater immunosuppression during the early post transplant critical period.

The LI dose regimen established for the Phase II study (IM103100) targeted a trough serum concentration (C_{min}) of 20 µg/mL through Day 29 post transplant and 5 µg/mL through Month 3, while the MI regimen targeted to achieve C_{min} of 20 µg/mL through Month 3 and 5 µg/mL through Month 6. During the maintenance phase (after 3 months for the LI and 6 months for the MI regimen) a q8-week versus a q4-week dosing schedule was evaluated to target a maintenance of 0.25 or 2 µg/mL, respectively, to identify the optimal maintenance regimen.

In this study, both belatacept regimens met the primary endpoint of non-inferiority to CsA in acute rejection (AR). Furthermore, compared to CsA both regimens demonstrated similar subject and graft survival, improved GFR and a lower incidence of CAN. Both regimens demonstrated acceptable efficacy and safety. However the following findings indicated a need to modify the regimens for the Phase III studies:

- A higher frequency of subclinical rejection in the LI dosing regimen then either the MI dosing or the CsA regimen.
- Numerically higher rates of subclinical AR in subjects who were reallocated to the q-8 week maintenance schedule than in subjects on the q-4 week schedule.
- C_{min} for the LI regimen below the target of 20 µg/mL on Day 15 (approximately 11 µg/mL).

For the Phase III studies, the following modifications were made:

- A q-4 weeks maintenance schedule was given for both regimens
- An additional dose of 10 mg/kg was given on Day 5 in the LI dosing regimen to attain belatacept C_{min} of 20 µg/mL during Month 1 post-transplant.

The Phase III studies were 2 randomised, active controlled, partially-blinded global studies in de novo renal transplant patients receiving allografts from a range of donor types. Both studies evaluated 2 belatacept dose regimens which were compared to CsA.

Study IM10308 was a study of renal transplant recipients who received standard criteria organs; 666 transplanted subjects were randomised 1:1:1 to belatacept MI, belatacept LI or CsA. Study IM103027 was a study of renal transplant recipients who received higher risk, extended criteria organs. Some 543 transplanted subjects were randomised in the same manner to the same treatment groups as IM103008.

Both studies were designed to show that belatacept offers subject and graft survival that is comparable to CsA but with improved posttransplant renal function. AR was added as a third co-primary endpoint in Study IM103008 to assess the similarity of rates of AR between belatacept and CsA based regimens. AR was a secondary endpoint in IM103027. Additional endpoints for both studies included CAN and endpoints pertaining to cardiovascular and metabolic risk: diabetes mellitus, hypertension and lipid parameters. Both studies evaluated primary endpoints at 1 year but were designed as 3 year studies to characterise longer term efficacy and safety.

Cyclosporin was chosen as the comparator as is has been demonstrated to provide superior graft survival to azapthioprine, thereby supporting the establishment of non-inferiority margin for the primary endpoint of subject and graft survival in both Phase III studies.

Despite an increase in acute rejection in the belatacept treated subjects, subject and graft survival at 12 months and continuing to 36 months was comparable between belatacept regimens and CsA.

Renal function was superior in the belatacept treated subjects and numerous tests were employed to test the robustness of this finding. For all treatment groups, the trajectories for change in GFR established at Month 12 and 24 persists through Month 36 and the cumulative year-on-year effect of the differing slope analysis of GFR indicate a mean difference of approximately 21 mL/min/1.73m^2 in Study IM103008 and approximately 11 mL/min/1.73m^2 in Study IM103027. cGFR was approximately 35-45% higher with belatacept in both studies relative to CsA at 36 months.

Compared to CsA, belatacept treatment resulted in clinically meaningful reductions in NODM, improvements in blood pressure and favourable changes in lipid profile by Month 12. With extended follow up through Month 36, the improvement in lipid profiles was maintained. Improvements in blood pressure were maintained at Month 36 in Study IM103008 but not in Study IM103027. The significant difference in NODM seen at Month 12 did not persist through Month 36.

Clinical studies in special populations

No studies were conducted in any special populations other than renal transplant recipients.

Analysis performed across trials (pooled analyses)

Pooled analysis of efficacy and safety in pivotal studies confirmed results seen in individual trials.

Supportive studies

Not applicable.

Clinical safety

The characterisation of the safety of belatacept relies primarily on data from the 3 core studies of belatacept; IM103008, IM103027 and IM103100.

Patient exposure

949 subjects had received belatacept for a median of 3.3 years in IM103008 and IM103027 and 6.8 years in IM103100. Within the belatacept cohort, 81 and 75 subjects have received belatacept for at least 5 and 7 years.

Adverse events

Up to Month 12, nearly all subjects in the core studies experienced one or more AEs. The most common AEs were similarly distributed across the three treatment groups, with the highest frequency in the post surgical period, suggesting that many of the AEs may be associated with post-operative morbidity rather than study treatment. Up to 36 months the most common AEs (≥ 20%) in subjects treated with belatacept were anaemia, peripheral oedema, constipation, diarrhoea, urinary tract infection, hypertension, pyrexia, nausea, graft dysfunction, cough, vomiting, leucopoenia, hypophosphataemia and headache.

Serious adverse events and deaths

The main safety concerns associated with belatacept use are PTLD, with a preponderance of CNS PTLD, and serious infections including PML. These events are consistent with belatacept's immunosuppressant properties and are reported risks of immunosuppressive therapies used in renal transplant.

As of the June 2010 database lock a total of 14 cases of PTLD were reported in the combined belatacept groups (8 MI and 6 LI) of which 9 (6MI and 3LI) presented in the CNS. The frequency of CNS PTLD in the belatacept MI group was approximately twice that of the belatacept LI group. There were 3 cases of fatal disseminated PTLD in the CsA group. The risk of PTLD was increased in subjects without immunity to EBV. Although the highest risk of PTLD with belatacept was observed in EBV-negative subjects EBV-positive subjects treated with belatacept also appeared to be at higher risk of PTLD compared to CsA treated subjects. The higher number of EBV-positive population treated with belatacept was largely accounted for by CNS PTLD: 2/406 (0.5%) for MI and 2/404 (0.5%) for LI versus none (0/399) for CsA. In the belatacept LI group, the absolute risk of any PTLD in EBV-positive subjects was low (4/404, 1%). It is noted that 2 of the 4 belatacept LI EBV-positive cases were classified in a post hoc assessment by an independent, blinded, pathologist with PTLD expertise as not compatible with the diagnosis of PTLD. Therefore, according to the central pathologist assessment, there are 2 (0.4%) confirmed CNS cases of PTLD in EBV-positive subjects in the belatacept LI group.

Laboratory findings

Belatacept was not associated with clinically significant adverse effects on haematology and biochemistry laboratory parameters.

Safety in special populations

Only special population studied was renal transplant recipients.

Immunological events

The incidence of autoimmune AEs was similar in the 3 treatment groups. The most common autoimmune disorder reported in belatacept treated subjects was psoriasis (4 cases). In the CsA treated subjects most common autoimmune disorder was hyperthyroidism (4 cases). One serous event of Guillain Barre syndrome led to discontinuation and subsequently resolved.

Safety related to drug-drug interactions and other interactions

Not applicable

Discontinuation due to adverse events

Up to 12 months, the cumulative frequency of AEs leading to discontinuations in the core studies was comparable in the 3 groups; (9.9% MI, 11.4% LI and 13.9% CsA) and continued up to Month 36 months (13.8% MI, 15.0% LI and 18.7% CsA). Most AEs leading to discontinuation up to Month 36 were reported in only 1 subject. AEs leading to discontinuation in ≥ 1% of belatacept subjects in either treatment group were transplant rejection, CMV infection, renal vein thrombosis and complications of transplanted kidney.

Benefit risk assessment

Belatacept is a new treatment option for renal transplant recipients, which addresses the current unmet need for an immunosuppressive treatment that provides short term outcomes comparable to the CNIs while avoiding their renal, cardiovascular and metabolic toxicities.

Benefits

The benefits of belatacept therapy are:

- Comparable subject and graft survival to cyclosporin.
- Improved renal function compared to cyclosporin; (removal of toxicity of CsA).
- No need for therapeutic drug monitoring.
- Small improvement in cardiovascular parameters and similar metabolic changes to cyclosporin.

Risks

The risks of belatacept are:

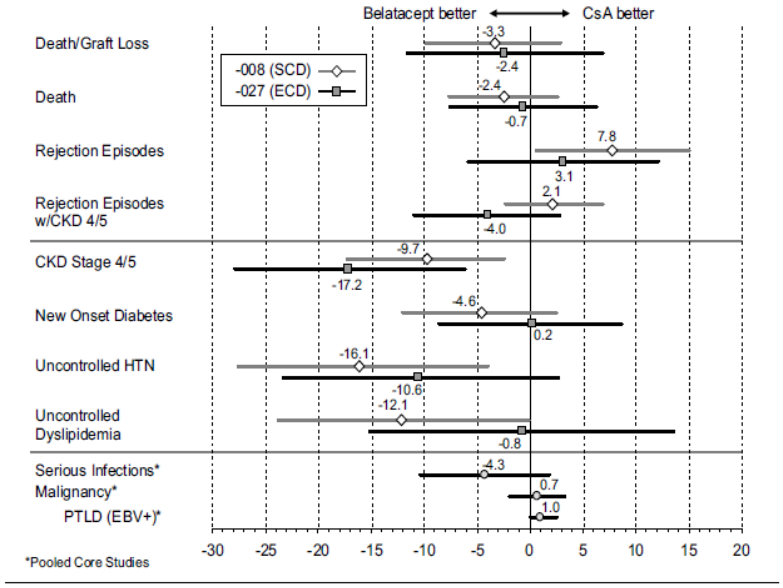
- Higher incidence of acute rejection compared to cyclosporin.
- Risk of malignancy with increased incidence of PTLD compared to cyclosporin.
- Risk of serious infections with occurrence of PML.
- Repeated IV infusion of belatacept versus oral therapy with CsA.

Balance

The company provided the following risk benefit summary. For each difference, the absolute difference in frequency between the belatacept LI group (the recommended clinical dose) and CsA are shown for both Phase III studies, with a solid line representing the confidence interval of the difference. The top portion presents the key efficacy endpoints at 3 years. The bottom panel presents serious infection, malignancies and PTLD.

In addition, the PTLD risk depicted is limited to EBV-positive recipients, consistent with the proposed contraindication.

Figure 21. Comprehensive Benefit-Risk Assessment for belatacept LI versus CsA. 36 Month data.



Note: measures are in absolute difference (%)

Conclusions

Overall the sponsor has demonstrated that belatacept is comparable to cyclosporin. There is a clear improvement in renal function compared to cyclosporin but despite this being known to be the greatest predictor of graft and subject survival the degree of improvement does not translate to a detectable improvement in graft and subject survival up to 36 months post transplant.

On the basis of the comparability to cyclosporin the clinical data submitted support registration of belatacept.

V. Pharmacovigilance Findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The summary of the Ongoing Safety Concerns as specified by the sponsor are shown in Table 56 below.

Table 56. Ongoing Safety Concerns

Ongoing safety concerns	
Important Identified risks	• Post-transplant lymphoproliferative disorder (PTLD) with a preponderance of central nervous system (CNS) location • Infections • Progressive multifocal leukoencephalopathy (PML)
Important Potential risks	• Malignancies (other than PTLD), including nonmelanoma skin cancers • Autoimmunity • Immunogenicity • Infusion-related reactions • Off-label use
Important Missing Information	• Pregnancy and lactation • Children • Hepatically impaired patients • Retreatment after discontinuation

OPR reviewer comment

The above summary of the Ongoing Safety Concerns was considered acceptable.

Pharmacovigilance plan

Proposed pharmacovigilance activities

Routine[19] and additional pharmacovigilance activities are proposed to monitor and further characterise the Ongoing Safety Concerns associated with belatacept. In addition, targeted questionnaires will follow-up cases of PTLD, infection (including PML and TB), autoimmune symptoms and pregnancy in clinical trials. Additional pharmacovigilance activities are outlined in Table 57 below.

[19] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 57. Additional pharmacovigilance activities.

Post-marketing study	Assigned safety concerns			Conducted in Australia?
	Identified	**Potential**	**Missing**	
Ongoing				
Ongoing Phase III trials		Immunogenicity		
Proposed				
Study IM103089	Infections PTLD/PTLD-CNS[1] PML[2]	Malignancies[3]	Children	Yes
Study IM103076	PTLD/PTLD-CNS [1] PML[2]			No
Study IM103077		Off-label use		Yes
Study IM103074		Off-label use		No
Study IM103075	PTLD/PTLD-CNS[1]			No
Study IM103061			Pregnancy and lactation	No

[1] PTLD-CNS=Post-transplant lymphoproliferative disorder (PTLD) with a preponderance of central nervous system (CNS) location [2] PML=Progressive multifocal leukoencephalopathy [3]Malignancies (other than PTLD), including nonmelanoma skin cancers.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The studies proposed as part of the pharmacovigilance plan are considered satisfactory to monitor and further inform their assigned safety concerns. Their design, outcome measurements, sample size and durations have been considered as part of this review. The proposed milestones for reporting the pharmacovigilance activities were also considered satisfactory.

The targeted follow-up questionnaires for cases of PTLD, infection (including PML and TB), autoimmune symptoms and pregnancy have been reviewed and the information collected is considered satisfactory.

Risk minimisation sctivities

Sponsor's conclusion in regard to the need for risk minimisation activities

In the RMP it is stated:

"*The Summary of Product Characteristics and the package leaflet prescribing information are the initial communication tools for risk minimization. Bristol-Myers Squibb supports the need for additional risk minimization activities, and proposes to proactively address the events of special interest by establishing a comprehensive risk minimization action plan."*

OPR reviewer comment

The sponsor's conclusions were considered acceptable

Potential for medication errors

The sponsor states in the RMP that no subjects discontinued treatment in the core clinical trials (two Phase III and one Phase II) used for the primary safety information. Medication errors will be closely monitored through routine safety surveillance.

