Assessment report

NULOJIX

International Nonproprietary Name: Belatacept

Procedure No. EMEA/H/C/2098

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AR	acute rejection
AUC	area under the concentration-time curve (over one dosing interval)
BMS	Bristol-Myers Squibb
CAN	chronic allograft nephropathy
CIT	cold ischemia time
CKD	chronic kidney disease
Cmax	maximum concentration
Cmin	trough serum concentration
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CRF	case report form
CsA	cyclosporine A
CTS	Collaborative Transplant Study
CV	cardiovascular
CYP450	cytochrome P450
DGF	delayed graft function
DMC	Data Monitoring Committee
EBV	Epstein Barr virus
ECD	extended criteria donor
ESRD	end-stage renal disease
GFR	glomerular filtration rate
HDL	high density lipoprotein
HLA	human leukocyte antigen
IL	Interleukin
ITT	intent-to-treat
LDL	low density lipoprotein
LDT	lymphocyte depleting therapy
LI	less intensive (belatacept regimen)
MDRD	Modification of Diet in Renal Disease (i e Levey formula)
MedDRA	Medical Dictionary for Regulatory Activities
MI	more intensive (belatacept regimen)
MMF	mycophenolate mofetil
MPA	mycophenolic acid
NKF	National Kidney Foundation
NODM	new onset diabetes mellitus
PMA	phorbol myristate acetate
PML	progressive multifocal leukoencephalopathy
PRA	panel reactive antibodies
PTLD	post-transplant lymphoproliferative disorder
SCD	standard criteria donors
SCr	serum creatinine
SD	standard deviation
SRL	sirolimus
TB	tuberculosis
UNOS	United Network of Organ Sharing
USRDS	United States Renal Data System
UTI	urinary tract infection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb Pharma EEIG submitted on 03 February 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for NULOJIX, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 April 2009.

The applicant applied for the following indication: prophylaxis of graft failure and dysfunction in adult patients receiving a renal transplant.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/99/2008 for the following condition:

- Renal transplantation

on the agreement of a paediatric investigation plan (PIP) with a deferral.

The PIP is not yet completed.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 18 February 2005. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: USA

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Dr. Tomas Salmonson (SE)	Co-Rapporteur: Dr. Romaldas Mačiulaitis (LT)

- The application was received by the EMA on 03 February 2010.
- The procedure started on 24 February 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 May 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2010.
- During the meeting in June 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 June 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 December 2010.
- The summary reports of the GMP inspection carried out at the following sites: BioReliance Corporation, 9900 Blackwell Road, Rockville, Maryland – USA, Bioreliance Corporation - 9630 Medical Center Drive - Rockville, Maryland – USA; Bioreliance Corporation, 14920 Broschart Road, Rockville, MD, USA between 20th – 24th September 2010; and C Beckman Coulter Genomics100 Perimeter Park Drive 27560 Morrisville, NC USA between 30th September – 1st October 2010 were issued on 21 January 2011 and 14 January 2011 respectively.
- A GCP inspection was carried out at two investigator sites in Argentina (20-24 September 2010 and 27-30 September 2010) in relation to the conduct of the two trials IM103008 and IM 103027. The final integrated inspection report was issued on 25 October 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 January 2011.
- During the CHMP meeting on 14-17 February 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 March 2011.
- During the meeting in April 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Nulojix on 14 April 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 13 April 2011.

2. Scientific discussion

2.1. Introduction

Problem statement

End stage renal disease (ESRD) is a global health issue with an incidence that is growing at an annual rate of 8%, outpacing the annual population growth rate of 1.3%. Renal transplantation is the preferred treatment for ESRD because it confers improved survival and quality of life over dialysis. After transplantation, recipients require lifelong immunosuppression to suppress the alloimmune response and maintain a functioning graft. Therapeutic advances, such as the calcineurin inhibitors, CNI, (ciclosporin, CsA, and tacrolimus) are the current mainstays of immunosuppressive therapy. Current immunosuppressive regimens yield 1-year graft survival rates of 90% for deceased-donor grafts and 95% for living-donor grafts. However, the reductions in acute rejection (AR) rates and improvements in short-term survival have not led to commensurate improvements in longer term

patient and graft survival, which remain suboptimal. For example, 5-year patient survival with a functioning graft is 68% and 77% for recipients of deceased donor transplants, and 80% and 86% for recipients of living donor transplants, in the United States and Europe, respectively.

Despite their favourable impact on short-term outcomes, the CNIs may contribute to poor long-term outcomes due to their associated renal, cardiovascular, and metabolic toxicities. The nephrotoxicity of CNIs is of particular concern because post-transplantation renal function has emerged as the strongest predictor of graft survival, cardiovascular events, and subject survival. Much research has focused on developing strategies to avoid or minimise CNIs to improve post-transplant renal function and, ultimately, longer term outcomes. Long-term transplant outcomes and the risk associated with CNIs are of growing importance due to the increasing reliance on higher risk extended criteria donor (ECD) kidneys to satisfy the critical shortage of organs for patients on the kidney transplant waiting list.

Therefore, an unmet medical need exists for new therapeutic agents that can provide short-term outcomes comparable to the CNIs, while preserving renal function over time and avoiding their off target cardiovascular and metabolic toxicities, thus supporting improved longer term graft and subject survival after renal transplantation of both standard criteria donor (SCD) and ECD kidneys. Belatacept has been developed as a new therapeutic option to address this unmet medical need.

About the product

Belatacept is a recombinant soluble fusion protein consisting of the extracellular domain of human CTLA-4 and a fragment (hinge–CH2–CH3 domains) of a modified Fc domain of human IgG1. Belatacept targets the blockade of CD28:CD80/CD86 interactions, key costimulatory signals required for T cell activation. T cells require at least 2 signals for full activation. The first signal needed for T cell activation is delivered by the T cell receptor and the second via costimulatory molecules. The interaction between CD28 and CD80 and/or CD86 is the most important costimulatory signal for the initial activation of naive T cells. Activated T cells are the most important immune mediators of allograft rejection.

The initially proposed indication reads as follows: "NULOJIX, in combination with corticosteroids and a mycophenolic acid, is indicated for prophylaxis of graft failure and dysfunction 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." The finally approved indication is as follows: "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".

The dosing regimen is the following:

Dose of belatacept 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	10 mg/kg
End of Week 8 and Week 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

Type of Application and aspects on development

This application has been submitted as complete and independent application according to Article 8.3 of Directive 2001/83/EC meaning that it includes complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature supporting certain tests or studies.

The CHMP guideline on the clinical investigation of immunosuppressants for solid organ transplantation (CHMP/EWP/263148/06) is relevant for this application. EMA/CHMP Scientific advice was received on 17 February 2005 for belatacept on clinical and nonclinical aspects of the development programme.

A Paediatric Investigation Programme was agreed for the condition "Renal transplantation", which is not yet complete. This includes a paediatric development in paediatric population from two years to less than 18 years; a deferral for initiation and completion of some or all of the studies was agreed. In terms of clinical studies, this plan includes a multicenter, multiple-dose, PK/conversion study in stable renal transplant adolescents, as well as an efficacy and safety study in de novo renal transplant recipients. For paediatric patients below the age of two years a waiver was agreed.

2.2. Quality aspects

2.2.1. Introduction

Belatacept is a genetically engineered fusion protein which consists of the functional binding domain of modified human cytotoxic T-lymphocyte antigen-4 (CTLA-4) and the Fc domain of human monoclonal immunoglobulin of the IgG1 subclass. It is produced by cell culture using a Chinese hamster ovary (CHO) mammalian cell expression system.

Belatacept has been used in combination with an interleukin-2 receptor antagonist, a mycophenolic acid, and corticosteroids.

The immunomodulatory biological activity of belatacept is based on its direct binding to B7-1 and B7-2 (CD80 and CD86, respectively) expressed on antigen presenting cells which then results in selectively blocking full activation (co-stimulation) and proliferation of T-lymphocytes.

The drug product, belatacept 250 mg powder for concentrate for solution for infusion, is a sterile, single use, non-pyrogenic lyophile for intravenous (IV) administration. The proposed dosing regimen of belatacept is 10 mg/kg intravenously, on Day 1 (day of transplant) and Day 5, then every other week for 2 weeks (end of Weeks 2 and 4), then every 4 weeks for 2 months, and then at 5 mg/kg monthly thereafter.