OPR reviewer comment

This was considered acceptable

Planned actions

Educational program

The sponsor has developed a plan to provide additional communication to health care professionals (HCP) and patients about the risks of belatacept. Specifically, the primary goals of plan are to communicate the risks of PTLD (specifically involving the CNS), serious infections and PML. In addition, information on the risk factors for developing these adverse events are also included in this plan, such as Epstein-Barr virus (EBV) serostatus, lymphocyte depleting agents, cytomegalovirus and overall immunosuppressant burden.

The specific tools to communicate the risks of belatacept to HCP and patients are: A Dear HCP letter, a patient alert card and an educational brochure.

Dear healthcare provider letter emphasises

- Testing EBV serostatus prior to initiation of therapy.
- Contraindication in people who are EBV negative and EBV-unknown serostatus.
- Restates the risks and risk factors of PTLM, serious infections and PML.
- Importance for monitoring new or worsening symptoms.

Educational brochures emphasises

- Risk of PTLD, CNS PTLD, infections and PML, recommendations for the evaluation of suspected cases and treatment considerations.

Patient alert card emphasises

- Encourages patient to report adverse events
- Reminds patients and other HCPs patient is treated with immunosuppressive drug

- Patient information as a source of comprehensive information

Implementation of the educational program

The sponsor plans to use the time between approval and launch to make contact with the transplant centres. Postapproval all transplant centre nephrologists and surgeons will receive relevant information about the benefits and risks of belatacept. In addition, the patient alert card will be included in the packaging and given at monthly infusions. It is intended the patient will carry it around with them at all times. Additional copies of the alert card will be available on the Nilojix website.

Assessment of the educational program

Globally, the drug utiliSation Studies IM103077 and IM103074 will inform the overall effectiveness of the educational program (only Study IM103077 will be conducted in Australia). These studies will assess the patterns of belatacept use through using the data obtained by the Collaborative Transplant Study (CTS). That is, outcomes such as prescriber's compliance with the labelled contraindication regarding the use of belatacept in patients with EBV-negative serostatus, EBV serostatus, demographics, clinical characteristics, cytomegalovirus serostatus, transplanted organ characteristics and concomitant medications will be reported. Study reports for IM103077 and IM103074 will be provided annually with the PSUR, for 5 and 7 years following market authorisation.

OPR reviewer comment

The sponsor has developed an educational program, an additional risk minimisation activity, to communicate the risks of belatacept to health care professionals (HCP) and patients. The specific tools to communicate the risks of belatacept to HCPs and patients are: a Dear HCP letter, a patient alert card and an educational brochure.

If this submission is approved, post-registration but prior to supply, the sponsor should provide to the TGA's OPR educational program documents, highlighting any differences including relevance to clinical practice, in the implementation and evaluation that may exist for Australia. A date or milestone that these documents will be provided should be submitted.

In regard to the proposed routine risk minimisation activities, the draft product information and consumer medicine documents were considered satisfactory.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application:

It is recommended to the Delegate that the sponsor:

- The implementation of RMP Version 2, dated Nov 2010, including the sponsor's response to the request for information/documents and any future updates be imposed as a condition of registration.
- If this submission is approved, postregistration but prior to supply, the sponsor should provide to OPR educational program documents, highlighting any differences including relevance to clinical practice in the implementation and evaluation that may exist for Australia. A date or milestone that these documents will be provided should be submitted.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Belatacept drug substance is manufactured in a recombinant CHO cell line using typical biotechnology based fermentation and chromatography process. The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. Some GMP issues were outstanding at the time of this Overview. Batch release will be a condition of registration.

Nonclinical

Belatacept is intended to inhibit the interaction of CD80/CD86 co-stimulatory molecules and CD28, reducing T cell activation. The rationale for action of belatacept is that for full T cell activation to occur, resting T cells require a signal through the antigen specific CD28 receptor and a second "co-stimulatory" signal to CD28 from CD80 and CD86 on antigen presenting cells. Activated T cells are the predominant mediators of immunological rejection of transplanted organs. *In vitro*, belatacept inhibited both CD80 and CD86-mediated T cell proliferation and reduced cytokine release in co-stimulation assays. Belatacept suppressed T cell dependent antibody responses in mice, rats, rabbits and monkeys. At equivalent exposures, belatacept was less or equipotent to abatacept in rodents and rabbits but more potent in monkeys and humans. In a non-human primate kidney transplant model belatacept, in combination with MMF and a corticosteroid, or in combination with the IL-2 receptor antagonist basilixumab, prolonged survival and maintained good renal function for longer than treatment in the absence of belatacept..

The most notable toxicities of clinical relevance are an increased risk of opportunistic infections and virally-induced malignancies. Anti-belatacept antibodies were only detected when serum belatacept levels had dropped below immunosuppressive levels. There is a theoretical risk that antibodies against belatacept may cross-react with endogenous CTLA-4, leading to autoimmune reactions, particularly if belatacept treatment is ceased. If belatacept treatment is ceased, anti-belatacept antibody production may reduce the efficacy of the drug if administration is recommenced.

Belatacept should not be used in pregnancy or when breast-feeding. Should belatacept treatment cease due to pregnancy, there is an unknown risk to the mother and fetus in the event of anti-belatacept antibody production.

There were no objections on nonclinical grounds to the registration of belatacept for the proposed indication.

Clinical

The pivotal studies were planned as 3 years duration with the primary efficacy analysis scheduled for 6 or 12 months. Reports were written at end of 1, 2 and 3 years and then since long term extension studies have not completed various "pooled data" and post database lock updates were provided. The clinical submission was very large, poorly navigable, contained reports and tabulations with slight differences in the 12 month data (primary efficacy outcomes), due to the unusual practice of including updates of the

clinical databases after database lock and provided no integrated summaries for 3 year data.

Pharmacokinetics

Pharmacokinetics were determined in 2 single dose studies in healthy volunteers and in 3 Phase II studies in renal transplant recipients. Most PK data were obtained through samples collected in core clinical studies to establish population pharmacokinetics. The current Australian submission also includes PK results in subjects with rheumatoid arthritis and with SC administration. The clinical evaluation report (CER) provides a summary of design of clinical pharmacology studies and pharmacokinetic objectives. These studies involve belatacept manufactured by 3 processes. Process C is the process intended for marketed product. Study IM103024 compared a single dose of 10 mg/kg belatacept from process B and process C in healthy volunteers. The C_{max},$T_{1/2}$ and V_{ss} were similar for the two process drugs. There were small differences (10.6% and11.9% higher for process C) in $AUC_{(0-T)}$ and $AUC_{(INF)}$ not considered to be clinically significant.

The CER presented PK results from Study IM103001, an ascending single dose study in healthy volunteers in which belatacept dosage levels were 0.1, 1, 5, 10 or 20 mg/kg IV. Kinetics were linear and volume of distribution was low and consistent with distribution to extracellular space. PK results at Week 12 from Study 103047, a multiple dose study in renal transplant recipients who received belatacept 10 mg/kg on Days 1 and 5 and Weeks 2, 4, 8 and 12 are also presented in the CER. Mean C_{min} was 7.29 ug/mL and mean $T_{1/2}$ was around 10 days. Comparison of target population and healthy volunteers shows similar PK parameters as shown in the CER. The variability of exposure in renal transplant recipients was generally low. The pattern of C_{min} was consistent in Studies IM103008 with highest C_{min} during the first month. Trough levels were stable in Study IM103100 LTE through 5 years of exposure.

Population pharmacokinetics analysis was conducted with 749 and 12,139 serum concentration values from 60 healthy subjects and 924 renal transplant subjects taken up to 1 year. PP parameters are shown in the CER. The overall mean variability (day-to-day range) for belatacept C_{max}, C_{avg} and C_{min} were 15% (14% - 16%), 23% (14% - 27%) and 47% (19% - 57%), respectively. The dosing of belatacept was designed to achieve C_{min} concentrations of approximately 20 µg/mL for 30 days followed by approximately 7 µg/mL to day 90 (initial phase), and approximately 2 or 0.25 µg/mL in the maintenance phase to Day 365. The CER shows these C_{min} target concentrations were achieved in>80% of patients with LI or MI dosing regimens. In the PP analyses PK was not impacted by gender, race, age, renal function, hepatic function, diabetes, concomitant dialysis or subject type (healthy versus renal transplant recipient). Baseline body weight had a significant effect on all PK parameters. This supports a weight based dose of belatacept.

Formal interaction studies were not conducted to investigate the impact of background immunosuppressive therapy (MMF + corticosteroids) on the PK of belatacept. It is known that CsA lowers mycophenolic acid (MPA) exposure by inhibiting the enterohepatic recirculation of MPA and so an evaluation of the PK of MPA and mycophenolic acid glucuronide (MPAG) was conducted in renal transplant recipients who received belatacept or CsA based treatment with mycophenolate mofetil (MMF) (IM103027 PK substudy). MPA C_{max} was approximately 22% higher and $AUC_{(TAU)}$ as approximately 41% higher in subjects receiving belatacept compared to subjects receiving CsA, and MPAG C_{max} was approximately 26% lower and $AUC_{(TAU)}$ approximately 30% lower in subjects receiving belatacept compared to subject receiving CsA. The observed difference in the exposure to MPA between MMF + CsA and MMF + belatacept was consistent with other reported data.

Pharmacodynamics

Pharmacodynamics Study IM103034 assessed receptor occupancy at baseline prior to belatacept infusion and over time following transplant in 57 subjects. CD86 receptor occupancy was assessed with a flow cytometric based competition assay. Subjects received belatacept 10 mg/kg IV on Days 1 and 5 and then every other week through Month 6 and then maintenance dose of 5 mg/kg every 4 weeks until 12 months. Approximately 94% saturation of CD86 receptors on the surface of antigen presenting cells in the peripheral blood was observed at predose on Day 5 following the Day 1 infusion of the 10 mg/kg dose. Receptor occupancy tapered to 65% by Month 12. At these belatacept concentrations, *in vitro* data suggested complete saturation of CD86 receptors by belatacept.

The PK-PD relationship of free CD86 levels and belatacept concentration is shown in the CER. Receptor occupancy stabalised at belatacept concentration > 20 μg/mL. The PK-PD relationship predicted approximately 90% saturation of CD86 receptors on surface of antigen-presenting cells in peripheral blood following initial administration of belatacept. The CER shows expected CD86 receptor occupancy at time periods to 12 months based on target C_{min} concentrations.

The incidence of developing anti-donor HLA antibodies was evaluated in the pivotal clinical trials using flow cytometry. Overall, few subjects had anti-donor HLA antibodies at baseline or after treatment with belatacept.

Numerically fewer subjects in each belatacept treatment group (4-5%) had detectable circulating antibodies directed against donor-specific HLA antigens following transplantation than subjects in the cyclosporin (CsA) treatment arm (8-12%).

Data from the phase 3 studies demonstrated that among the belatacept treated subjects who had an acute rejection (AR) episode within the first 24 months of the study only 4-5% of the subjects with AR had detectable anti-donor HLA antibodies at any time. In the CsA treatment group, 15-22% of subjects who experienced AR within the first 24 months had detectable anti-donor HLA antibodies post transplantation.

Efficacy

Efficacy data are based on 3 clinical studies. There were two Phase III studies in renal transplant recipients, the first (IM103008) in subjects who received kidneys based on standard donor criteria and the second (IM103027) in subjects who received kidneys based on extended donor criteria. In addition, Phase II Study IM103100 had a primary efficacy objective. The dose selection for the Phase III studies was based on two belatacept regimens used in IM103100 with modifications to include a 4 week maintenance period and an additional Day 5 dose of 10 mg/kg in the Belatacept Lower Intensity regimen.

Study IM103008

Study IM103008 was a Phase III randomised, active controlled, parallel-group study conducted at 104 sites worldwide. Study participants were adult de novo renal transplant patients who received a living donor or deceased donor kidney transplant with anticipated cold ischaemic time <24 hours. Subjects were randomised 1:1:1 to receive belatacept in either a MI or LI regimen or to receive CsA. All subjects also received a background regimen of basiliximab induction and maintenance therapy with mycophenolate mofetil (MMF) and corticosteroid maintenance therapy.

In Bel MI regimen, subjects received IV belatacept (10 mg/kg) on Day 1 (intended to be given pre-operatively) and Day 5 during the first week, and then every other week through 3 months (Weeks 2, 4, 6, 8, 10, and 12), and then every 4 weeks until 6 months

(Weeks 16, 20 and 24). After 6 months, subjects were to receive belatacept at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial at 36 months.

In Bel LI regimen, subjects received IV belatacept (10 mg/kg) on Day 1 (intended to be given pre-operatively) and Day 5 during the first week, then every other week for 2 weeks (Weeks 2, and 4), and then every 4 weeks for 2 months (Weeks 8, and 12). After 3 months, subjects were to receive belatacept at the maintenance dose of 5 mg/kg every 4 weeks until completion of the trial at 36 months.

In the CsA regimen the initial daily dose was 7 $\pm$ 3 mg/kg was administered in 2 divided doses . Subsequent doses were adjusted to maintain pre-defined tough serum concentrations.

The primary efficacy outcome was planned for evaluation at 12 months because of the likelihood of rejection occurring in the first 12 months. The follow up period of 36 months was to assess long term efficacy and safety.

The primary efficacy objective for each belatacept regimen was comparison to the CsA based regimen on the following 3 co-primary efficacy measures:

- Composite endpoint of subject and graft survival by 12 months, using a non-inferiority design with a margin of 10%,
- Composite endpoint of measured GFR < 60 mL/min/1.73m^2 at Month 12 or a decrease in measured GFR > 10 mL/min/1.73m^2 from Month 3 to Month 12, using a superiority test,
- Incidence of acute rejection (AR) by 12 months, using a non-inferiority design with a margin of 20%.

Chronic allograft rejection was a key secondary endpoint. Other secondary objectives were new onset diabetes mellitus, subject death or graft loss, hypertension and dyslipidaemia.