2.2.2. Active Substance

Belatacept is a genetically engineered fusion protein which consists of the functional binding domain of modified human cytotoxic T-lymphocyte antigen-4 (CTLA-4) and the Fc domain of human monoclonal immunoglobulin of the IgG1 subclass. It is produced by cell culture using a Chinese hamster ovary (CHO) mammalian cell expression system.

Manufacture

Belatacept is produced at the Bristol-Myers Squibb Company facilities located in East Syracuse, New York, USA. Belatacept is produced by large-scale cell culture using a genetically engineered Chinese hamster ovary (CHO) cell line and is purified from the clarified (cell-free) harvest material using standard chromatography and filtration steps.

The manufacturing process is initiated with the thaw of a manufacturer's working cell bank (MWCB) vial. The cell culture is expanded using a series of flask and seed bioreactor steps, until reaching sufficient density for inoculation into the production bioreactor. The cell culture from the bioreactor content is harvested and clarified in preparation for downstream processing.

Belatacept is purified using a series of chromatographic and filtration steps. The downstream belatacept manufacturing process includes chromatography steps like affinity chromatography step, an anion exchange chromatography step and a hydrophobic interaction chromatography step etc. The downstream processing steps also include a viral inactivation step and a viral filtration step to clear potential adventitious viral agents.

Process controls

In the Day 150 Assessment Report, there were still a number of main deficiencies noted in the documentation supporting the proposed system for in-process controls. The provided documentation did not fully justify the classification of critical and non-critical process parameters and the proposed process operation ranges. Of particular concern was the operation control of the downstream chromatography steps because indications of variability for CQAs over the currently defined operation range for both critical and non-critical process parameters. Furthermore, there were indications that the IEF method could not reliably resolve product variants for quantification in the more basic pI region, as within this pI region, variability in charge forms was noted.

Within the responses provided by the applicant, an acceptable review of the IPC system has been provided. The limits for operation control have been tightened in order to reduce variability in the bioreactor and the three chromatography steps.

In addition, acceptable documentation has been provided supporting that IEF has capacity to resolve for enumeration/quantification of different charge forms of belatacep over the pI range required to control consistency in production.

Drug Substance Characterisation

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 contains both *N*-linked and *O*-linked oligosaccharides and the glycosylated molecule have an average molecular weight of 90,619 daltons.

The coding sequences for belatacept are closely similar to the sequences encoding abatacept, the active ingredient in Orencia (EMEA/H/C/701). The cDNA fragment coding for LEA29Y was generated during the mutagenesis of CTLA-4 Ig (abatacept) to identify high-avidity molecules with slower rates of

dissociation from B7 ligands. An acceptable overview is provided on the construction of the expression vector and development of the production cell line.

In the process of establishment, the cell line was then adapted to a chemically defined, animal-component free medium. No animal derived raw materials are used in production. Overall, the cell banks are acceptably characterized. Some further information is however required on the control of new working cell banks.

Satisfactory studies, using state-of-the-art techniques, are reported for characterisation of general structure, covering the full amino acid sequence, average molecular weight, mapping of N- and C-terminal sequences, carbohydrate profile, intra- and inter-chain disulphide bonds, secondary structure and biological activity.

The weak point in the documentation is the characterisation of the key degradation pathways (oxidation, deamidation and formation of charge forms) where further studies were required. Additional studies addressing the degradation of product have been provided; thereby the characterisation of the product is considered acceptable.

Specification

The drug substance specification includes tests and acceptance criteria for appearance, identity (capillary electrophoresis), purity (peptide mapping, IEF, SDS-PAGE, SE-HPLC), sialic acid content (NANA,NAGA), N-linked glycan profile, process-related impurities, total protein, as well as pH, endotoxin and bioburden.

The selection of these tests is generally considered appropriate, as they cover most of the observed or expected variability. There were, however, concerns raised on the performance of some of the analytical methods. The control in performance of analytical methods has been improved and is by large considered acceptable.

The applicant is recommended to perform optimisation/validation studies to further improve the control of biological activity and purity in analysis by the B7 bioassay and the SDS-PAGE analysis.

Resulting from the requested review of the proposed limits for control by specifications, the specifications have been revised and are considered acceptable.

Stability

A shelf life of 30 months at the long-term storage condition of -40°C with interim storage at 5°C for an additional 12 months was originally proposed for drug substance.

As significant increase is seen for some product-related impurities during storage under refrigerated conditions, yielding levels clearly above those qualified in clinical studies, storage under refrigerated conditions was not accepted. The applicant has now shortened the time-period for refrigerated storage and storage for up to three months can be accepted.

For drug substance stored under the proposed long-term condition, no trend in stability can be detected. Stability data covering proposed storage time has now been provided and with a reservation for the outcome of the investigations requested supporting adequate performance of IEF method, a shelf-life of 30 months can be assigned for drug substance stored at -40°C.

In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

Comparability exercise for Active Substance

N/A

2.2.3. Finished Medicinal Product

The drug product, belatacept 250 mg powder for concentrate for solution for infusion, is a sterile, single use, non-pyrogenic lyophile for intravenous (IV) administration. The proposed dosing regimen of belatacept is 10 mg/kg intravenously, on Day 1 (day of transplant) and Day 5, then every other week for 2 weeks (end of Weeks 2 and 4), then every 4 weeks for 2 months, and then at 5 mg/kg monthly thereafter.

Pharmaceutical Development

Although the documentation presented by the Applicant provides an acceptable overview of the development of the formulation of drug product, and the identification of adequate parameters to be used for in-process in commercial production, the reports did not include extended studies for "process understanding," challenging the effect by exceeding the in-process limits that were established in development or studying the interaction between different process parameters. Further data has been presented now providing satisfactory supporting the classification of critical and non-critical parameters for operation control.

Compatibility issues were assessed to identify possible formulation problems. Appearance of visible particles in some of the samples was confirmed during reconstitution and compatibility studies. Evaluation of the particles revealed the presence of numerous air bubbles along with a few particles for most of the samples. Attempts to characterize the particles were unsuccessful because an insufficient amount of material was obtained. The finding is rare, only seen in one out of six experiments, and the particles has been shown to be removed by the final in-line filters during IV administration.

Manufacture of the product

NULOJIX is manufactured by Bristol-Myers Squibb Holdings Pharma, LTD at its facility in Manati, Puerto Rico (BMS-MAN).

The process for manufacture of drug product, including fairly conventional steps for compounding, sterile filtration, aseptic filling, lyophilisation and stoppering, is satisfactorily described and validated.

Manufacturing facilities have been described. Satisfactory presentation of floor diagrams and indication of flow of equipment, personnel and materials, and information concerning the building utilities, confirm adequate environment for belatacept production.

Product specification

The drug product specification includes tests and acceptance criteria for appearance of lyophilisate, identity (capillary electrphoresis), purity (peptide mapping, IEF, SDS-PAGE, SE-HPLC), total protein, as well as pH, constitution time, particulate matter, uniformity of content, moisture, osmolarity, endotoxin and sterility. Besides pharmacopendial methods used exclusively for control of drug product, basically the same tests apply for control for drug substance and drug product, and thus also the same concerns raised on drug substance applies for drug product.

Stability of the product

Similarly as noted for drug substance, additional stability data has been provided. Thus, with a reservation for the outcome of the investigations requested supporting adequate performance of IEF method, a shelf-life of 30 months can be approved for drug product stored under refrigerated conditions, with protection from light.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

Adventitious agents

The estimated value for Particles per Dose seems to be acceptable. The requested relevant study protocols have been presented.

A reduction of the capacity to remove the naked model virus PPV was seen at the elevated pressure of 14 psi and to improve control for this parameter defined an acceptable action limit at the virus filtration step.

Additional documentation has been provided, but as naked virus such as MMV can be present, a filter of as high capacity as possible is needed and further documentation was required to justify why only the Planova 15N filter is used. Acceptable conditions have since been established to control an adequate performance of the ViroSart CPV and Planova 15N filters for removal of virus.

Comparability Exercise for Finished Medicinal Drug Product

N/A

GMO

N/A

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

During the procedure of NULOJIX, a Major Objection related to Quality was initially identified. This Major Objection concern to the following:

- Supportive documentation to the proposed system for In – Process Controls (IPC)

Although additional information was requested during the procedure, the applicant was able to provide in a satisfactorily manner the majority information requested.