Participant flow

A total of 686 participants were randomised, 666 were transplanted and 660 received study drug. The ITT dataset included 666 subjects (219 Bel MI, 226 Bel LI and 221 CsA). The PP dataset included 646 subjects at 12 months. In the Bel MI, Bel LI and CsA groups respectively; 173, 181 and 173 completed 12 months; 164, 176 and 153 completed 24 months; 153, 170 and 143 completed 36 months; and 148, 157 and 118 were in a long term extension study at July 2010.

Baseline characteristics were balanced between treatment groups. The majority of subjects were White males. Mean age was 43 years.

The CER presented results for the 3 co-primary endpoints in ITT analysis from the 36 month report. Overall subject and graft survival rates reported at Month 12 were 95.4% in the Bel MI group, 96.5% in the Bel LI group and 92.8% in the CsA group. The prespecified non-inferiority criteria met for both Bel groups. Subject and graft survival rates reported at month 36 were 92.2% in the Bel MI, 92% in the Bel LI and 88.7% in the CsA groups. For death and graft loss considered separately, rates of death (4%, 4% and 7%, respectively) and graft loss (5%, 4%, and 5%, respectively) from transplantation up to Month 36 were observed across the Bel MI, Bel LI and CsA treatment groups. Measured GFR (mL/min/1.73 m^2) < 60 or decrease $\geq$ 10 from Month 3 to 12 rates were 55% in Bel MI, 54.2% in Bel LI and 77.9% in the CsA groups at Month 12. Both Bel groups showed superiority over CsA. This endpoint was not reported at Month 36. For renal function assessed by measured GFR and calculated GFR, both Bel groups showed superiority over CsA maintained over 2 or 3 years. For calculated GFR at Month 36 differences between both belatacept groups and CsA were ~ 21 mL/min/1.73m^2.

Acute Rejection rates were 22.4% in Bel MI, 17.3% in Bel LI and 7.2% in CsA groups at Month 12. The upper bound of 97.3% CI was within non-inferiority margin of 20% for the Bel LI and CsA comparison but not within criteria for the Bel MI and CsA comparison. For the secondary objective chronic allograph nephropathy, the reported rates at Month 12 were 18% in the Bel MI, 24% in the Bel LI and 32% in the CsA groups. Other secondary endpoints are presented in the CER. At Month 36 the incidence of NODM was similar across groups. At Month 36, blood pressure values and use of antihypertensive medications were lower in Bel groups compared to CsA. At Month 36 dylipidaemia and use of lipid-lowering medications were lower in Bel groups compared to CsA.

Study IM103027 was a Phase III, randomised, active controlled, parallel-group study conducted at 79 sites worldwide. Study participants were first time recipients of a kidney from a donor with 'expanded criteria'. Subjects were randomised 1:1:1 to receive Bel MI, Bel LI or CsA. All subjects also received a background regimen of basiliximab induction and maintenance therapy with mycophenolate mofetil (MMF) and corticosteroid maintenance therapy. The Bel MI, Bel LI and CsA regimens were the same as in Study IM103008.

The primary efficacy outcome was planned for evaluation at 12 months. The follow up period through 36 months was to assess long term efficacy and safety. The two co-primary objectives were:

- Composite endpoint of subject and graft survival by 12 months, using a non-inferiority design with a margin of 10%,
- Composite endpoint of measured GFR < 60 mL/min/1.73m^2 at Month 12 or a decrease in measured GFR > 10 mL/min/1.73m^2 from Month 3 to Month 12, using a superiority test.

Secondary objectives included acute rejection and preservation of renal function.

A total of 578 participants were randomised, 543 were transplanted and 536 received study drug. The ITT dataset included 543 subjects (184 Bel MI, 175 Bel LI, 184 CsA). In the Bel MI, Bel LI and CsA groups, respectively; 73%, 75% and 70% completed 12 months; 63%, 68% and 63% completed 24 months; 60%, 66% and 56% completed 36 months; and 56%, 65% and 47% entered a long term extension study.

Baseline characteristics were balanced between treatment groups. The majority of subjects were white males. Mean age was 56 years.

The CER presented results for the 2 co-primary endpoints in ITT analysis from the 36 month report. Overall subject and graft survival rates reported at Month 12 were 86.4% in Bel MI, 88.6% in Bel LI and 85.3% in CsA groups. The prespecified non-inferiority criteria met for both Bel groups compared to CsA. Subject and graft survival rates reported at Month 36 were 80.4% in the Bel MI, 82.3% in the Bel LI and 79.9% in the CsA groups. For death and graft loss considered separately, rates of death were 12%, 9% and 9% and graft loss were 10%, 12% and 13% from transplantation up to Month 36 observed across the treatment groups, Bel MI, Bel LI and CsA, respectively. Measured GFR (mL/min/1.73 m^2) < 60 or decrease ≥ 10 from Month 3 to 12 rates were 70.5% in the Bel MI, 76.6 % in the Bel LI and the 84.8% in CsA groups at Month 12. Both Bel groups showed superiority over CsA. For renal function assessed by measured GFR or calculated GFR, both Bel groups showed superiority over CsA maintained for 2 or 3 years. For calculated GFR at Month 36, differences between both belatacept groups and CsA were approximately 11 mL/min/1.73 m^2 higher. Acute Rejection rates were 17.4% in the Bel MI, 17.7% in the Bel LI and 14.1% in the CsA groups at Month 12. The upper bound of 97.3% CI was within non-inferiority margin of 20% for both Bel groups compared to CsA. Other secondary endpoints are presented in the CER. Diastolic and systolic were lower in both Bel groups compared to placebo and use of anti-hypertensive medicines was

numerically lower. At Month 36 diffrences in NODM and dyslipidaemia were not statistically significant between Bel and CsA groups.

Study IM103100

Study IM103100 was a Phase II, randomised, open label, partially blinded, active control, parallel group study conducted at 41 sites worldwide. Study participants were adult recipients of a kidney from a cadaveric or living donor. Subjects were randomised 1:1:1 to receive belatacept in either a MI or LI regimen or to receiveCsA. All subjects also received a background regimen of basiliximab induction and maintenance therapy with mycophenolate mofetil (MMF) and corticosteroid maintenance therapy. The Bel MI and Bel LI regimens differed from Study IM103008 and Study IM103027 with a maintenance dose of 5mg/kg every 4 **or** 8 weeks, and with Bel LI regimen not including a Day 5 dose of 10 mg/kg.

The study was planned with duration of 12 months and optional long term extension for 3 years. Long term extension was ongoing when the study report was written. The primary efficacy endpoint was clinically suspected and biopsy proven acute rejection at 6 months.

A total of 228 participants were randomised and transplanted. A total of 169 completed 12 months, The ITT dataset included 218 subjects (74 Bel MI, 71 Bel LI, 73 CsA).

Baseline characteristics were balanced between treatment groups. The majority of subjects were White males. Mean age was 45 years.

The CER presents results for the primary endpoint, acute rejection up to 6 months in ITT analysis. The event rates were 6.8% in the Bel MI , 5.6% in the Bel LI and 8.2% in the CsA groups. The difference in event rates were -1.5 (95% CI; -10.7, 7) in Bel MI-CsA comparison and -2.6% (-10.9, 5.7) for Bel LI-CsA comparison, with non-inferiority criteria met. Similar acute rejection rates were seen at 12 months in each treatment arm. None of the subjects experienced severe (Grade III rejections). Few subjects in any treatment group experienced > 1 episode of BPAR. By Month 12, 5 deaths had been reported (1 and 4 in the belatacept MI and CsA groups respectively). One death (pneumonia) in CsA group was considered possibly treatment related. Seven graft losses were reported (3 each in the Bel MI and CsA groups and 1 in the Bel LI group.

Pooled Core Studies

The CER describes a post hoc analysis of select long term efficacy and safety parameters from the 3 pivotal studies. The CER shows that the proportion of subjects treated with belatacept, in LI and MI regimens, who died or who experienced graft failure, were similar to CsA.

A comprehensive assessment of immunogenicity was conducted in all studies using belacept. This is discussed in the CER. The cumulative antibody prescence was 5.3 % during treatment and 6.5% following discontinuation of belatacept for more than 55 days. Titres of anti-belatacept antibodies were generally low and often did not increase over baseline predose titre. Analyses did not demonstrate an apparent effect of anti-belatacept antibodies on PK, efficacy or safety.

Clinical safety

The CER presents a summary of clinical safety in the 3 pivotal clinical studies. The CER notes that the sponsor's Clinical Overview dated December 2010 and Pooled Study Report dated November 2010 provide more up to date information than the 3 year reports of pivotal studies. The 3 pivotal studies assessed safety in a total of 477 subjects who received Bel MI, 472 subjects who received Bel LI and 476 who received CsA.

Adverse events were observed in nearly all subjects. The most frequent adverse events in subjects treated with a belatacept regimen up to Month 36 were anaemia, peripheral

oedema, constipation, diarrhoea, urinary tract infection, hypertension, pyrexia, nausea, graft dysfunction, cough, vomiting, leukopoenia, hypophosphataemia, and headache. Up to Month 36, the frequency of AEs that were considered by the investigator to be treatment-related was lower in the belatacept groups (64.8% MI and 63.6%LI) compared with the CsA group (78.2%). This was mostly due to higher frequencies of dyslipidaemia, increased blood creatinine and hypertension. Up to Month 12 the frequency of AEs leading to discontinuation in the pivotal studies was slightly lower in the MI (9.9%) and LI group (11.4%) compared to CsA (13.9%). This trend was also seen up to Month 36 months; MI (13.8%), LI (15.0%) and CsA (18.7%). AEs leading to discontinuation seen >1% in Bel groups were transplant rejection, CMV infection, renal vein thrombosis and complications of transplanted kidney.

The CER shows up to Month 12 and continuing to Month 36 the frequencies of all deaths and of AEs with outcomes of death were numerically lower in the Bel LI group compared with the CsA or Bel MI group. Review of the narratives for all deaths indicates that most deaths were due to infections, operative complications, cardiac disorders, respiratory disorders and neoplasms. The CER summaries the frequency of malignancies. Overall there was a lower frequency of all malignancies in the LI group, largely driven by a lower frequency of non-melanoma skin cancers.

PTLD is spectrum of disorders which range in severity to a high grade malignant lymphoma. Transplant recipients who are seronegative for EBV are at high risk for infection if they receive organs from seropositive donors. In Month 12 analysis PTLD was reported in 4 subjects in the Bel MI, in 4 subjects in the Bel LI and in 1 subject in the CsA groups. In Month 36 analysis cumulative PTLD events reported were 8 in the Bel MI, 6 in the Bel LI and 3 in the CsA group. A total of 11 of 17 subjects with PTLD died during the studies. Of the 8 fatalities who received belatacept, 6 had CNS involvement and two had renal PTLD. While EBV–negative subjects comprised 11% of the study population, 50% of PTLD cases occurred in EBV-negative subjects. The overall frequency of serious infections up to Month 36 was lower in the LI group compared to MI and CsA. The most common (≥ 2%) serious infections were urinary tract infections, CMV infection, pyelonephritis, gastroenteritis and pneumonia. The cumulative frequency of TB (13 cases) was higher in the Bel groups than in the CsA group.

PML is a usually fatal viral disease that is characterised by progressive damage or inflammation of the white matter of the brain at multiple locations. It is caused by the reactivation of a common virus Polyomavirus JC (often called JC virus) in the central nervous system of immune-compromised individuals. Two cases of PML, both fatal, have been reported in belatacept MI treated subjects up to database lock; 1 renal transplant recipient and 1 liver transplant recipients.

The frequency of autoimmune AEs was low and similar in the three treatment groups. Three autoimmune events in the belatacept groups were reported as serious: sarcoidosis (LI), Guillain Barre syndrome (MI) and panuveitis (MI).

CER conclusion

The CER presents a summary of the evaluation and recommendations. The Phase III studies were 2 randomised, active controlled, partially-blinded global studies in de novo renal transplant patients receiving allografts from a range of donor types. Both studies evaluated 2 belatacept dose regimens which were compared to CsA.

Both studies were designed to show that belatacept offers subject and graft survival that is comparable to CsA but with improved post-transplant renal function. AR was added as a third co-primary endpoint in Study IM103008.

Overall the survival rate of subjects with a functioning graft was similar in the belatacept MI (95% and 86%) and LI (97% and 89%) groups and CsA (93% and 85%) group for

study IM103008 and IM103027, respectively. This met the pre-specified 10% non-inferiority margin. The lower margin of the 97.3% CIs for the difference between belatacept LI and CsA was 2% in Study IM103008 and 5% in Study 103027. The rates of the individual components were similar across treatment groups within each study. While there is a consistently increased acute rejection rate with belatacept at 12 months this does not appear to translate to an impact on subject or graft loss.

Belatacept treatment resulted in a statistically significant improvement in renal function over CsA as assessed by both measured and calculated GFR. The differences were seen as early as 4 weeks after transplantation and were maintained for over 3 years after transplantation. the trajectories for change in GFR established at Month 12 and 24 persists through Month 36 and the cumulative year-on-year effect of the differing slope analysis of GFR indicate a mean difference of approximately 21 mL/min/1.73m^2 in Study IM103008 and approximately 11 mL/min/1.73m^2 in Study IM103027.

Belatacept resulted in improvements in blood pressure and lipid profile compared to CsA at 12 months that were maintained to 36 months for lipid profile but maintained for blood pressure in only 1 study.

The most common AEs were similarly distributed across the three treatment groups. Up to 36 months the most common AEs (≥ 20%) in subjects treated with belatacept were anaemia, peripheral oedema, constipation, diarrhoea, urinary tract infection, hypertension, pyrexia, nausea, graft dysfunction, cough, vomiting, leukopoenia, hypophosphataemia and headache.

The main safety concerns associated with belatacept use are PTLD, which was reported with a higher number of cases in both belatacept groups compared to CsA, and serious infections, including PML.