Acceptable documentation to support that IEF has capacity to resolve for enumeration/quantitation of different charge forms of belatacep over the pI range required to control consistency in production has been provided. The working range of IEF has been extended and the limits for operation control in order to reduce variability in the bioreactor and chromatography steps have been tightened.

The current SDS-PAGE analysis has only been validated for quantitition of the main component. Although the control of impurities is indirectly addressed in the validation, and the analysis could in this aspect be considered acceptable for confirmation of consistency in production using an established, validated process, it is not considered sufficient for confirmation of comparability of product in conjunction with the introduction of major process changes. Supporting comparable impurity profile, a validated quantitative method is required, both to show that the individual species remain within the

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

amount qualified in clinical studies, and to confirm similar trends for these species in stability studies (Quality Obligation).

In addition, in order to ensure consistent biological activity of product in commercial production, the control in routine analysis of the B7 binding should be improved. Currently, two bioassays are applied for release control of drug substance and drug product. Both these assay are claimed validated in accordance with the requirements in the ICH Q2 guideline, using the Four-Parameter Logistic Curve model (Statistical analysis of results of biological assays and tests, Ph. Eur. 5.3) for statistical evaluation of data. However, the control elicited by the statistical evaluation of data during validation was apparently not implanted in the procedures for the analyses in routine use and consequently, no assay criteria were established to ensure that results obtained in routine analysis of batches would be "statistically valid".

Therefore, to prevent a shift in biological activity of Nulojix in conjunction with the introduction of future changes in the commercial production process, it is crucial that at least one of the bioassays used for analysis adheres to the requirement in Ph. Eur. 5.3 (Quality Obligation).

Thus, at the time of the responses of the List of Outstanding issues, the applicant was able to satisfactorily address the quality questions. The applicant has been requested to provide further information through some Post Authorisation Commitments (please see section 2.7).

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

At the time of the CHMP opinion, there were a number of obligations and recommendations in regards to quality issues which were not considered to impact on the Risk-benefit balance of the product.

2.3. Non-clinical aspects

2.3.1. Introduction

Belatacept is a soluble human-human chimeric protein consisting of the modified extracellular domain of human CTLA4 fused to a modified fragment (hinge-CH2-CH3 domains) of the Fc domain of a human IgG1 antibody. The modification in the CD80/CD86 binding domain consists of point mutations that result in 2 amino acid substitutions (L104 to E and A29 to Y). In the IgG1 Fc domain four amino acids were genetically engineered to reduce complement fixation and decreased antibody dependent cellular cytotoxicity. Belatacept is produced by large-scale cell culture using a genetically engineered Chinese hamster ovary (CHO) cell line and is purified from the clarified (cell-free) harvest material using standard chromatography and filtration steps. The drug product, belatacept for Injection, 250 mg/vial, is a sterile, single use, non-pyrogenic lyophile for intravenous administration.

Scientific advice on the toxico-pharmacological development for belatacept was received from the EMA/CHMP.

All pivotal toxicology studies, including toxicokinetic evaluations, supporting the safety of belatacept or abatacept have been performed under GLP conditions.

2.3.2. Pharmacology

The intended function of belatacept is to inhibit CD28 binding to CD80/CD86 by blocking/binding to CD80/CD86. Belatacept binds to CD80/CD86 by containing CD80/CD86 binding elements from CTLA-4, a surface molecule normally expressed on activated T cells that serves as a vital molecule for the self-regulating/inhibiting part of an adaptive T cell immune response. The CD80/CD86 binding motif MYPPPY is shared by both CTLA-4 and CD28, but CTLA-4 binds to CD80/CD86 with much higher avidity (10 to 100 times). The inhibited CD28 binding deprives the T cells of the second activation signal needed for the full induction of an adaptive immune response. Belatacept is a further development of abatacept (centrally approved in 2007 as Orencia, indicated in rheumatoid arthritis and polyarticular juvenile idiopathic arthritis) as to intended function, i.e. to inhibit costimulation of T cells. In belatacept the Applicant has made two point mutations in the amino acid sequence of abatacept to increase binding to CD80 and CD86 in order to increase the immunsuppressive capability of belatacept in comparison to abatacept.

Abatacept studies in rodents were used to support belatacept registration requirements because: 1) abatacept binds more avidly than does belatacept to murine CD80/86; 2) abatacept has greater in vitro and in vivo bioactivity in rodents than belatacept; and 3) abatacept is very similar to belatacept in both its mechanism of action and its structure.

The binding of belatacept to CD80/CD86 most likely also has direct implications on the CTLA-4 expressing T cells by disrupting the inhibitory signals delivered by CTLA-4 though its cytoplastic tail. The exact intracellular signals delivered by CTLA-4 remains uncertain; however CTLA-4 signalling down regulates cytokine production by inhibiting the accumulation of AP-1, NF-κβ and NFAT in the nucleus of activated T cells. CTLA-4 also regulates cell proliferation by inhibiting cyclin D3, cyclin-dependent kinases 4 and 6, and the degradation of cell-cycle inhibitor $p27^{kip1}$.

Primary pharmacodynamic studies

In vitro binding studies

In biochemical binding studies using radiolabeled abatacept, it was shown that abatacept binds to CD80 with approximately 2-fold greater affinity than to CD86. Additionally, abatacept binds with approximately 100-fold higher avidity to CD80 and CD86 than human CD28-Ig does, and is therefore an effective competitor for CD28:CD80/86 interactions. As a result of the 2 amino acid modifications, belatacept binds to its target receptors CD80 and CD86 with greater avidity than the parent CTLA4-Ig molecule, abatacept. A series of Biacore binding studies demonstrated that belatacept binds to CD86-Ig with approximately 4.3-fold higher avidity than the parent molecule. Likewise, these studies demonstrated that belatacept binds CD80-Ig with approximately 1.8-fold greater avidity than Abatacept.

In vitro functional analysis

Effect of belatacept and CTLA-4Ig on CD80- or CD86-mediated stimulation of CD4+ T cells.
The concentration of belatacept required inhibiting 50% (EC50) of CD80-mediated costimulation of CD4+ T cell proliferation was 0.001 µg/mL and the EC50 for belatacept inhibition of CD86-mediated costimulation of CD4+ T cell proliferation was 0.0025 µg/mL. The EC50's for belatacept and abatacept for inhibition of CD80 mediated T cell proliferation was 0.001 ug/ml vs 0.005 ug/ml respectively. The EC50's for belatacept and abatacept for inhibition of CD86 mediated T cell proliferation was 0.0025 ug/ml vs 0.032 ug/ml respectively. Therefore, the high avidity ligand binding properties of belatacept were reflected functionally, with the belatacept variant being a more potent inhibitor of both CD80- and CD86-mediated costimulation of T cells compared to abatacept.

Inhibition of primary and secondary allogenic mixed lymphocyte reaction by belatacept treatment

A series of mixed lymphocyte reaction assays were conducted to evaluate the ability of belatacept to inhibit allo-responses in vitro. The EC50 of belatacept for inhibition of proliferation in the primary mixed lymphocyte reaction (MLR) was 0.18 µg/mL. The EC50 of belatacept for inhibition of proliferation in the secondary MLR was 0.20 µg/mL.

Measurement of IL-2, IL-4 and IFN-γ was performed on culture supernatants collected 24 hours post primary and secondary stimulation. In the primary MLR assay, only IL-2 was detectable and the EC50 of belatacept for inhibition of IL-2 production in the primary MLR was 0.04 µg/mL. In the secondary MLR IL-2, IL-4 and IFN-γ were produced at detectable levels and it appeared that belatacept's EC50 for inhibition of IL-2, IL-4 and IFN-γ production in the secondary MLR were 0.03 µg/mL, 0.20 µg/mL, and 0.14 µg/mL respectively. A number of additional in vitro experiments were performed to evaluate the effect of belatacept on T cell responses stimulated by allogeneic monocyte-derived dendritic cells. The data showed consistency in terms of inhibition of proliferation and cytokine release.

Target saturation in human whole blood and allo-response assay

In these studies, the concentrations of belatacept required for the saturation of CD86 (IC50 = 0.102 ± 0.019 µg/mL) paralleled those required for the inhibition of alloantigen stimulation in vitro (IC50 = 0.185 ± 0.08 µg/mL). The concentrations of belatacept required for the saturation of CD80 (IC50 = 0.009 ± 0.004 µg/mL) were substantially lower. Additionally, belatacept CD80/CD86-receptor occupancy was compared directly with the degree of alloresponse inhibition induced by belatacept in a dendritic cell-stimulated MLR. The belatacept concentration required for saturation of CD86 correlated more directly with the inhibition of the alloresponse. At a concentration of 0.1 µg/mL of belatacept, >90% of the CD80 receptors appeared to be saturated while only achieving approximately 35% inhibition of the allo-response. At this same concentration of belatacept, only ~35% of the CD86 receptors also appeared to be saturated.

Fc Receptor-mediated functions

Since the Fc portion of Ig fusion proteins has the potential to bind Fc receptors and mediate antibody-dependent cellular cytotoxicity (ADCC) as well as complement-dependent cytotoxicity (CDC), studies were conducted to evaluate the capacity of belatacept to mediate ADCC and CDC. The studies demonstrated that belatacept at 30 µg/mL, did not mediate ADCC of a CD80/86 expressing human B-cell line (PM-LCL) by PBMC from 13 different normal donors. The LCL B cell line was exposed to either complement alone or in combination with increasing concentrations of anti-CD80/anti-CD86 antibodies or belatacept. The background level of cell lysis in the presence of complement alone was about 22%. Increasing concentrations of either anti-CD80 or anti-CD86 resulting in complement-mediated cell killing, with a maximal response at 100 ng/ml. In contrast, increasing concentrations of belatacept up to 30 µg/ml did not increase complement-mediated killing above the background level observed with complement alone.

In vivo functional studies

Belatacept suppression of KLH antibody response in mouse, rat, rabbit and monkey

To identify the appropriate species and CD28 blocker to use for efficacy and toxicology studies, a series of studies comparing the bioactivity of belatacept with that of abatacept have been conducted in mice, rats, rabbits, and monkeys in a primary T cell-dependent antibody response model using either keyhole limpet hemocyanin (KLH) or sheep erythrocytes (SRBC) as the antigen.

- Murine studies

Studies 092804KLH, 102704KLH, 02085KLH

A series of experiments were performed to test the ability of abatacept and belatacept to block a murine primary immune response to KLH. Both abatacept and belatacept were capable of inhibiting the murine primary immune response to KLH in vivo in a dose-dependent manner. Mice treated with abatacept demonstrated a dose-responsive inhibition of KLH-specific IgG on Day 14. Mice treated with belatacept also demonstrated a dose-responsive inhibition of KLH-specific IgG on Day 14. Abatacept appears to be more potent by dose as > 90% inhibition of the response is achieved at doses of 3 mg/kg and above whereas >90% inhibition with belatacept was achieved only at the 30 mg/kg dose. This finding justifies using abatacept mice data when addressing belatacept safety and efficacy.

- Rat studies

Study DS04256

This study was conducted to compare the bioactivity of belatacept to abatacept in rats at a dose of abatacept known to be immunosuppressive in rodents. Marked suppression (≥ 99%) of total T-cell-dependent antibody response to KLH was observed in all female rats (10/10 per group) administered intravenously 20 mg/kg belatacept or abatacept on Days 1 and 8.

Study DS04284

This study was conducted to compare the dose-response for the bioactivity of belatacept to abatacept in rats relative to exposure. Systemic exposures to belatacept ranged from 51 to 67%, as determined from the AUC0-168 h (first dosing interval and prior to onset of immunogenicity), and 40 to 55%, based on AUC0-t, where t is time of last measurable serum concentration, of the exposure to abatacept achieved following administration at the same doses. When given the same doses, the incidence and onset of drug-specific antibodies was increased in groups given belatacept relative to groups given abatacept. The development of belatacept or abatacept-specific antibodies in individual rats strongly correlated with a rapid decline in serum drug levels. Onset of immunogenicity was generally observed after the first dosing interval.

Study DS05055

The objective of this study was to compare the bioactivity of belatacept to abatacept relative to exposures. Based on AUC (0-T, where T is the last detectable time point), exposure to belatacept was 144%, 85%, 62% and 35% of the exposure to abatacept at doses of 0.03, 0.1, 0.3, or 1 mg/kg, respectively.

Overall in rat, abatacept showed similar improved efficacy over belatacept as to suppressive capability, immunogenicity and clearance.

- Rabbit studies

Study DS04252

The objectives of this study were to determine if belatacept is pharmacologically active in rabbit and compare its bioactivity to that of abatacept. Systemic exposures to belatacept, as determined from the AUC0-168 h and AUC0-840 h, were 50 and 32%, respectively, of that achieved following similar doses of abatacept. The clearance of belatacept was approximately 4-fold greater than that of abatacept. Marked suppression (≥ 99%) of the T-cell-dependent antibody response to KLH was observed on Days 8, 15, and 22 in rabbits that received abatacept. In rabbits given belatacept, 99, 96, and 67% suppression was observed on Days 8, 15, and 22, respectively. Abatacept-specific antibodies were detected in 1 out of 6 rabbits given abatacept from Day 15 to Day 36, whereas belatacept -specific antibodies were detected in 3 out of 5 rabbits by Day 15 and in all rabbits (5/5) given belatacept by

Day 29. The development of abatacept- or belatacept -specific antibodies in individual rabbits strongly correlated with a rapid decline in serum drug levels.

Study DS04287

This study was conducted to compare the dose-response for the bioactivity of belatacept to abatacept in rabbits relative to exposure. Systemic exposures to belatacept, as determined from the AUC0-last, were 41% and 38% of that achieved with abatacept at 3 and 10 mg/kg doses, respectively. The clearance of belatacept was approximately 2.1- and 2.6-fold greater than that of abatacept. Overall, most animals developed drug directed antibodies at day 36 with the exception of the abatacept high dose (20 mg/kg) group (2/6 animals developed antibodies).

The above mentioned studies in rabbit showed that belatacept suppressed the formation of antigen-specific antibodies as effective as abatacept. However clearance of belatacept was higher than for abatacept which reduces belatacept exposure in rabbit.

- Monkey studies

Study 97607

The objective of this study was to establish and compare the immunosuppressive activity of belatacept and abatacept. Overall, the serum concentrations of belatacept were generally lower than serum concentration of abatacept. At higher doses (≥0.125 mg/kg) belatacept was shown to be more immunosuppressive than abatacept.

Renal transplants in Rhesus Macaques (Larsen et al and Final reports on phase I, II and islet studies. Emory University study report; 2002).

To evaluate the efficacy of belatacept in a model of renal transplantation, a series of primate transplant studies were conducted with belatacept. The data show that belatacept are more potent in a Rhesus renal transplant model than abatacept. The addition of belatacept to other immunsuppressive drugs prolongs engraftment. In addition, belatacept addition to methylprednisolone and steroids seems to inhibit formation of donor directed antibodies.

Islet cell transplantation in Rhesus macaques Adams et al.

In rhesus macaques, total pancreatectomy without duodenectomy or splenectomy was performed at least 1 week before transplant. Overall the data show that belatacept improves islet function after transplantation.

Studies in monkey showed that that belatacept is more potent in a Rhesus renal transplant model than abatacept. The addition of belatacept to other immunosuppressive drugs prolongs engraftment. In addition, belatacept addition to methylprednisolone and steroids seems to inhibit formation of donor directed antibodies. In antigen challenging studies belatacept was shown to be more immunosuppressive than abatacept at doses ≥0.125 mg/kg.

Effect of CD80/CD86 blockade on host pathogen defense

Numerous nonclinical studies have been conducted to assess the CD28 costimulation dependence of host defense against different types of pathogens, including viruses, intracellular bacteria, fungi and parasites. The studies presented by the applicant have been conducted using either abatacept, CTLA4-Ig from sources other than the applicant, or other means of CD28 modulation. Since the majority of the animal models assessing host defense are in mice, and belatacept has limited biological activity in mice compared to abatacept, evaluation of the CD28 dependency in these models was conducted with abatacept in place of belatacept. The overall data on host viral immunity suggests a risk of reactivation of dormant viruses in the models studied. However, some data also suggests that viral immunity is

preserved after CTLA4-Ig treatment. Since most of the studied viruses are species specific it is difficult to extrapolate these studies to humans. The increased risks for infections are well known for in clinical use immunosuppressants and relevant also for belatacept.