Of the two belatacept dosing regimens evaluated in the core studies, the LI regimen demonstrated a more favourable safety profile. Up to Month 36, the frequency of death was lower in the LI group (5.5%) compared with the MI group (6.9%). The frequency of serious infections, serious fungal infections, and malignant neoplasms, CNS PTLD, polyoma virus, CNS infections and fungal infections were also less frequent in the LI group compared with the MI group. No cases of PML have been reported with the LI regimen. The sponsor is only seeking approval for the LI dose regimen.

The CER lists the benefits of belatacept LI regimen compared to a CsA regimen as comparable subject and graft survival, improved renal function; removal of toxicity of CsA, no need for therapeutic drug monitoring and small improvement in cardiovascular parameters. The CER lists the risks of belatacept LI regimen compared to a CsA regimen as higher incidence of acute rejection, malignancy with increased incidence of PTLD, serious infections with occurrence of PML and repeated IV infusion of belatacept versus oral therapy with CsA. Risk benefit balance for Bel LI versus CsA is presented in Figure 21 of the CER

The CER supports registration of belatacept LI as it is comparable to cyclosporine. Although belatacept shows improvement in renal function compared to cyclosporine, which is known to be the greatest predictor of graft and subject survival, the degree of improvement does not translate to a detectable improvement in graft and subject survival up to 36 months post transplant. The CER recommended amendment of Indications and that consideration should be given to a black box warning in product information in relation to PTLD.

Risk management plan

The sponsor has developed an educational program, an additional risk minimisation activity, to communicate the risks of belatacept to health care professionals (HCP) and

patients. Specifically, the primary goals of plan are to communicate the risks of PTLD (specifically involving the CNS), serious infections and PML. In addition, information on the risk factors for developing these adverse events are also included in this plan, such as EBV serostatus, lymphocyte depleting agents, cytomegalovirus and overall immunosuppressant burden. The specific tools to communicate the risks of belatacept to HCPs and patients are: a Dear HCP letter and relevant information on the risks and benefits of belatacept will be sent to all transplant centre nephrologists and surgeons. A patient alert card will be included in packaging and provided at monthly infusions and an educational brochure distributed to patients.

Risk-benefit analysis

Delegate considerations

The Phase III clinical studies in this application had primary efficacy endpoints scheduled for assessment at 12 months although planned study duration was 36 months. In view of significant risks that emerged in clinical studies (PTLD, PML) decision of the application was made by US FDA and European Medicines Agency (EMA) only after the availability of 36 month data. Longer term follow-up is continuing in a voluntary subgroup in these studies.

The Phase III clinical studies were commenced before the EU Guideline on Solid Organ Transplantation[20] was adopted. The co-primary efficacy endpoints in Study IM103008 are broadly consistent with this guideline whereas IM103027 did not include biopsy confirmed acute rejection as a co-primary endpoint. The CER raised concern over the appropriateness of the 20% non-inferiority margin for acute rejection used in these studies.

The CER notes the higher incidence of acute rejection with belatacept compared to CsA does not appear to an impact on survival or graft survival. The CER also noted the degree of improvement in renal function with belatacept compared to CsA does not translate to a detectable improvement in graft and subject survival up to 36 months.

The clinical development program does not include assessment of belacept with immunosuppressants other than baxilixumab induction, mycophenolate mofetil and corticosteroids, and antithymocyte globulin for treatment of acute rejection. Belatacpt has only been compared with cyclosporine and not assessed against tacrolimus or mTOR inhibitors.

The clinical development program has not included assessment in special populations except renal transplant recipients.

The Australian PI includes a Black-Box Warning related to PTLD. The warning includes statements

> *"Use in EBV seropositive patients only. Do not use Nulojix in transplant recipients who are EBV seronegative or with unknown serostatus".*

In the clinical study program 50% of PTLD cases were in EBV seropositive subjects so PTLD remains a fundamental risk.

Autoimmune disease is a theoretical concern with belatacept. The limited numbers of patients who have received belatacept does not allow definitive conclusions.

[20] CHMP/EWP/263148/06
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003593.pdf

The Delegate concurred with the clinical evaluator that belatacept, at the recommended dose, may be registered with the indication:

> *"Nulojix (belatacept) is indicated for prophylaxis of organ rejection in adults receiving a renal transplant. Nulojix is to be used in combination with basilixumab induction, mycophenolate mofetil and corticosteroids".*

Various amendments to the PI were recommended but these are beyond the scope of the AusPAR.

Delegate's proposed action

The Delegate proposed to register belatacept (Nulojix) 250 mg vial powder for injection for:

> *"Nulojix (belatacept) is indicated for prophylaxis of organ rejection in adults receiving a renal transplant . Nulojix is to be used in combination with basilixumab induction, mycophenolate mofetil and corticosteroids."*

The advice of ACPM was requested.

The consideration and comment of ACPM was specifically requested on the following aspects:

- Whether benefit risk balance is positive for belatacept lower intensity regimen based on 36 month clinical study results;
- whether available safety data based on 949 patients followed for 36 months are adequate to support registration;
- whether the limited clinical developmental program, in respect of comparator and combination immunosuppressants, is adequate to support registration, taking account of current clinical practise in Australia;
- a boxed warning is proposed for inclusion in PI in relation to PTLD. If registration is supported ACPM are requested to endorse status as a black box warning and to advise of appropriateness of current statements;
- whether proposed Risk Minimisations Activities in relation to risks of PTLD, serious infections and PML are adequate.

Response from sponsor

Introduction

Belatacept represents a new immunosuppressive therapy for use in renal transplant recipients. It addresses the unmet need for a therapy which can provide acceptable control of the alloimmune response and comparable short-term outcomes to the calcineurin inhibitors (CNIs), while avoiding their renal, CV and metabolic toxicities, in order to support improved long-term patient and graft survival.

Bristol-Myers Squibb Australia Pty Ltd acknowledged the clinical evaluator's recommendation and the Delegate's proposed action to support the registration ofNulojix (belatacept) on the basis of the comparability of the clinical data to cyclosporin. The sponsor accepted the Delegate's proposed indication:

> *"Nulojix (belatacept) is indicated for prophylaxis of organ rejection in adults receiving a renal transplant. Nulojix is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids."*

The Delegate requested the addition of two statements in the Precautions section of the Product Information. These suggestions have been incorporated by the sponsor in the PI.

Purpose of document

The advice of the ACPM has been requested by the Delegate on five specific aspects of the application for registration. The purpose of this document is to present a brief summary of the sponsor's position on each of these five aspects. Key findings from the pivotal clinical trials are highlighted, with cross-reference to the appropriate section within the original dossier.

Delegate domment #1

Whether benefit risk balance is positive for belatacept lower intensity regimen based on 36 month clinical study results.

Response

The CER supports registration of belatacept LI as it is comparable to cyclosporin in terms of patient and graft survival through 36 months of follow-up, with a clear benefit in terms of renal function. Summarised below are the key benefits and risks associated with the betatacept LI regimen, followed by an assessment of the overall balance of benefits versus risks.

Benefits

The most notable benefit associated with belatacept is preservation of renal function over time, an area of significant unmet need. In the pivotal Phase II studies, this included a broad range of standard (Study IMI03008) and extended criteria (Study IMI03027) donor kidneys, the mean difference in calculated GFR between belatacept versus CsA-treated patients increased over time, to 22 mL/min in IMI03008 and 11 mL/min in IMI03027 at 36 months. Given the association between advanced renal dysfunction and subsequent graft loss or death, a post hoc analysis assessing time to cGFR < 30 mL/minl 1.73m^2, graft loss, or death was conducted. In both studies, the survival curves demonstrate a marked advantage for subjects receiving belatacept within the time period studied in the clinical trials. Improvements in blood pressure and lipid profiles were also observed. Favourable 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.

Risks

An important risk observed with belatacept was PTLD, with the CNS being the predominant site of presentation. The risk of PTLD with belatacept was approximately 10-fold higher in subjects who lacked immunity to EBV. While there may be an increased risk in EBV-positive subjects, the absolute risk in this population appears low. This is risk factor can be prospectively ascertained in the pretransplant setting and avoiding use in patients without EBV immunity will help address this risk, and that is part of the proposed labelling. As with all immunosuppressive agents, serious infection is a concern. However, the frequencies of serious infections were lower with betatacept LI compared to the betatacept MI and CsA regimens. Two cases of PML were reported; one in a renal transplant recipient and one in a liver transplant recipient. Both received belatacept MI, MMF and corticosteroids. No PML cases have been reported with the LI regimen. An early imbalance in the incidence and grade of acute rejection was observed in belatacept treated subjects in both Phase III studies but most prominently in IMI0300S. Acute rejection occurred early, was not recurrent and was not associated with anti-donor antibodies. Further, the data suggest that AR had limited impact on overall subject and graft survival and on renal function.

Overall benefit risk profile for the LI regimen

A comprehensive assessment of Month 36 outcomes with belatacept LI versus CsA confirms the overall favourable benefit risk profile for the LI regimen. Belatacept treated

groups continued to experience high rates of patient and graft survival, with point estimates that consistently favour belatacept over CsA. The renal function benefit endures and the difference relative to CsA continues to increase. The principal risks associated with belatacept are PTLD with CNS involvement and serious infections including PML. The impact of these concerns was captured in the primary patient and graft survival endpoint, indicating that while important, they did not outweigh the overall benefits ofbelatacept to the patient or the allograft.

Delegate comment #2

Whether available safety data based on 949 patients followed for 36 months are adequate to support registration.

Response

The Phase III studies enrolled a broad range of renal transplant recipients and donor types, reflecting the diversity of patients in the renal transplant population. The safety profile of belatacept is well characterised in these patients and is consistent with its immunosuppressive properties. At the time of the submission, median exposure was 3.3 years for belatacept-treated subjects in the Phase III studies and approximately 6.5 years in the Phase II study. The principle risks associated with belatacept generally appear early (PTLD, PML, serious infection and acute rejection), and follow-up through 36 months has enabled characterisation of the longer-term impact of these risks. As noted in the response to Delegate Comment #1, the long-term benefit risk balance remains positive. No new safety findings have been identified since the time of the submission.

The degree of experience with belatacept at the time of filing (n=949) is comparable to that of other transplant immunosuppressants (tacrolimus, approximately 500 kidney transplant patients; sirolimus and everolimus approximately 1000 patients each). For each, 12 month data is presented in the product label.

Based upon the totality of data available, the sponsor believes that the safety data presented on 949 belatacept-treated patients followed over 36 months in the Phase III studies and up to 7 years for the patients in the Phase II trials is adequate to support registration.

Delegate comment #3

Whether the limited clinical developmental program, in respect of comparator and combination immunosuppressants, is adequate to support registration, taking account of current clinical practise in Australia.

Response

CsA was used as a comparator in the Phase II and III belatacept studies at the time when the studies were designed because CsA (not tacrolimus) was approved in combination with the background medications used across all the regimens, thereby facilitating comparison between belatacept and CsA. Data on CsA were also available to inform the non-inferiority margin for the primary endpoint on death and graft loss. However, extensive information on use with other immunosuppressant agents (basiliximab, thymoglobulin, tacrolimus, MMF, MPA and sirolimus) has been generated through the Phase II and III studies. The sponsor acknowledged that today, tacrolimus and MMF are used in approximately 80% of the renal transplant recipients[21]. Therefore, as part of the ongoing development of belatacept, and to understand its role in clinical practice, the sponsor conducted an exploratory Phase II study comparing belatacept to tacrolimus in de

[21]ANZDATA Registry Report, 2010,

http://www.anzdata.org.auianzdatalAnzdataReportl33rdReport/Ch08.pdf

novo renal transplant receipients in the context of a steroid avoidance immunosuppressive regimen. In this 3 arm study (IM103034)6, comparing belataceptlMMF, belatacept/SRL and *TACIMMF:*

- AR rates were 15% for belalMMF; 4% for bela/SRL 3% for *TACIMMF* at 12 months
- Both belatacept arms showed a renal function (GFR) benefit of 8-10 ml over Tacrolimus
- Safety was comparable across treatment groups

Although the sample size of this Phase II study precludes definitive conclusions, the findings do appear consistent with those in the Phase III studies: renal function benefits despite higher rates of acute rejection with belatacept + MMF as compared to tacrolimus + MMF.

Delegate comment #4

A boxed warning is proposed for inclusion in PI in relation to PTLD. If registration is supported ACPM are requested to endorse status as a black box warning and to advise of appropriateness of current statements.

Response

Due to the risk of PTLD with belatacept, especially in patients without EBV immunity, and in reponse to a request for information following the first round assessment of this application, consideration was requested by the TGA for the inclusion of a boxed warning.. In response, the sponsor proposed the following boxed warning be added to the Product Information:

> *Warning: Belatacept may be associated with an increased risk for developing post transplant lymphoproliferative disorder (PTLD), predominantly involving the central nervous system (eNS). Recipients without immunity to Epstein Barr virus (EBV) are at a particularly increased risk; therefore, use in EBV seropositive patients only. Do not use NULOJIX in transplant recipients who are EBV seronegative or with unknown serostatus.*

This boxed warning, in conjunction with additional warnings and information provided throughout the PI, adequately addresses the need to highlight the potential risk of PTLD with belatacept, and the Sponsor accepts the inclusion in the PI.

Delegate comment #5

Whether proposed Risk Minimisations Activities in relation to risks of PTLD, serious infections and PML are adequate.

Response

The sponsor has created a robust Risk Minimization Plan comprised of the product label,

enhanced pharmacovigilance, and postmarketing epidemiology studies.

Label

For PTLD, the label includes a contraindication for use in EBV seronegative and serostatus unknown patients, as the former represents the most significant risk factor for development of PTLD both in general, and for belatacept in particular. For serious infections, including PML, the sponsor recommended approval of the belatacept LI regimen, as it was associated with a more favourable safety profile than the MI regimen. Specifically,

- there have been no events of PML reported with the LI regimen, and

- the frequency of serious infections was lower with the LI regimen as compared to both the MI and CsA regimens.