Secondary pharmacodynamic studies

No studies to specifically assess any secondary pharmacodynamics were conducted since there is no evidence of off target biological effects with belatacept.

Safety pharmacology programme

No *in vitro* safety pharmacology studies have been performed by the applicant. *In vivo* evaluations of the potential effects of intravenous administration of belatacept on the cardiovascular, central/peripheral nervous and/or respiratory systems in monkeys were included as part of the pivotal (GLP) single and repeat-dose studies. The data provided show that Belatacept does not interfere with cardiovascular, neurological or respiratory functions.

Pharmacodynamic drug interactions

The non-human primate transplant studies described investigated the efficacy of belatacept for prophylaxis of graft loss in combination with other standard immunosuppressive compounds. In general, combinations of belatacept with corticosteroid, MMF, basiliximab and/or sirolimus demonstrated enhanced efficacy compared to monotherapy.

2.3.3. Pharmacokinetics

The pharmacokinetics of belatacept and rodent homolog abatacept has been studied after intravenous administration in different animal species: mice, rats, rabbits and monkeys. Studies using subcutaneous administration have been performed in mice and rats. The drugs were administered as solutions and doses ranged from 0.03 mg/kg in bioactivity studies to 200 mg/kg in drug safety evaluation studies; product comparability studies were conducted at the potential human therapeutic induction dose (10 mg/kg).

Two manufacturing process changes were made during the development of belatacept. The first, from Process A to Process B, included an increase in production bioreactor working volume and the elimination, addition, and modification of various production steps. The second, from Process B to Process C (used to produce drug substance for Phase 3 clinical trials and intended to produce drug substance for commercial use) included elimination and addition of various medium additives, the latter to improve product consistency and productivity.

The pharmacokinetic profiles, efficacy and safety were comparable in cynomolgus monkeys receiving a single intravenous 10-mg/kg dose of belatacept was comparable throughout the product development, i.e. A material, B material, C material (lyophilized drug product) or belatacept as a liquid ready-to-use clinical formulation.

Methods of analysis

The concentration of belatacept and abatacept in serum was measured using double antibody sandwich enzyme-linked immunoassay (ELISA). The methods used are validated and reliable.

Absorption

Dose-dependent PK was observed in rats (and, to a lesser degree, in rabbits) following single doses of either belatacept or abatacept. In a dose range of 0.03 to 1 mg/kg, these were characterized by decreasing elimination with increasing dose, resulting in a greater than proportional increase in exposure with dose. This phenomenon, which occurred at mean serum belatacept and abatacept concentrations of ≤10 and 20 µg/mL, respectively, is consistent with saturation of elimination via receptor-mediated endocytosis, which has been shown to lead to nonlinear PK of monoclonal antibodies. In contrast, in rats receiving repeated abatacept SC and/or IV doses of 20 to 200 mg/kg, there was a trend for both CLT and Vss to increase with dose resulting in a less than dose-proportional increase in exposure. This phenomenon is consistent with a saturation of FcRn, which protects antibodies of the human IgG1 isotype from elimination. There was little evidence for dose-dependent PK in monkeys receiving intermediate-range single doses of belatacept (9 to 90 mg/kg; Cmax range = 233 to 2850 µg/mL) or abatacept (10 to 50 mg/kg doses; Cmax range = 280 to 1460 µg/mL). While this is a cross-study and cross-species comparison, these data suggest that the nature of the dose dependency of abatacept (and potentially belatacept) PK may vary depending on the dose range, with increases in exposure being roughly proportional to dose in the clinical dose range. This is consistent with the dose proportionality of belatacept exposure in humans receiving 1 to 20 mg/kg doses of belatacept (Cmax = 28.7 to 468 µg/mL).

Distribution

No radiolabeled tissue distribution studies were conducted. The Vss for belatacept was low in all tested species, with mean values ranging from 39 to 149 mL/kg. These values are only slightly higher than the reported plasma volume in these species (31 to 52 mL/kg), indicating limited extravascular distribution.

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. A confirmatory study was conducted in monkeys. Belatacept concentrations in homogenates of brain samples taken 24 hours after the final 10 or 50 mg/kg dose were very low (91.1 ± 42.5 and 356 ± 108 ng/g tissue, respectively), representing only 0.067 and 0.055%, respectively, of the corresponding serum belatacept concentrations. A number of additional observations in drug-treated monkeys were consistent with this conclusion.

Metabolism

No studies were conducted to evaluate the metabolism and metabolic pathways of belatacept in animals since belatacept consists of amino acids.

Excretion

No studies were conducted to evaluate the excretion of belatacept or abatacept in animals. This is acceptable since belatacept consists of amino acids. Secretion of belatacept into milk was demonstrated following the administration to lactating rats.

Pharmacokinetic drug interactions

Since belatacept is a protein it does not undergo metabolism by the cytochrome P450 enzymes and, thus, it is not expected to have direct PK interactions with molecules that are metabolized by these enzymes. No studies were therefore conducted to determine the potential for any drug-drug interactions of belatacept with any other molecules.

2.3.4. Toxicology

Single dose toxicity

Study number 98642 was conducted to assess the single-dose toxicity, toxicokinetics and immunogenicity of belatacept in monkeys. Belatacept (lyophylized Process A) was administered to 3 cynomolgus monkeys/sex/group at single intravenous doses of 9, 30, or 90 mg/kg. Cmax values increased in proportion to dose. Although the increase in AUC(INF) was dose proportional in male monkeys, it was greater than the dose increment in female monkeys. Both CLT and Vss values appeared comparable among the dose groups. The lower T-HALF estimates at the 9- and 30-mg/kg dose levels (75.2-88.3 hours) as compared to the 90-mg/kg dose level (116-132 hours) were attributed to the formation of anti-drug antibodies that accelerated the elimination of belatacept. Belatacept-specific antibody titers were evident in low- and intermediate-dose monkeys at 5 and 6 weeks postdose, respectively.

There were no clinical signs of toxicity, decreases in body weights or food intakes, electrocardiographic alteration, or changes in body temperatures that were considered drug-related. Additionally, there were no changes in histamine, complement C3a, TNFα or IL-6 levels, or alterations in serum immunoglobulin levels or changes in the phenotypic expression of peripheral-blood or splenic lymphocytes that were clearly drug-related.

Necropsies were conducted on 1 monkey/sex/group on Day 15 and there were no drug-related clinicopathologic, gross pathologic or histopathologic changes observed.

Repeat-dose toxicity

Belatacept and abatacept have been studied in several repeat-dose toxicity studies (table 1).

Table 1. Repeat-dose toxicity studies.

Study ID Test substans GLP status	Species/Number and Sex/Group	Dose/Route	Duration	Major findings
98699 Belatacept GLP	Monkey/3M,3F	0, 10, 22 or 50 mg/kg/iv	1 month with administration every other day, 6 week post dose observation	AUC(TAU) values at the end of treatment were 2.2- to 2.7-fold greater than on Day 1, suggesting drug accumulation over the treatment period. No antibodies to belatacept or host-cell (CHO) proteins were detected during the study. Increased complement (C3a) levels were evident in one high-dose female monkey immediately following dosing on Days 1, 15, and 22. Minimal mean decreases of 10, 34, and 32% from pretreatment serum IgG levels were observed at the end of treatment at doses of 10, 22, and 50 mg/kg/day, respectively, with levels generally returning towards baseline values during the dose-free observation period. Other drug-related changes included minimal lymphoid depletion of germinal centers of spleen and/or lymph nodes.

99655 Belatacept GLP	Monkey/5M,5F	0, 10, 22 or 50 mg/kg/iv	6 months with administration once a week, 3 months post dose observation	Reversible, minimal decreases in serum IgG levels were noted. There were no drug effects on clinical pathology parameters and no gross pathologic findings associated with administration of belatacept. At the end of dosing, minimal to moderate, non-dose-dependent decreases in the number and diameter of germinal centers in lymph nodes and spleen. Following completion of treatment, functional activity of the immune system was demonstrated by a robust antibody response to KLH following immunization after a 2-month recovery period. Drug-specific antibodies were not detected during the treatment period, but were observed in 4 of 6 recovery monkeys 12 weeks after completion of treatment, after belatacept serum levels had dropped below immunosuppressive levels. Viral status was not assessed in these monkeys.
DS02008 Abatacept GLP	Monkey/5M,5F	0, 10, 22 or 50 mg/kg/iv	1 year with administration once weekly, 13 weeks post dose observation	Systemic exposure to abatacept increased in a dose-related manner with no apparent gender differences. No drug-related clinical signs of toxicity were observed. No remarkable changes in peripheral blood lymphocyte phenotypes. Histopathologic changes were limited to the spleen and mandibular lymph node. In both of these organs, mild to moderate decreases in the number and diameter of germinal centers, containing fewer centrally located blast cells (centrocytes) and peripherally located small lymphocytes, were observed reflecting decreased germinal center activity. These findings were evident at all doses and were present to a very slight degree (background level) in the controls. Complete recovery occurred during the 3-month dose-free recovery period. Abatacept treatment did not result in any clinical manifestation associated with a viral infection even though prestudy viral screening indicated previous exposure of all monkeys to one or more of the following viruses: LCV (EBV-like virus), Herpes B, rhesus CMV, and simian papovavirus (SV40; JC-like virus).
96633 Abatacept GLP	Mouse/20M,20F	0, 20, 65 or 200 mg/kg/sc	6 months with administration once weekly, 4 months post dose observation	The absorption of abatacept following subcutaneous administration was prolonged with time to reach Cmax (Tmax) ranging from 6 to 24 h. No drug-related deaths or clinical observations occurred during the study and there were no drug-related changes in clinical athology parameters or gross pathology findings at any dose. At doses of 65 and 200 mg/kg, decreases in the percentages of splenic B-cells (~ 61 to 85%) and inhibition of ex vivo B- and T-cell activation in males and a transient decrease in serum IgG were observed at the end of the 6-month dosing period, but both recovered by the end of the 4-month dose-free observation period.

DS07166 Abatacept GLP	Rat/20M,20F	0, 65 or 200 mg/kg/iv	3 months with administration once every 3 days, 3 month post dose observation	In both sexes, abatacept administration resulted in generally dose-independent effects on immune parameters. These changes included increases in total T-cell counts that correlated with increased counts of total lymphocytes and that were primarily due to increases in T-helper cell counts (CD4+CD8-; 1.32 to 2.01x controls), and decreases in the counts of a subset of peripheral-blood T-regulatory cells. There were no effects on the T-cytotoxic cell (CD8+CD4-) population. Another pharmacologic effect of abatacept was decreased total serum globulin levels secondary to a decrease in serum IgG concentrations. In lymphoid organs, drug-related microscopic findings at both doses included an increased incidence of: 1) decreased B-cell areas characterized by decreased number and size of germinal centers in spleen and mesenteric/mandibular lymph nodes, and 2) increased size of T-cell areas. In non-lymphoid organs, both doses of abatacept were associated with lymphocytic inflammation of thyroid (thyroiditis; 6%) and pancreatic islets (18%) with higher incidence at Week 21 than at Week 14. These findings are consistent with a possible autoimmune etiology. In general, the incidence and severity of these non-lymphoid changes were independent of dose and sex (except inflammation of the pancreatic islets that affected more males than females).

- **Toxicokinetics**

The toxicokinetics between various animal studies and human is presented in table 2.

Table 2. Toxicokinetic comparisons.

Species	Study	Dose (mg/kg)	AUC (28/30 days) (ug*h/ml)	Multiple of human exposure
Human	Multiple doses, iv, belatacept	10[a]	47,900	NA
		10[b]	21,241	NA
		5[c]	13,587	NA
Monkey	1 month, every other day, iv, belatacept, study nr 98699	10	169,540	3.5, 8, 12,5
		22	314,510	6.5, 14.8, 23
		50	717,808	14.9, 33.8, 52.8
Monkey	6 months, once weekly, iv, belatacept, study nr 99655	10	55,992	1.2, 2.6, 4.1
		22	131,396	2.7, 6.2, 9.7
		50	279,266	5.8, 13.1, 20.6
Monkey	1 year, once weekly, iv, abatacept, DS02008	10	88,368	1.8, 2.4, 6.5
		22	189,012	3.9, 8.9, 13.9
		50	429, 608	8.9, 20.2, 31.6
Mouse	6 months, once weekly, sc, abatacept, 96633	20	40,132	0.8, 5.3, 3.0
		65	118,324	2.5, 5.6, 8.7
		200	217,912	4.5, 10.3, 16
Rat	3 months, once every 3 days, iv,	65F	362,700	7.5, 17, 27
		65M	232,500	4.8, 11, 17

	abatacept, DS07166	200F	862,110	18, 41, 63
		200M	549,270	11, 26, 40

[a]Exposure (AUC 28 days) in LI regimen during first month of treatment when administered at 10 mg/kg on Days 1, 5, and 14; source of human AUC data - Population PK data.
[b]Exposure (AUC 28 days) in LI regimen during fourth month when administered at 10 mg/kg once every 28 days; source of human AUC data - Study IM103047.
[c]Exposure (AUC 28 days) in LI regimen at steady state during maintenance phase when administered at 5 mg/kg once every 4 weeks; source of human AUC data - Study IM103100 long-term extension.
[d]Exposure multiples based on AUCs in humans given belatacept during the first month, fourth month, or maintenance phase of LI regimen, respectively.

Genotoxicity

Genotoxicity testing is generally not required for protein therapeutics. No genotoxicity studies were conducted with belatacept. However, a battery of validated in vitro genotoxicity assays was conducted with abatacept.

Carcinogenicity

Long-term studies

A carcinogenicity study was not conducted with belatacept. A lifetime study (study nr 97610) in mice was conducted with abatacept to determine the carcinogenic potential of CD28 blockade. In this pivotal carcinogenicity study abatacept was administered at weekly intervals for up to 88 weeks. Mice were dosed at 20, 65 or 200 mg/kg providing exposure multiples of 0.7, 1.6, and 2.5 times at 20 mg/kg; 2, 4, and 7 times and at 65 mg/kg; and 3, 7, and 10 times at 200 mg/kg the AUCs in patients given belatacept during the first month, fourth month, or maintenance phase of the LI regimen, respectively. The Applicant claims that the presence of retroviruses can account for the increased frequency of lymphomas (1.7%M/11.7%F in the vehicle control group, 30%M/45%F in the 20 mg/kg/week group, 36.7%M/58.3%F in the 65 mg/kg/week group, 28.3%M/56.7%F in the 200 mg/kg/week group) and mammary tumours (4 females in the vehicle group, 3 females in the 20 mg/kg/week group, 7 females in the 65 mg/kg/week group and 10 females in the 200 mg/kg/week group) in this study.

Reproduction Toxicity

A complete battery of reproductive toxicity studies was conducted with belatacept, in addition to abatacept, to assess potential effects on fertility, reproductive function, gestation, parturition, and lactation of the parental generation in rats; on embryonic and fetal development in rats and rabbits; and on growth, development, reproductive performance and immune function of progeny in rats. In these studies belatacept was dosed daily to increase exposure relative to abatacept when dosed every 3 days.

Study DN06032 – Intravenous study of fertility and embryonic development in rats

Belatacept was administered intravenously once daily to groups of male and female rats at doses of 20, 65, or 200 mg/kg. The data shows that there were no effects of belatacept on male or female reproductive function (mating and fertility; estrous cycling in females) or early embryonic development of the offspring at doses as high as 200 mg/kg/day, the highest dose tested in this study.

Study DN06008 – Intravenous study of embryo-fetal development in rats

Belatacept was administered intravenously to groups of time-mated rats once daily on GD 6 through 15 at doses of 20, 65, or 200 mg/kg. There were no effects of belatacept on the dams at 20 or 65 mg/kg/day or on the fetuses at any dose tested. At 200 mg/kg/day, drug-related maternal toxicity consisting of a reduction in maternal body-weight gain (25% less than controls) was noted during the first few days of dosing (Days 6 to 9 of gestation). No other drug-related changes occurred during this study. There were no effects in the fetuses at any dose tested. Fetal exposures to belatacept were

verified in all treated groups, demonstrating that belatacept crosses the placenta. Fetal serum concentrations were found to be approximately 8 to 9% of maternal concentrations.