The proposed label also includes information on early diagnosis and management of these conditions, as early intervention may improve outcomes.

Enhanced Pharmacovigilance

For all postmarketing reports of PTLD and PML, standardised questionnaires will be issued to the reporting center. The resulting data will be evaluated by the sponsor on a regular basis as part of our commitment to monitor the evolving safety profile of belatacept with real-world use.

Postmarketing Epidemiology Studies

The sponsor committed to conduct postmarketing epidemiology studies which will evaluate the patterns of use and the evolving safety profile of belatacept in the USA through the United Network of Organ Sharing database and globally through the Collaborative Transplant Study. The data obtained from the epidemiology studies will provide valuable information on the evolving safety profile of belatacept and the effectiveness of the risk minimization plan.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM agreed with the Delegate that there was sufficient evidence of efficacy, safety and quality to support a positive benefit–risk benefit profile for the indication;

> *Nulojix is indicated for prophylaxis of organ rejection in adults receiving a renal transplant. Nulojix is to be used in combination with basilixumab induction, mycophenolate mofetil and corticosteroids.*

The ACPM was concerned that there were limited long term data on use of this product, given the clinical context for long term use. The boxed warning on Post Transplantation Lymphoproliferative Disorder (PTLD) was also supported.

The ACPM supported the amendments proposed by the delegate to the Product Information (PI) and Consumer Medicines Information (CMI).

The ACPM agreed with the Delegate on the proposed specific conditions of registration which include implementation of the risk management plan with specific reference to the proposed direct contact by the sponsor and the prescriber for patient alert cards.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Nulojix (belatacept [rch]) 250 mg powder for IV infusion vial, indicated for:

> *Nulojix (belatacept) is indicated for prophylaxis of organ rejection in adults receiving a renal transplant. Nulojix is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.*

Specific conditions applying to these therapeutic goods

1. The implementation in Australia of the belatacept [rch] Risk Management Plan (RMP Version 2), dated November 2010 and any subsequent revisions, as agreed with the TGA and its Office of Product Review (OPR). Also, prior to supply, the sponsor should provide to the OPR educational program documents, highlighting any differences including relevance to clinical practice, in the implementation and evaluation that may exist for Australia. A date or milestone that these documents will be provided should be submitted.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au
Reference/Publication #

PRODUCT INFORMATION

NULOJIXÒ

(belatacept)

(LYOPHILIZED POWDER FOR IV INFUSION)

Warning: Belatacept may be associated with an increased risk for developing post-transplant lymphoproliferative disorder (PTLD), predominantly involving the central nervous system (CNS). Recipients without immunity to Epstein-Barr virus (EBV) are at a particularly increased risk; therefore, use in EBV seropositive patients only. Do not use NULOJIX in transplant recipients who are EBV seronegative or with unknown serostatus.

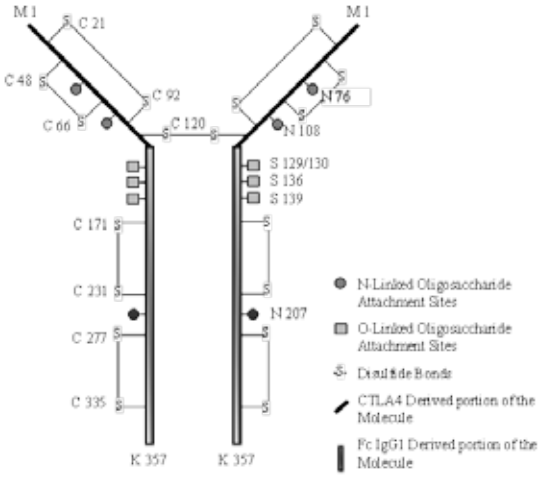
NAME OF THE MEDICINE

NULOJIX^{Ò} (belatacept (rch)).

Belatacept, a costimulation blocker, is a soluble fusion protein consisting of the modified extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) fused to a portion (hinge-CH2-CH3 domains) of the Fc domain of a human immunoglobulin G1 antibody. Belatacept is produced by recombinant DNA technology in a mammalian cell expression system. Two amino acid substitutions (L104 to E; A29 to Y) were made in the ligand binding region of CTLA-4. As a result of these modifications, belatacept binds CD80 and CD86 more avidly than the parent CTLA4-Ig molecule. The molecular weight of belatacept is approximately 90 kilodaltons.

DESCRIPTION

Belatacept structure:



CAS number: 706808-37-9

NULOJIX^{Ò} is supplied as a sterile, white or off-white lyophilized powder for intravenous administration. Prior to use, the lyophile is constituted with sterile water for injection, 0.9% sodium chloride injection, or 5% glucose injection, to obtain a clear, colorless to slightly opalescent pale yellow solution, with a pH range of 7.2 to 7.8. Each single-use vial of NULOJIX^{Ò} provides 250 mg belatacept, 500 mg sucrose, 34.5 mg monobasic sodium phosphate and 5.8 mg sodium chloride.

PHARMACOLOGY

Mechanism of Action

Belatacept, binds to CD80 and CD86 on antigen presenting cells. As a result, belatacept blocks CD28 mediated co-stimulation of T cells inhibiting their activation. Activated T cells are the predominant mediators of immunologic rejection of transplanted organs. Belatacept, a modified form of CTLA4-Ig, binds CD80 and CD86 more avidly than the parent CTLA4-Ig molecule from which it is derived providing a level of immunosuppression that is necessary for preventing allograft rejection. In primate models of renal and islet transplantation, belatacept in combination with other standard antirejection therapies, significantly prolonged graft survival and inhibited the production of anti-donor antibodies.

In vitro, belatacept inhibits T cell proliferation and the production of the cytokines interleukin-2, interferon-g, and interleukin-4. Inhibition of T cell responses to allogeneic antigen is critical for preventing graft rejection following solid organ transplantation.

Pharmacodynamics

In a clinical study, approximately 90% saturation of CD86 receptors on the surface of antigen-presenting cells in the peripheral blood was observed following the initial administration of NULOJIX®. During the first month post-transplantation, 85% saturation of CD86 was maintained. Up to month 3 post-transplantation with the recommended dose, the level of CD86 saturation was maintained at approximately 70%and at month 12 approximately 65%.

In clinical studies, fewer belatacept-treated patients had detectable antibodies to donor-specific human leukocyte antigens (HLA) compared to cyclosporin-treated patients. Production of antibodies to donor specific HLA antigens is associated with antibody-mediated rejection and poor graft outcomes.

Several reports indicate that belatacept maintains the proportion and function of regulatory T cells after transplantation. The mean proportion of regulatory T cells in the peripheral blood was approximately 4 to 6% of CD4+ T cells in all groups studied. Belatacept may also be associated with an increased number of regulatory T cells infiltrating the grafts during an episode of acute rejection.

Pharmacokinetics

Table 1 summarizes the pharmacokinetic parameters of NULOJIX® in healthy adult subjects after a single 10mg/kg intravenous infusion and in renal transplant after multiple 10 and 5 mg/kg intravenous infusions.

Table 1: Pharmacokinetic Parameters (Mean±SD [Range]) in Healthy Subjects and Kidney Transplant Patients After 5 and 10 mg/kg Intravenous Infusions Administered Over 30 Minutes

Pharmacokinetic Parameter	Healthy Subjects (After 10 mg/kg Single Dose) N=15	Kidney Transplant Patients (After 10 mg/kg Multiple Doses) N=10	Kidney Transplant Patients (After 5 mg/kg Multiple Doses) N=14
Peak concentration (C_{max}) [µg/mL]	300±77 (190-492)	247±68 (161-340)	139±28 (80-176)
AUC* [mg·h/mL]	26398±5175 (18964-40684)	22252±7868 (13575-42144)	14090±3860 (7906-20510)
Terminal half-life ($t_{1/2}$) [days]	9.8±2.8 (6.4-15.6)	9.8±3.2 (6.1-15.1)	8.2±2.4 (3.1-11.9)
Systemic clearance (CL) [mL/h/kg]	0.39±0.07 (0.25-0.53)	0.49±0.13 (0.23-0.70)	0.51±0.14 (0.33-0.75)
Volume of distribution (Vss) [L/kg]	0.09±0.02 (0.07-0.15)	0.11±0.03 (0.067-0.17)	0.12±0.03 (0.09-0.17)

* AUC=AUC (INF) after single dose and AUC (TAU) after multiple dose, where TAU=4 weeks

The pharmacokinetics of belatacept in renal transplant patients and healthy subjects were comparable. The pharmacokinetics of belatacept was linear and the exposure to belatacept increased proportionally in healthy subjects after single intravenous infusion dose of 1 to 20 mg/kg. At the recommended dose regimen, serum concentration generally reached steady-state by Week 8 in the initial phase following transplantation and by Month 6 during the maintenance phase. Based on population pharmacokinetic analysis of 944 renal transplant patients up to 1 year post transplant, the pharmacokinetics of belatacept were similar at different time periods post transplant. The trough concentration of belatacept was consistently maintained up to 5 years post transplant. Minimal systemic accumulation of belatacept occurred upon multiple infusions of 5 or 10 mg/kg doses in renal transplant patients every 4 weeks. The accumulation index for belatacept at steady state is 1.1.

Population pharmacokinetic analyses in renal transplant patients revealed that there was a trend toward higher clearance of belatacept with increasing body weight, supporting body weight based dosing of belatacept. Age, gender, race, renal function as measured by calculated glomerular filtration rate (GFR), diabetes, and concomitant dialysis did not affect clearance of belatacept.

Absorption

Belatacept is administered intravenously.

Distribution

The volume of distribution at steady state of belatacept is low at approximately 0.1 L/kg. Which is similar to the vascular space and suggests the distribution of belatacept is limited to the extracellular fluid volume.

Metabolism and elimination

Studies were not carried out to evaluate the metabolism or routes of elimination of belatacept in humans. As a large therapeutic protein, belatacept is not expected to be metabolized by liver cytochrome P450 enzymes or undergo metabolism via the conjugation pathways. Belatacept is expected to be metabolized by proteolytic enzymes via the same catabolic pathways as endogenous or dietary proteins leading to amino acids that can be reutilized for the biosynthesis of structural or functional body proteins. Population pharmacokinetic analysis indicated that renal function as measured by calculated GFR did not affect the clearance of belatacept, suggesting renal elimination was not be a major elimination pathway for belatacept.

Special populations

The pharmacokinetics of belatacept has not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of belatacept. However, population pharmacokinetic analyses showed that no dose adjustments are necessary based on age, gender, race, hepatic function (measured by albumin) or calculated GFR, diabetes, and concomitant dialysis did not affect clearance of belatacept for renal transplant patients.

Age, gender, race, renal function (measured by calculated glomerular filtration rate [GFR]), hepatic function (measured by albumin), diabetes, and concomitant dialysis did not affect clearance of belatacept.

CLINICAL TRIALS

Study 1 and 2: Phase 3 studies in renal transplant recipients

The safety and efficacy of NULOJIX^{Ò} as part of an immunosuppressive regimen following renal transplantation were assessed in two randomized, partially-blinded, multicenter, 3 year studies with the primary endpoint specified at Year 1. These studies compared two dose regimens of belatacept (MI and LI) with cyclosporin in recipients of standard criteria (Study 1) or extended criteria (Study 2) donor organs. All patients received basiliximab, MMF, and corticosteroids. The more intensive (MI) regimen, which included higher and more frequent dosing during the first 6 months post transplant, resulted in 2-fold higher exposure to belatacept than the less intensive (LI) regimen during Months 2 through 7 post transplant. Efficacy was similar between MI and LI while the overall safety profile was better for the LI. Therefore, the recommended dose of NULOJIX^{Ò} is the LI dosage regimen.

Study 1: Recipients of Living Donor and Standard Criteria Deceased Donor Kidneys

Standard criteria donor organs were defined as organs from a living donor, or a deceased donor with anticipated cold ischemia time of < 24 hours and not meeting the definition of extended criteria donor organs.

In this study, 666 patients were enrolled, randomized, and transplanted; 219 to NULOJIX^{Ò} MI, 226 to NULOJIX^{Ò} LI, and 221 to cyclosporin.

Study 2: Recipients of Extended Criteria Donor Kidneys

Extended criteria donors were defined as deceased donors with at least one of the following: (1) donor age ≥ 60 years; (2) donor age ≥ 50 years and other donor co-morbidities (≥ 2 of the following: stroke, hypertension, serum creatinine > 1.5 mg/dl (approximately greater than 130 micromol/L); (3) donation after cardiac death or (4) anticipated cold ischemia time of ≥ 24 hours.

In this study, 543 patients were enrolled, randomized, and transplanted;184 to NULOJIX^{Ò} MI, 175 to NULOJIX^{Ò} LI, and 184 to cyclosporin.

Table 2 summarizes results for belatacept LI compared with cyclosporin for the co-primary efficacy endpoints of death and graft loss, composite renal impairment, and acute rejection (defined as clinically suspected biopsy proven acute rejection). Patient and graft survival were similar between belatacept and cyclosporin. Fewer patients met the composite renal impairment endpoint and mean GFR was higher with belatacept compared to cyclosporin.

Acute rejection (AR) occurred more frequently with belatacept versus cyclosporin in Study 1 and with similar frequency with belatacept versus cyclosporin in Study 2. Approximately 80% of AR episodes occurred by Month 3 and were infrequent after Month 6. In Study 1, 11/39 belatacept and 3/21 cyclosporin acute rejections were Banff 97 grade≥ IIb by Year 3. In Study 2, 9/33 belatacept

and 5/29 cyclosporin acute rejections were Banff 97 grade≥ IIb by Year 3. AR was treated more often with lymphocyte depleting therapy (a risk factor for PTLD; see **PRECAUTIONS)** in the belatacept group than the cyclosporin group. In both studies, in patients with AR by Year 3, donor-specific antibodies, one of the criteria for diagnosis of antibody-mediated rejection, were present in 6-8% and 19-25% in the belatacept and cyclosporin groups, respectively. By Year 3 recurrent AR was similar across groups (< 3%) and subclinical AR identified on the 1 year protocol biopsy was 5% in both groups. In Study 1, 5/39 belatacept patients versus 1/21 cyclosporin patients with AR had experienced graft loss, and 5/39 belatacept patients and no cyclosporin patients with AR had died by Year 3. In Study 2, 5/33 belatacept patients versus 6/29 cyclosporin patients with AR had experienced graft loss, and 5/33 belatacept patients versus 5/29 cyclosporin patients with AR had died by Year 3. In both studies, mean GFR following AR was similar in belatacept and cyclosporin treated patients.