Study DN06002 – Intravenous study of pre- and postnatal development in rats

Belatacept was administered intravenously to time-mated rats (55/group) once daily at doses of 20, 65, or 200 mg/kg from GD 6 through lactation day (LD) 20. The rats were allowed to deliver naturally, and their litters were monitored for viability at birth and postnatal survival and growth. The data showed that belatacept-specific antibodies were not detected in serum or milk of drug-treated dams. Serum concentrations of belatacept in PND-21 pups were low (1.4% to 3.2% of maternal Cmax on LD 12), dose-related, and comparable between males and females. Belatacept was generally not detected in pups on PNDs 62-64. In these offspring, low incidence (10/120 rats) and magnitude (endpoint titers 11 to 77) of belatacept immunogenicity were noted on PNDs 62 to 112.

Belatacept at all doses was associated with changes in the dams and their F1-generation offspring.

Study DN06056 – Intravenous study of embryo-fetal development in rabbits

Belatacept was administered intravenously once daily to 4 groups of presumed-pregnant females (27 per group) on days 7 through 19 of gestation at doses of 10, 30, or 100 mg/kg. Fetal exposures to belatacept were verified in all treated groups, demonstrating that belatacept crosses the placenta. Fetal serum concentrations were found to be approximately 0.7 to 1.3% of maternal concentrations. There were no effects on the dose or fetuses at any dose. Belatacept did not affect embryo-development in rabbits at doses up to 100 mg/kg/day.

Juvenile studies

The toxicity of belatacept in juvenile animals has not been evaluated. However, the toxicity of abatacept (more active analogue in rodents) in juvenile animals was evaluated in a study in juvenile rats administered abatacept parenterally from postnatal day 4 to 93. Two additional pivotal studies (Study DN07013 and DS07165) were conducted in juvenile and adult rats to further investigate the etiology of the findings observed in the initial juvenile rat study.

The data show that abatacept has impact on the developing immune system as shown by increased bacterial infections and altered immune parameters. These animals also showed signs of autoimmunity (lymphocytic infiltration of the thyroid gland and pancreatic islets). Some of these findings were reversible over a 3-month treatment-free period. However, the infiltration of the pancreatic islet and thyroid gland increased in incidence and severity during the post dosing period. When administration was postponed to postnatal day 28, the amount of infections decreased but the immunological parameters and signs of pancreatic islets autoimmunity remained similar to animals administered on postnatal day 4. The lower incidence and severity of infections in this study, as compared to the first juvenile study, may be due to the conduct of the study under more microbiologically controlled conditions.

Local tolerance

Several studies were completed to assess the irritation potential following intravenous, intra-arterial, paravenous, or subcutaneous administration at concentrations or doses associated with human use. Overall, no significant injection-site irritation was observed.

Other toxicity studies

Study 99722 - Belatacept, mycophenolate mofetil (MMF), solumedrol, and Simulect®: Mono- and combination-therapy repeat-dose intravenous study in renal transplant recipient monkeys; histopathological evaluation

This study was conducted to evaluate the therapeutic effects of treatment with belatacept alone, in combination with MMF and solumedrol, or in combination with Simulect® (IL-2 receptor antagonist, bailiximab) following renal transplantation in rhesus monkey. From a safety point of view belatacept does not contribute to any significant histopathological findings in the transplanted kidney. Efficacy (duration of survival) is improved by belatacept addition to MMF, and solumedrol. The applicant has presented data showing the generation of allo-specific antibodies. The data show that belatacept is able to inhibit the formation such antibodies. The reason for not performing skin grafts was discussed by the applicant and considered as acceptable.

Study DS09027 – A 1-month intravenous investigative study in male monkeys

The objective of this investigative study was to assess the ability of belatacept to cross the blood-brain barrier and to investigate its effects on the presence of immune cells and the expression of CD80 or CD86 in the brain of healthy monkeys. The data showed that belatacept is not able to cross the blood-brain barrier in male monkeys.

Antigenicity

Belatacept, a fully human protein, was immunogenic in mice, rats, rabbits, and monkeys as shown by the ability of each species to induce belatacept-specific antibodies. However belatacept-specific antibodies were generally not detected during the treatment period of a study, suggesting that they were not formed until after belatacept serum levels had dropped below immunosuppressive levels; however, it cannot be ruled out that high serum belatacept levels may also have interfered with the detection of antibodies during and immediately after the dosing phase. Thus, in each species tested, belatacept appeared to suppress the antibody response against itself, allowing exposure to be maintained throughout the treatment period of each study. Once belatacept-specific antibodies were present, clearance of drug from the blood vascular compartment was often accelerated. In monkeys, the majority of the belatacept-specific antibody response was found to be directed toward the Ig domains, with a minor portion of the response directed toward the CTLA4 (CD80/86 binding) domains. The neutralizing properties of the response were not evaluated as this response generally appeared only after the treatment period was completed. The appearance of belatacept-specific antibodies was not associated with any acute or target-organ toxicity in any species.

2.3.5. Ecotoxicity/environmental risk assessment

No dedicated ecotoxicity/environmental risk assessment was performed for this medicinal product, which is in accordance with the applicable guidance. The active substance is a protein, the use of which is unlikely to result in significant risk to the environment. Therefore, belatacept is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

With regard to the mode of action, the CHMP raised that the potential of belatacept to block the inhibitory receptor CTLA-4 could enhance the immune response. Data from pharmacological studies suggested such activity at low doses. Such activity could also be part of the explanation to the unexpectedly strong immunogenicity of belatacept after a single dose in healthy volunteers. There was a concern that when belatacept exposure falls below a certain level (such as after an intended or

accidental treatment interruption), the enhanced immune response could have negative consequences on graft and patient survival. In response to this discussion of immune enhancement at low belatacept doses the Applicant has re-evaluated the data by performing an individual statistical intrapolation of antigen-specific endpoint titers from the mentioned mouse, rat and monkey studies. This re-evaluation has generated new figures in which end point titers from individual animals are presented in a way which makes the data more exhaustive. The new figures show no immune enhancement at low belatacept doses.

The Applicant has addressed the concern for immune enhancement after discontinuation of belatacept treatment by re-evaluating study 99655. In this study monkeys were treated weekly with belatacept for 6 months before KLH immunization followed 2 months of recovery. No statistically significant differences ($p \leq 0.05$) in endpoint titers of monkeys in the belatacept dose groups relative to vehicle control or evidence of a rebound effect was seen. In addition, the Applicant has evaluated the clinical data in search for signs of increased autoimmune events in patients treated with low doses. No such trend was found. Also, the Applicant has re-evaluated clinical data from subjects discontinuing belatacept treatment in search for signs of increased autoimmunity. In the phase 3 trials of the 14 autoimmune events observed, 13 were observed while on study drug when the belatacept concentrations are typically >2 μg/mL and one autoimmune event was observed at 45 days post discontinuation. There were no auto-immune events reported beyond 56 days post discontinuation of study medication when belatacept concentrations would be expected to be approximately 0.2-0.4 μg/mL. Again, the data show no signs of immune enhancement in form of increased risk for autoimmunity. Also, in the study in healthy volunteers there was no reported autoimmune event during the 116 days follow-up.

The mechanism by which belatacept could influence the function of CTLA-4 has been addressed indirectly by the Applicant by presenting data on CD86 expression on LPS stimulated dendritic cells after co-culture with CTLA-4 expressing Jurkat T cells in combination with belatacept. In this assay CTLA-4 expressing Jurkat cells are able to reduce the increased CD86 expression to background levels showing that CTLA-4 is able to negatively influence the maturation of dendritic cells. The data also show that belatacept is able to influence the CD86 expression in a dose-dependent manner by blocking the negative effects inflicted by the CTLA-4 expressing Jurkat cells, thus proving that belatacept could inhibit the negative function of CTLA-4. The Applicant claims that the effect seen is only observed at high belatacept concentrations, which are not reached in the clinic. Also, the concern originally raised was on effects at low belatacept concentrations, at which no impact on the negative function of CTLA-4 could be observed in the presented study. The Applicant also states that future studies into the actual function/signalling of CTLA-4 in T cells is difficult to perform due to limitation in available techniques and knowledge.