Table 2: Key Efficacy Outcomes at Years 1 and 3

	Study 1: living and standard criteria deceased donors		**Study 2: extended criteria donors**	
Parameter	**Belatacept LI**	**Cyclosporin**	**Belatacept LI**	**Cyclosporin**
	N = 226	**N = 221**	**N = 175**	**N = 184**
Patient and Graft Survival (%)				
Year 1 [95% CI]	96.5 [94.1-98.9]	93.2 [89.9-96.5]	88.6 [83.9-93.3]	85.3 [80.2-90.4]
Year 3 [95% CI]	92.0 [88.5-95.6]	88.7 [84.5-92.9]	82.3 [76.6-87.9]	79.9 [74.1-85.7]
Death (%)				
Year 1	1.8	3.2	2.9	4.3
Year 3	4.4	6.8	8.6	9.2
Graft Loss (%)				
Year 1	2.2	3.6	9.1	10.9
Year 3	4.0	4.5	12.0	12.5
% of Patients meeting Composite renal impairment endpoint at Year 1[a]				
Year 1	54.2	77.9	76.6	84.8
P-value	< 0.0001	-	< 0.07	-
AR (%)				
Year 1 (%) [95% CI]	17.3 [12.3-22.2]	7.2 [3.8-10.7]	17.7 [12.1-23.4]	14.1 [9.1-19.2]
Year 3 (%) [95% CI]	17.3 [12.3-22.2]	9.5 [5.6-13.4]	18.9 [13.1-24.7]	15.8 [10.5-21.0]

	Study 1: living and standard criteria deceased donors		Study 2: extended criteria donors	
Parameter	**Belatacept LI**	**Cyclosporin**	**Belatacept LI**	**Cyclosporin**
Mean Measured GFR[b] *ml/min/1.73 m²*				
Year 1	63.4	50.4	49.6	45.2
Year 2	67.9	50.5	49.7	45.0
Mean Calculated GFR[c] *ml/min/1.73 m²*				
Month 1	61.5	48.1	39.6	31.8
Year 1	65.4	50.1	44.5	36.5
Year 2	65.4	47.9	42.8	34.9
Year 3	65.8	44.4	42.2	31.5

[a]Proportion of Patients with Measured GFR < 60 ml/min/1.73 m^2 or with a Decrease in Measured GFR ≥ 10 ml/min/1.73 m^2 from Month 3 to Month 12.

[b] Measured GFR was assessed by iothalamate at Year 1 and 2 only

[c] Calculated GFR was assessed by MDRD formula at Month 1, Years 1, 2, and 3

Progression of Chronic Kidney Disease (CKD) Staging

In Study 1 by Year 3, mean calculated GFR was 21 ml/min/1.73 m^2 higher with belatacept, and 10% and 20% of patients reached CKD stage 4/5 (GFR < 30 ml/min/1.73 m^2) with belatacept versus cyclosporin, respectively. In Study 2 by Year 3, mean calculated GFR was 11 ml/min/1.73 m^2 higher with belatacept, and 27% and 44% of patients reached CKD stage 4/5 (GFR < 30 ml/min/1.73 m^2) with belatacept versus cyclosporin, respectively.

Chronic Allograft Nephropathy (CAN)

In a pre-specified pooled analysis of prevalence of CAN at Year 1 in Studies 1 and 2, the frequency of CAN was lower with belatacept (34%) than cyclosporin (42%).

New Onset Diabetes Mellitus and other Cardiovascular and Metabolic Endpoints

In a pre-specified pooled analysis of Studies 1 and 2 at Year 1, the incidence of new onset diabetes mellitus (NODM), defined as use of an antidiabetic agent for ≥ 30 days or ≥ 2 fasting plasma glucose values > 126 mg/dl (7.0 mmol/l) post-transplantation, was 5% with belatacept and 10% with cyclosporin. At Year 3, the incidence of NODM was 8% with belatacept and 10% with cyclosporin.

For Studies 1and 2 at Years 1 and 3, belatacept was associated with a 6 to 9 mmHg lower mean systolic blood pressure and 2 to 4 mmHg lower mean diastolic blood pressure, and less use of antihypertensive medication than cyclosporin. Patients in the belatacept groups had decreases in triglycerides and smaller increases in non-HDL cholesterol compared with patients in the cyclosporin group through Year 3.

Phase 2 liver transplant study

A single, randomized, multi-center, controlled phase 2 trial of belatacept in *de novo* orthotopic liver transplant recipients was conducted. A total of 250 subjects were randomized to 1 of 5 treatment groups (3 belatacept and 2 tacrolimus groups). The belatacept dosing used in this liver study was higher in all 3 belatacept arms than the belatacept dosing used in the Phase 2 and 3 renal transplant studies.

An excess in mortality and graft loss was observed in the belatatacept LI + MMF group and an excess in mortality was observed in the belatacept MI + MMF group. No pattern was identified in

the causes of death. There was an increase in viral and fungal infections in the belatacept groups versus the tacrolimus groups, however overall frequency of serious infections was not different among all treatment groups (see **PRECAUTIONS**).

Elderly

217 patients 65 years and older received belatacept across one Phase 2 and two Phase 3 studies.

Elderly patients demonstrated consistency with the overall study population for safety and efficacy as assessed by patient and graft survival, renal function, and acute rejection.

Phase 2 study in renal transplant recipients

The Phase 2 trial evaluated the efficacy and safety of NULOJIX versus cyclosporin in 218 *de novo* renal transplant recipients, 145 who received belatacept (74 received the MI regimen and 71 received the LI regimen) and 73 who received cyclosporin. Additional immunosuppressive medications were MPA, corticosteroids, and basiliximab as an induction agent.

The primary endpoint,clinically suspected and biopsy-proven acute rejection at 6 months, occurred with similar frequency in all treatment groups. The distribution of acute rejection episodes by severity (as assessed by histological grade) was similar across the 3 treatment groups. Identical results were observed at Year 1. The frequency of death or graft loss was similar, for both belatacept dose regimens and cyclosporin. Assessments of renal function and (CAN) favored both the belatacept MI and LI regimens compared with cyclosporin. Efficacy parameters through 6 years have been maintained during treatment with belatacept maintenance regimen.

INDICATIONS

Adult Renal Transplant Recipients

NULOJIX® (belatacept) is indicated for prophylaxis of organ rejection in adults receiving a renal transplant. NULOJIX®is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.

CONTRAINDICATIONS

NULOJIX® should not be administered to recipients who are Epstein-Barr virus (EBV) seronegative or serostatus unknown.

NULOJIX® should not be administered to recipients who are hypersensitive to the active substance or to any of the excipients.

PRECAUTIONS

Post –Transplant Lymphoproliferative Disorder (PTLD)

In the Phase 2 and 3 studies (3 studies), the incidence of PTLD was higher in NULOJIX®-treated patients than in cyclosporin-treated patients (see **ADVERSE EFFECTS**). In these clinical studies, the frequency of PTLD was higher in the NULOJIX MI treatment regimen than in the NULOJIX LI recommended regimen (see **ADVERSE EFFECTS**). Therefore, administration of higher than recommended doses or more frequent dosing of NULOJIX is not recommended. NULOJIX®-treated transplant recipients who are EBV seronegative are at an increased risk for PTLD compared with those who are EBV seropositive (see see **ADVERSE EFFECTS**). EBV serology should be ascertained before starting administration of NULOJIX®. Transplant recipients who are EBV seronegative or serostatus unknown should not receive NULOJIX® (see **CONTRAINDICATIONS**).

In addition to EBV seronegative status, other known risk factors for PTLD include cytomegalovirus (CMV) infection and T-cell-depleting therapy, which was more commonly used to treat acute rejection in belatacept-treated patients in Phase 3 clinical studies (see **CLINICAL TRIALS**).

PTLD in NULOJIX^{Ò}-treated patients most often presented in the central nervous system (CNS). Physicians should consider PTLD in the differential diagnosis in patients with new or worsening neurologic, cognitive or behavioural signs or symptoms.

Infections

Use of immunosuppressants can increase susceptibility to infection, including fatal infections, opportunistic infections, tuberculosis, and herpes (see Progressive multifocal leukoencephalopathy (PML) warning and **ADVERSE EFFECTS**).

Cytomegalovirus prophylaxis is recommended for 3 months after transplantation, particularly for patients at increased risk for CMV infection. Pneumocystis pneumonia prophylaxis is recommended for 6 months following transplantation.

Tuberculosis was more frequently Cases of tuberculosis have been observed in patients receiving NULOJIX^{Ò} than cyclosporin in clinical studies. The majority of cases of tuberculosis occurred in patients who currently live or previously lived in countries with a high prevalence of tuberculosis. Patients should be evaluated for tuberculosis and tested for latent infection prior to initiating NULOJIX.^{Ò} Adequate treatment of latent tuberculosis infection should be instituted prior to NULOJIX^{Ò} use.

Progressive multifocal leukoencephalopathy (PML)

PML is a rare, often rapidly progressive and fatal, opportunistic infection of the CNS that is caused by the JC virus. In clinical studies with NULOJIX^{Ò}, 2 cases of PML were reported in patients receiving NULOJIX^{Ò} at doses higher than the recommended regimen. In the renal transplant studies of NULOJIX^{Ò}, one case of PML was reported in a patient who received an IL-2 receptor antagonist, mycophenolate mofetil (MMF) and corticosteroids as concomitant treatment. In the liver transplant study, the patient received MMF and corticosteroids as concomitant treatment. (see **ADVERSE EFFECTS**). As an increased risk of PML and of other infections has been associated with high levels of overall immunosuppression, the recommended doses of NULOJIX^{Ò} and concomitant immunosuppressives, including MMF or MPA, should not be exceeded.

Early diagnosis and treatment may mitigate the impact of PML. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurologic, cognitive or behavioural signs or symptoms. PML is usually diagnosed by brain imaging, including magnetic resonance imaging (MRI) or computed tomography (CT) scan, and cerebrospinal fluid (CSF) testing for JC viral DNA by polymerase chain reaction (PCR). When the clinical suspicion for PML is high, brain biopsy should be considered in subjects if the diagnosis of PML cannot be established via CSF PCR and neuroimaging. Consultation with a specialist (e.g., neurologist and/or infectious disease) is recommended for any suspected or confirmed cases of PML.

If PML is diagnosed, reduction or withdrawal of immunosuppression is recommended taking into account the risk to the graft. Plasmapheresis may accelerate the removal of belatacept from the body.

Malignancies

In addition to PTLD, patients on immunosuppressive therapy are at increased risk of malignancies, including the skin (see **PRECAUTIONS**). Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Liver, Lung or other Transplantation

The safety and efficacy of belatacept as immunosuppressive therapy has not yet been established in other solid organ transplant patients and, therefore, such use is not recommended. In a single Phase 2 clinical study in *de novo* liver transplant patients, an increase in the number of deaths was observed in 2 of 3 belatacept-containing regimens studied. These belatacept dosing regimens differed from those studied in renal transplant recipients (see CLINICAL TRIALS). Use in liver transplant patients is not recommended due to an increased risk of graft loss and death.

Concomitant use with other immunosuppressive agents

As the total burden of immunosuppression is a risk factor for malignancies and opportunistic infections, higher than the recommended doses of concomitant immunosuppressive agents should be avoided. Lymphocyte depleting therapies to treat acute rejection should be used cautiously.

Belatacept has been administered with the following immunosuppressive agents in clinical studies: basiliximab, MPA and corticosteroids.

For patients who may be switched from belatacept to another immunosuppressant, physicians should be aware of the 8-10 day half-life of belatacept to avoid potential under- or over-immunosuppression following discontinuation of belatacept.

Allergic reactions

Infusion-related reactions have been reported with belatacept administration in the clinical studies. Patients were not required to be pre-treated to prevent allergic reactions (see **ADVERSE EFFECTS**). Special caution should be exercised in patients with a history of allergic reactions to belatacept or to any of the excipients. In clinical studies, there were no reports of anaphylaxis. If any serious allergic or anaphylactic reaction occurs, NULOJIX® therapy should be discontinued immediately and appropriate therapy initiated.

Immunisations

Immunosuppressant therapy may affect response to immunizations. Therefore during treatment with NULOJIX®, immunizations may be less effective. The use of live vaccines should be avoided.

Patients on controlled sodium diet

This medicinal product contains 1.95 mmol (or 45 mg) sodium per maximum dose of 3 vials (0.65 mmol or 15 mg sodium per vial). This should be taken into consideration when treating patients on a controlled sodium diet.

Autoimmune process

There is a theoretical concern that treatment with NULOJIX® might increase the risk of autoimmune processes (see **ADVERSE EFFECTS**).

Immunogenicity

Although there were few patients that developed antibodies and there was no apparent correlation of antibody development to clinical response or adverse events, the data are too limited to make a definitive assessment.

The potential impact of pre-existing antibodies to belatacept should be taken into account if retreatment with belatacept is considered following prolonged discontinuation, particularly in patients who have not received continuous immunosuppression. The safety and efficacy of retreatment with belatacept has not been studied.

Drug Interactions

Formal drug interaction studies have not been conducted with NULOJIX®

Belatacept is a fusion protein that is not expected to be metabolized by the cytochrome P450 enzymes (CYPs) and UDP-glucuronosyltransferases (UGTs), and is not expected to have an effect on the CYPs and UGTs in terms of inhibition or induction.

Mycophenolate Mofetil

Belatacept is a fusion protein that is not expected to be metabolized by the cytochrome P450 enzymes (CYPs) and UDP-glucuronosyltransferases (UGTs), and is not expected to have an effect on the CYPs and UGTs in terms of inhibition or induction.

NULOJIX® is not expected to interrupt the enterohepatic recirculation of MPA. At a given dose of MMF, MPA exposure is approximately 40% higher with NULOJIX® coadministration than with cyclosporin coadministration.

Carcinogenicity

A carcinogenicity study was not conducted with belatacept. However, a carcinogenicity study in mice was conducted with abatacept (a more active analogue in rodents) to determine the carcinogenic potential of CD28 blockade. Weekly subcutaneous injections of 20, 65, or 200 mg/kg of abatacept administered for up to 84 weeks in males and 88 weeks in females were associated with increases in the incidence of malignant lymphomas (all doses) and mammary gland tumors (intermediate- and high-dose in females) at clinically-relevant exposures. The mice from this study were infected with murine leukemia virus and mouse mammary tumour virus. These viruses are associated with an increased incidence of lymphomas and mammary gland tumours, respectively, in immunosuppressed mice. These findings indicate a risk of virally-induced malignancies during the clinical use of NULOJIX®.

Genotoxicity

Genotoxicity testing is not required for protein therapeutics, therefore, no genotoxicity studies were conducted with belatacept. However, the analogue abatacept was not genotoxic in the *in vitro* bacterial reverse mutation (Ames) or Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward point mutation assays with or without metabolic activation, and no chromosomal aberrations were observed in human lymphocytes treated with abatacept with or without metabolic activation.

Effects of fertility

Belatacept had no adverse effects on male or female fertility in rats at intravenous doses up to 200 mg/kg daily (25 times the exposure at the MRHD).

Use in pregnancy (Category C)

There are no studies of NULOJIX® treatment in pregnant women. NULOJIX® should be used in pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Belatacept was shown to cross the placenta of rats and rabbits.

Belatacept was not teratogenic when administered to pregnant rats and rabbits at intravenous doses up to 200 mg/kg and 100 mg/kg daily, respectively, representing approximately 16 and 19 times the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg administered over the first month of treatment based on area under the concentration time curve (AUC). Belatacept administered to female rats daily during gestation and throughout the lactation period was associated with infections in some dams at doses of 20 mg/kg or greater (at least 3 times

the exposure based on AUC at theMRHD) and produced no direct adverse effects in offspring at doses up to 200 mg/kg representing 19 times the exposure at the MRHD.

Abatacept, a fusion protein that differs from belatacept by 2 amino acids in the CD80/86 binding domains, is more active than belatacept in rodents. Therefore, nonclinical studies conducted with abatacept are also relevant for assessing the safety of belatacept. Abatacept, administered to female rats every 3 days during early gestation and throughout the lactation period, produced no adverse effects in offspring at doses up to 45 mg/kg (3 times the exposure at the MRHD of belatacept). However, at 200 mg/kg (11 times the exposure at the MRHD), a 9-fold increase in T-cell-dependent antibody response in female pups, and thyroid inflammation in a single female pup, were observed.

Use in lactation

It is not known whether belatacept is excreted in human milk or absorbed systemically after ingestion by a nursing infant. However, belatacept was excreted in rat milk and was detected in the serum of suckling pups.. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from NULOJIX^{Ò} 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. The long half-life of belatacept should be considered when discontinuing therapy.

Pediatric Use

The safety and efficacy of NULOJIX^{Ò} in patients under 18 years of age have not been established.

Elderly use

A total of 217 patients 65 years of age and older, including 25 patients 75 years and older received NULOJIX^{Ò} in clinical studies. Similar efficacy was observed in elderly patients versus younger patients. The frequencies of adverse reactions and serious adverse reactions were similar in elderly versus younger patients.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Belatacept may cause fatigue, malaise and/or nausea. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

ADVERSE EFFECTS

The adverse reaction profile associated with immunosuppressive agents is often difficult to establish due to the clinical events associated with the underlying disease and the concurrent use of multiple medicinal products.

The safety of NULOJIX^{Ò} in renal transplantation was assessed in 3 multicenter, controlled trials, one Phase 2 and two Phase 3 trials (see **CLINICAL TRIALS**) studying two different dose regimens of belatacept (more intensive [MI] and less intensive [LI]) versus. cyclosporin, each in combination with basiliximab, MMF, and corticosteroids. NULOJIX^{Ò} should be dosed according to the LI regimen (see **DOSAGE AND ADMINISTRATION**). The MI regimen, which included higher and more frequent dosing than the LI regimen during the first six months post-transplantation, resulted in 2-fold higher exposure to belatacept than the LI regimen during Months 2 through 7 post-transplantation. The LI regimen showed lower frequencies of deaths, serious adverse reactions and serious infections versus cyclosporin. The LI regimen was also associated with lower frequencies of serious infections, malignant neoplasms, CNS PTLD, polyoma virus, CNS and fungal infections compared with the MI regimen. Most other adverse reactions were similar between the MI and LI regimens.

The safety population included 949 belatacept patients (477 for the MI regimen and 472 for the LI regimen) and 476 cyclosporin patients. Median treatment was > 3 years across the 3 studies. For the Phase 2 study, 75/145 belatacept patients and 13/71 cyclosporin patients were still on treatment at 7 years. The majority of patients in all treatment groups received prophylactic antiviral and antibacterial therapy.

The most common serious adverse reactions (≥ 2%) reported with belatacept in either regimen at Year 3 were urinary tract infection, CMV infection, pyrexia, increased blood creatinine, pyelonephritis, diarrhoea, gastroenteritis, graft dysfunction, leukopenia, pneumonia, basal cell carcinoma, anaemia, dehydration.

The most commonly reported adverse reactions (≥ 20%) among patients treated with a belatacept-based regimen at Year 3 are diarrhoea, anaemia, urinary tract infection, peripheral oedema, constipation, hypertension, pyrexia, nausea, graft dysfunction, cough, vomiting, leukopenia, hypophosphataemia and headache.

Adverse reactions resulting in interruption or discontinuation of belatacept in≥ 1% of patients at Year 3 were renal vein thrombosis and CMV infection.

Adverse events, regardless of causality, reported in ≥5 % of patients in any treatment group up to 36 months. These advents are presented by system organ class and frequency.

Table 3 Adverse Events reported in ≥5% of Patients in the NULOJIX clinical trials

System Organ Class **Preferred Term**	**NULOJIX®** **Percentage (%) of patients** **N=472**	**Cyclosporin** **Percentage (%) of patients** **N=476**
Total Subjects With an Event	99.6	99.2
Infections and Infestations	82.0	80.7
Urinary tract infection	36.4	35.7
Upper respiratory tract infection	15.5	15.8
Nasopharyngitis	14.6	17.2
Cytomegalovirus infection	12.1	12.8
Bronchitis	11.0	6.7
Influenza	10.2	7.4
Sinusitis	7.0	7.1
Oral Herpes	7.0	3.6
Gastroenteritis	6.6	6.5
Pharyngitis	5.9	2.9
Pneumonia	4.7	6.1
Oral candidiasis	4.2	6.3
Gastrointestinal Disorders	77.5	76.7
Diarrhoea	37.9	34.5
Constipation	32.8	33.8
Nausea	24.6	27.1
Vomiting	22.2	20.0
Abdominal pain	17.4	15.5
Abdominal pain upper	8.3	10.1
Dyspepsia	8.1	8.2
Flatulence	5.3	5.7

System Organ Class Preferred Term	NULOJIX® Percentage (%) of patients N=472	Cyclosporin Percentage (%) of patients N=476
Abdominal distension	4.9	5.7
Gingival hyperplasia	0.0	5.0
Metabolism and Nutrition Disorders	75.2	77.1
Hypophosphataemia	21.4	14.1
Hypokalaemia	19.1	13.9
Hyperkalaemia	18.2	18.1
Dyslipidaemia	16.3	20.8
Hyperglycaemia	14.4	15.8
Hypocalcaemia	11.4	9.7
Hypercholesterolaemia	10.4	11.3
Hyperlipidaemia	7.6	7.6
Hypomagnesaemia	7.0	10.3
Hypercalcaemia	6.6	7.6
Diabetes mellitus	6.4	8.4
Decreased appetite	5.7	4.8
Metabolic acidosis	5.5	6.1
Hypoglycaemia	4.9	6.3
Acidosis	4.7	6.3
Hyperuricaemia	4.0	10.9
Hypertriglyceridaemia	2.5	5.5
Injury, Poisoning and Procedural Complications	66.5	72.7
Graft dysfunction	23.7	30.7
Procedural pain	19.9	18.7
Incision site pain	14.2	17.4
Complications of transplanted kidney	7.4	7.8
Chronic allograft nephropathy	3.4	8.4
Therapeutic agent toxicity	0.0	8.2
General Disorders and Administration Site Conditions	65.5	66.6
Oedema peripheral	33.9	40.3
Pyrexia	28.8	25.2
Fatigue	9.5	10.3
Oedema	8.7	10.5
Asthenia	6.4	7.8
Chest pain	6.1	9.5
Pain	5.3	7.6
Blood and Lymphatic System Disorders	59.1	60.3
Anaemia	40.5	41.8
Leukopenia	19.7	23.5
Neutropenia	5.7	5.3
Polycythaemia	5.1	3.8

System Organ Class Preferred Term	NULOJIX® Percentage (%) of patients N=472	Cyclosporin Percentage (%) of patients N=476
Leukocytosis	5.1	2.3
Thrombocytopenia	3.4	6.3
Renal and Urinary Disorders	57.8	60.5
Proteinuria	15.5	10.5
Hematuria	15.3	16.2
Dysuria	10.2	9.5
Renal tubular necrosis	8.3	12.2
Renal impairment	5.3	8.0
Vascular Disorders	52.3	55.5
Hypertension	30.5	36.6
Hypotension	15.9	11.6
Haemotoma	5.3	6.1
Lymphocele	4.2	8.6
Respiratory, Thoracic, and Mediastinal Disorders	49.6	43.1
Cough	23.3	17.6
Dyspnoea	11.7	14.5
Oropharyngeal pain	6.4	5.5
Investigations	48.5	47.7
Blood creatinine increased	14.6	20.6
Weight increased	7.0	6.3
Weight decreased	5.1	2.7
Musculoskeletal and Connective Tissue Disorders	44.3	42.6
Arthralgia	16.1	12.4
Back pain	12.1	13.0
Pain in extremity	11.9	12.8
Myalgia	5.5	4.8
Muscle spasms	4.4	6.9
Nervous System Disorders	41.5	43.5
Headache	20.1	16.8
Tremor	8.9	17.6
Dizziness	8.3	9.2
Paraesthesia	3.8	6.3
Skin and Subcutaneous Tissue Disorders	37.7	39.7
Acne	7.4	9.9
Alopecia	5.5	2.1
Rash	4.4	5.7
Hirsutism	1.1	5.0

System Organ Class Preferred Term	NULOJIX® Percentage (%) of patients N=472	Cyclosporin Percentage (%) of patients N=476
Psychiatric Disorders	29.7	31.3
Insomnia	16.9	18.7
Anxiety	10.0	10.1
Depression	5.7	6.5
Cardiac Disorders	27.5	31.1
Tachycardia	7.4	7.6
Immune System Disorders	11.2	6.9
Transplant rejection	5.7	2.7

Selected adverse events occuring in <5% with a >1% difference between the NULOJIX-treated and CsA- treated patients through 3 years are listed below:

- Infections and Infestations (See Table 5): acute pyelonephritis, sepsis, tinea versicolor, bacteremia
- Gastrointestinal Disorders: stomatitis, including aphthous stomatitis, esophagitis, umbilical hernia, abdominal hernia, paralytic ileus, gingival hypertrophy and dental caries
- Metabolism and Nutrition Disorders: vitamin D deficiency, increased appetite
- Injury, Poisoning and Procedural Complications: fall, joint sprain, excoriation, contusion, post procedural discharge, ankle fracture, arteriovenous fistula thrombosis
- Blood and Lymphatic System Disorders: pancytopenia
- Renal and Urinary Disorders: acute renal failure, urinary retention, ureteric stenosis, nocturia, pyuria, toxic nephropathy, renal tubular disorder, hydronephrosis
- Vascular Disorders: orthostatic hypotension, deep vein thrombosis, hypertensive crisis
- Investigations: urine output decreased, AST increased
- Respiratory, Thoracic and Mediastinal Disorders: sleep apnea syndrome, pulmonary embolism
- Musculoskeletal and Connective Tissue Disorders: musculoskeletal pain, osteoporosis, flank pain, muscular weakness
- Nervous System Disorders: hypoaesthesia, burning sensation, Guillian-Barre syndrome (1 case seen only with the MI regimen)
- Skin and Subcutaneous Tissue Disorders: hyperhidrosis, ecchymosis, night sweats, actinic keratosis, skin lesion
- Psychiatric Disorders: restlessness
- Cardiac Disorders: atrial fibrillation, bradycardia, left ventricular hypertrophy, angina pectoris, cardiac arrest
- Reproductive System and Breast Disorders: erectile dysfunction, prostatitis
- Eye Disorders: cataract, ocular hyperaemia
- Ear and Labyrinth Disorders: vertigo, ear pain
- Neoplasms Benign, Malignant and Unspecified (See Table 4): skin papilloma, basal cell carcinoma, squamous cell carcinoma of skin
- Hepatobiliary Disorders: cholelithiasis, hepatic cyst
- Immune System Disorders: seasonal allergy
- Endocrine Disorders: cushingoid, hyperparathyroidism, hypothyroidism

Malignancies and post-transplant lymphoproliferative disease

Year 1 and 3 frequencies of malignancies are shown in Table 4, except for cases of PTLD which are presented at 1 year and > 3 years (median days of follow-up were 1199 days for belatacept MI,

1206 days for belatacept LI, and 1139 days for cyclosporin). The Year 3 frequency of malignant neoplasms, excluding non-melanoma skin cancers, was similar in the belatacept LI and cyclosporin groups and higher in the belatacept MI group. PTLD occurred at a higher rate in both belatacept treatment groups versus cyclosporin (see **PRECAUTIONS**). Non-melanoma skin cancers occurred less frequently with the belatacept LI regimen than with the cyclosporin or belatacept MI regimens.

In the 3 studies, the cumulative frequency of PTLD was higher in belatacept treated patients at the recommended dosing regimen (LI) (1.3%; 6/472) than in the cyclosporin group (0.6%; 3/476), and was highest in the belatacept MI group (1.7%; 8/477). Nine of 14 cases of PTLD in belatacept-treated patients were located in the CNS; within the observation period, 8 of 14 cases were fatal (6 of the fatal cases involved the CNS). Of the 6 PTLD cases in the LI regimen, 3 involved the CNS and were fatal.

EBV seronegative patients receiving immunosuppressants are at a particularly increased risk for PTLD. In clinical studies, belatacept-treated transplant recipients with EBV seronegative status were at an increased risk for PTLD compared with those who were EBV seropositive (7.7%; 7/91 vs. 0.7%; 6/810, respectively). At the recommended dosing regimen of NULOJIX® there were 404 EBV seropositive recipients and 4 cases of PTLD occurred (1.0%); two of these presented in the CNS.

Table 4: Malignancies Occurring by Treatment Group (%)

	Up to Year 1		Up to Year 3*	
	Belatacept LI N= 472	**Cyclosporin N= 476**	**Belatacept LI N= 472**	**Cyclosporin N= 476**
Any malignant neoplasm	1.9	3.4	5.7	7.1
Non-melanoma skin cancer	0.2	1.5	1.5	3.6
Malignant neoplasms excluding non-melanoma skin cancers	1.7	1.9	4.2	3.6
PTLD**	0.8	0.2	1.3	0.6
Malignancies excluding non-melanoma skin cancer and PTLD	0.8	1.7	3.2	3.4

*Median follow-up excluding PTLD for pooled studies is 1092 days for each treatment group.

**Median follow-up: for PTLD for pooled studies is, 1206 days for LI, and 1139 days for cyclosporin

Infections

Year 1 and Year 3 frequencies of infections occurring by treatment group are shown in Table 5. The overall occurrence of tuberculosis infections and non-serious herpes infections were higher for belatacept regimens than for the cyclosporin regimen. The majority of cases of tuberculosis occurred in patients who currently live or previously lived in countries with a high prevalence of tuberculosis (see **PRECAUTIONS**). Overall occurrences of polyoma virus infections and fungal

infections were numerically lower in the belatacept LI group compared with the belatacept MI and cyclosporin groups.

Within the belatacept clinical program, there were 2 patients diagnosed with PML. One fatal case of PML was reported in a renal transplant recipient treated with belatacept MI regimen, an IL-2 receptor antagonist, MMF, and corticosteroids for 2 years in a Phase 3 trial. The other case of PML was reported in a liver transplant recipient in a Phase 2 trial who received 6 months of treatment with an augmented belatacept MI regimen, MMF at doses higher than the recommended dose and corticosteroids (see **PRECAUTIONS**).

Infections involving the CNS were more frequent in the belatacept MI group (8 cases, including the PML case discussed above; 1.7%) than the belatacept LI (2 cases, 0.4%) and cyclosporin groups (one case; 0.2% group). The most common CNS infection was cryptococcal meningitis.

Table 5: Infections Occurring by Treatment Group (%)

	Up to Year 1		Up to Year 3*	
	Belatacept LI N= 472	**Cyclosporin N= 476**	**Belatacept LI N= 472**	**Cyclosporin N= 476**
Infections and infestations	71.8	73.7	82.0	80.6
Serious infections	23.3	27.3	33.5	37.8
Viral infections	25.0	27.7	39.0	36.1
CMV	11.9	13.7	13.8	14.7
Polyomavirus	2.3	4.8	3.8	5.7
Herpes	6.6	6.1	14.2	10.7
Fungal infections	11.0	15.1	16.7	20.6
Tuberculosis	0.4	0.2	1.3	0.2

*Median exposure for pooled studies: 864 is 1092 days for each treatment group

Graft thrombosis

In a phase 3 study in recipients of extended criteria donor (ECD) kidneys (Study 2), graft thrombosis occurred more frequently in the belatacept groups (4.3% and 5.1% for the MI and LI regimens respectively), versus 2.2% for cyclosporin. In another phase 3 study in recipients of living donor and standard criteria deceased donor kidneys (Study 1), the incidence of graft thrombosis was 2.3% and 0.4% for the MI and LI regimens respectively, versus 1.8% for cyclosporin. In a phase 2 study, there were 2 cases of graft thrombosis, 1 each in MI and LI (incidence of 1.4% for both) versus 0 in the cyclosporin group. In general, these events occurred early and the majority resulted in graft loss

Infusion-related reactions

Up to Year 3, there were no reports of anaphylaxis or drug hypersensitivity.

Acute infusion-related reactions (reactions occurring within one hour of infusion) occurred in 5.5% of patients in the belatacept MI group and 4.4% of patients in the belatacept LI group up to Year 3. The most frequently reported acute infusion-related reactions in combined belatacept regimens were hypotension, hypertension, flushing and headache. Most events were not serious, were mild to moderate in intensity, and did not recur. When belatacept was compared to placebo infusions, there were no differences in event rates (placebo infusions were administered at Weeks 6 and 10 of the belatacept LI regimen to blind the MI and LI regimens).

Immunogenicity

Antibodies directed against the belatacept molecule were assessed in 796 kidney transplant recipients (551 of these treated for at least 3 years) in the two Phase 3 studies. An additional 51 patients were treated for an average of 7 years in the long-term extension of a Phase 2 study. Anti-belatacept antibody development was not associated with altered clearance of belatacept.

A total of 45 of 847 patients (5.3%) developed antibodies during treatment with belatacept. In the individual studies, the percentage of patients with antibodies during treatment ranged from 4.5% and 5.2% in the Phase 3 studies to 11.8% in the long-term extension of the Phase 2 study. However, immunogenicity rate normalized for duration of exposure was consistent at 2.0 to 2.1 per 100 patient years among the three studies. In 153 patients assessed for antibodies at least 56 days (approximately 7 half-lives) after discontinuation of belatacept, an additional 10 (6.5%) developed antibodies. In general, antibody titers were low, not usually persistent, and often became undetectable with continued treatment.

To assess for the presence of neutralizing antibodies, samples from 29 patients with confirmed binding activity to the modified cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) region of the molecule were assessed by an *in vitro* assay for the presence of neutralizing antibodies; 8 (27.6%) patients were shown to possess neutralizing antibodies. The clinical relevance of such antibodies is unclear.

Autoimmunity

The occurrence of autoimmune events across the core clinical studies was infrequent, occurring at rates of 1.7%, 1.7%, and 1.9% by Year 3 for the MI, LI, and cyclosporin groups respectively .One patient on belatacept MI regimen developed Guillian-Barre syndrome which led to treatment discontinuation and subsequently resolved. Overall, the few reports across clinical studies suggest that prolonged exposure to belatacept does not predispose patients to an increased risk of development of autoimmune events.

DOSAGE AND ADMINISTRATION

Renal Transplant Recipients

Treatment should be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and of renal transplant patients

For adult renal transplant recipients, NULOJIX^{Ò} should be prepared based on actual body weight and administered as a 30-minute intravenous infusion with the dosing recommendations in Table 6

Higher than the recommended dosing regimen of NULOJIX^{Ò} should not be administered.

Dose modification of NULOJIX^{Ò} is not recommended for a change in body weight of less than 10% or during episodes of acute rejection.

Table 6: Dose of NULOJIX^{Ò} for Renal Transplant Recipients

Dose for Initial Phase	**Dose**
Day of transplantation, prior to implantation (Day 1)	10 mg/kg
Day 5, Day 14, and Day 28 (4 weeks after transplantation)	10 mg/kg
End of Week 8 and 12 after transplantation	10 mg/kg
Dose for Maintenance Phase	**Dose**
Every 4 weeks (± 3 days), starting at the end of Week 16 after transplantation	5 mg/kg

Patients do not require pre-medication prior to administration of NULOJIX®

Infusion-related reactions have been reported with belatacept administration in clinical studies. There were no reports of anaphylaxis on NULOJIX. If any serious allergic or anaphylactic reaction occurs, NULOJIX therapy should be discontinued immediately and appropriate therapy initiated (see **PRECAUTIONS**)

Therapeutic monitoring of belatacept is not required.

Renal impairment, hepatic impairment

No dose adjustment is recommended in patients with renal impairment or undergoing dialysis. No dose adjustment is recommended in patients with hepatic impairment.

Paediatric and adolescent

The safety and efficacy of NULOJIX® in patients under the age of 18 have not been established.

Elderly

No dose adjustment is required.

Concomitant therapy

NULOJIX® has been used in combination with an IL-2 antagonist, a mycophenolic acid, and corticosteroids. NULOJIX® has also been used in combination with antithymocyte globulin for treatment of acute rejection.

PREPARATION AND ADMINISTRATION INSTRUCTIONS

Use aseptic technique

NULOJIX® is provided as a lyophilized powder in preservative-free, single-use vials. Each NULOJIX® vial provides 250 mg of belatacept for intravenous administration. The NULOJIX® powder in each vial must be reconstituted with 10.5 mL of a suitable reconstitution fluid, using **ONLY THE SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL** and an 18- to 21-gauge needle. Suitable fluids for reconstitution include sterile water for injection, BP (SWFI), 0.9% sodium chloride injection, BP (NS), or 5% glucose injection, BP (G5W). The concentration of belatacept in the vial will be 25 mg/mL. If the NULOJIX® powder is accidentally reconstituted using a siliconized syringe, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes.

During reconstitution, to minimize foam formation in solutions of NULOJIX®, the vial should be rotated and inverted with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. DO NOT SHAKE. The solution should be clear to slightly opalescent and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present. It is recommended to transfer the reconstituted solution from the vial to the intravenous container immediately.

- Calculate the dose and number of NULOJIX® vials required. Each NULOJIX® vial provides 250 mg of belatacept.

Weight (kg) × *dose (mg/kg)* (5 or 10 mg/kg, see Table 6) = *total dosage (mg)*

Syringes are marked in units of 0.5 mL; therefore, the calculated dose should be rounded to the nearest 0.5 mL. Dose modification of NULOJIX® is not recommended for a change in body weight of less than 10%.

- To reconstitute the NULOJIX® powder, remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of reconstitution fluid (10.5 mL of SWFI, NS, or G5W) to the glass wall of the vial. Do not use the vial if the vacuum is not present. Rotate the vial and invert with gentle swirling until the contents are completely dissolved.
- Prior to intravenous administration, the reconstituted NULOJIX® solution must be further diluted with a suitable infusion fluid (NS or G5W) to final belatacept concentrations ranging from 2 to 10 mg/mL. NULOJIX® reconstituted with:
  - SWFI should be further diluted with either NS or G5W.
  - NS should be further diluted with NS.
  - G5W should be further diluted with G5W.

From the appropriate size infusion container; typically a 100 mL bag is used, (typically an infusion volume of 100 ml will be appropriate for most patients and doses, but total infusion volume ranging from 50 ml to 250 ml may be used) withdraw a volume of infusion fluid that is equal to the volume of the reconstituted NULOJIX® solution required to provide the dose. With the same silicone-free syringe used for reconstitution, withdraw the required amount of belatacept solution from the vial, inject it into the infusion container and gently rotate the infusion container to ensure mixing. Any unused portions in the vials must be discarded immediately.

- Prior to administration, the NULOJIX® infusion should be inspected visually for particulate matter and discoloration. Discard the infusion if any particulate matter or discoloration is observed.
- The entire NULOJIX® infusion should be administered over a period of 30 minutes and must be administered with an infusion set and a **STERILE**, **NON-PYROGENIC**, **LOW-PROTEIN-BINDING FILTER** (with a pore size of 0.2-1.2 μm).
- The NULOJIX® infusion must be completed within 24 hours of reconstitution of the NULOJIX® lyophilized powder. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°-8°C) for up to 24 hours (a maximum of 4 hours of the total 24 hours can be at room temperature [20°-25°C] and room light).
- NULOJIX® should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of NULOJIX® with other agents.
- Each vial of NULOJIX® is for single use in one patient only. Use in one patient only. Discard any residue.

If the **SILICONE-FREE DISPOSABLE SYRINGE** is dropped or becomes contaminated, use a new **SILICONE-FREE DISPOSABLE SYRINGE**. For information on obtaining additional **SILICONE-FREE DISPOSABLE SYRINGES**, contact Bristol-Myers Squibb Australia 1800-067567.

OVERDOSE

Single doses up to 20 mg/kg of NULOJIX® have been administered without apparent toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

In the event of an overdose or poisoning contact the Poisons Information Centre on 131126.

PRESENTATION

NULOJIX^{Ò} is a lyophilized powder for intravenous infusion; it is supplied as single-use vials with silicone-free disposable syringes. All components of the syringe are latex-free. The product is available in the strength of 250 mg of belatacept.

Pack sizes: 1 vial and 1 silicone-free syringe or 2 vials and 2 silicone-free syringes.

STORAGE CONDITIONS

NULOJIX^{Ò} lyophilized powder must be refrigerated at 2°C to 8°C. For storage of the diluted NULOJIX^{Ò} solution, see PREPARATION AND ADMINISTRATION.

Protect the vials from light by storing in the original package until time of use.

Do not use beyond the expiration date.

POISONS SCHEDULE: S4

DISTRIBUTED BY

Bristol-Myers Squibb Australia Pty Ltd

556 Princes Highway

NOBLE PARK VIC 3174

AUSTRALIAN REGISTRATION NUMBERS

NULOJIX^{Ò} is a lyophilized powder for intravenous infusion: AUST R **179687**

DATE OF TGA APPROVAL

27 February 2012