In conclusion, the Applicant has presented a re-evaluation of *in vivo* and clinical data to address the issue of possible immune enhancement. This re-evaluation has resulted in: new figures generated from the *in vivo* data which show no immune enhancement at low belatacept doses, data showing no signs of increased autoimmune events in patients treated with low doses, data showing no signs of increased autoimmunity in subjects discontinuing belatacept treatment and data reporting no autoimmune event in healthy volunteers during the 116 days follow-up. However, newly generated *in vitro* data indeed show that belatacept can influence the function of CTLA-4, but at concentrations which are much higher than the ones reached in the clinic. Also, the initial concern was for immune enhancement at low concentrations, at which no distortion of CLTA-4-fuction was observed *in vitro.* Thus, since the *in vivo* and clinical data do not support the initial concern of immune enhancement and since the newly generated *in vitro* data only show distortion of CTLA-4 function at high concentrations a possible immune enhancement effect is not a concern for belatacept.

Since the Fc portion of Ig fusion proteins has the potential to bind Fc receptors and mediate antibody-dependent cellular cytotoxicity (ADCC) as well as complement-dependent cytotoxicity (CDC), studies were conducted to evaluate the capacity of belatacept to mediate ADCC and CDC. The studies demonstrated that belatacept, at 30 µg/mL, did not mediate ADCC of a CD80/86 expressing human B-cell line (PM-LCL) by PBMC from 13 different normal donors. Increasing concentrations of belatacept up to 30 µg/ml, did not increase complement-mediated killing above the background level observed with complement alone.

In all species evaluated (mouse, rat, rabbit, monkey) belatacept is biologically active and complete suppression (≥98%) can be achieved at a species-dependent dose level or serum concentration. As such the efficacy and safety data generated in these species are considered relevant for the non-clinical assessment of belatacept.

Due to its normal inhibitory function, autoimmune reactions are a theoretical risk when blocking the function of CTLA-4. The collective data suggests that autoimmune reactions are not induced or exacerbated when blocking CD28/CTLA-4 binding to CD80/CD86. There are a few a signals that do indicate autoimmunity:

a) In a spontaneous model of diabetes (NOD mouse), CTLA4-Ig injections before diabetes onset resulted in faster diabetes onset.

b) CD28 deficient NOD mice spontaneously develop autoimmune pancreatitis.

c) Administration of high doses of abatacept resulted in inflammation in the thyroid and pancreas.

In general, the pharmacology study program is adequate and supports the concept of belatacept immunosuppression.

The PK of belatacept is typical for an IgG1 fusion protein, being characterized by slow elimination, limited extravascular distribution, and sensitivity to the carbohydrate composition of the molecule. While there were differences between species in PK, of the species tested, the PK parameters in the primary toxicology species (monkey) were most similar to those observed in humans. While dose-dependent nonlinear PK was observed in some species, increases in exposure were roughly proportional to dose in the clinical dose range. Anti-belatacept antibodies were detected once serum belatacept concentrations had fallen to low levels; in some cases this was associated with a discernable acceleration in the decline in serum belatacept concentrations.

The presented toxicology program includes multiple studies in monkey (up to 1 year in repeat-dose studies), mice (6 months repeat-dose and lifetime carcinogenicity studies), rat (3 months repeat-dose and reproductive/developmental studies) and rabbit (local tolerance and embryo-foetal studies). As to improved function over abatacept monkey is the most relevant species. In rodents abatacept is more immunosuppressive than belatacept. However, in both cases similar immunosuppression could be achieved by increased dosing/exposure. Therefore, with respect to potency, exposure and dose all species used in the safety testing are regarded as relevant.

The most noteworthy findings in any of the repeat-dose toxicity studies are related to the pharmacology of the drug. Minimal mean decreases from pretreatment serum IgG levels were observed in monkey (one month treatment at AUC exposures 3.5 to 52.8 times the clinical), with levels generally returning towards baseline values during the dose-free observation period. At the end of dosing, minimal to moderate, non-dose-dependent decreases in the number and diameter of germinal centers in lymph nodes and spleen was also observed in monkey. In both of these organs, mild to moderate decreases in the number and diameter of germinal centers, containing fewer centrally located blast cells (centrocytes) and peripherally located small lymphocytes, were observed

reflecting decreased germinal center activity. These findings were evident at all doses (6 months treatment at AUC 1.2 to 20.6 times the clinical exposure) and were present to a very slight degree (background level) in the controls. Complete recovery occurred during dose-free recovery.

One year abatacept treatment (at exposures levels 1.8 to 31.6 times the clinical) did not result in any clinical manifestation associated with a viral infection even although prestudy viral screening indicated previous exposure of all monkeys to one or more of the following viruses: LCV (EBV-like virus), Herpes B, rhesus CMV, and simian papovavirus (SV40; JC-like virus). No viral screening was performed in any the belatacept monkey studies. Overall there is a lack of data on viral immunity throughout the belatacept monkey studies. It would have been valuable to the safety assessment to be able to address the levels of viral-specific antibodies and viral antigen-specific T cells after long-term belatacept treatment, especially since belatacept is a more potent immunosuppressant than abatacept and since clinical viral reactivation can contribute to graft rejection. In the clinic, belatacept will be administered together with several other immunosuppressants and prophylactic antiviral drugs. As such, data showing the impact of belatacept on viral immunity will be hard to extract from clinical experience. On the other hand there are major species differences between human and monkey viral tropism and in combination with the absence of clinical viral manifestations in the monkey studies the lack of specific viral immunity data is acceptable.

In the rat three month repeat-dose study, both doses of abatacept (4.8 to 63 times the clinical exposure) were associated with lymphocytic inflammation of thyroid (thyroiditis; 6%) and pancreatic islets (18%) with higher incidence at Week 21 than at Week 14. These findings are consistent with a possible autoimmune etiology. Similar findings were reported from juvenile toxicity studies. These data have been described in section 5.3 of the SPC.

In the pivotal carcinogenicity study abatacept was administered at weekly intervals for up to 88 weeks. Mice were dosed at 20, 65 or 200 mg/kg providing exposure multiples of 0.7, 1.6, and 2.5 times at 20 mg/kg; 2, 4, and 7 times and at 65 mg/kg; and 3, 7, and 10 times at 200 mg/kg the AUCs in patients given belatacept during the first month, fourth month, or maintenance phase of the LI regimen, respectively. The Applicant claims that the presence of retroviruses can account for the increased frequency of lymphomas (1.7%M/11.7%F in the vehicle control group, 30%M/45%F in the 20 mg/kg/week group, 36.7%M/58.3%F in the 65 mg/kg/week group, 28.3%M/56.7%F in the 200 mg/kg/week group) and mammary tumours (4 females in the vehicle group, 3 females in the 20 mg/kg/week group, 7 females in the 65 mg/kg/week group and 10 females in the 200 mg/kg/week group) in this study. It is the CHMP's opinion that this is a plausible explanation especially since abatacept has been show to be non-genotoxic. These data could refer to the human situation as an increased risk for virally induced malignancies. Breast cancer cases were reported in core clinical studies and mammograms were performed at inclusion and yearly thereafter (see clinical issues).

A complete battery of reproductive toxicity studies was conducted with belatacept to assess potential effects on fertility, reproductive function, gestation, parturition and lactation of the parental generation in rats; on embryonic and fetal development in rats and rabbits; and on growth, development, reproductive performance and immune function of progeny in rats.

Fetal exposures to belatacept were verified and demonstrated that belatacept crosses the placenta. Fetal serum concentrations were found to be approximately 0.7% (rabbit, at 3 to 66 times the clinical exposure) to 9% (rat, at 4 to 87 times the clinical exposure) of maternal concentrations. Additionally, dose-related levels of belatacept were present in maternal milk in rat at approximately 9 to 13% of those in the serum (at 4 to 87 times the clinical exposure).

In rats, belatacept at all doses was associated with changes in the dams and their F1-generation offspring (dosed 20, 65 or 200 mg/kg/day from gestation day 6 though lactation day 20, 4 to 87 times the clinical exposure). In the dams, there were dose-dependent clinical toxicities (2, 3 and 5 dams at

20, 65 and 200 mg/kg/day, respectively) including signs of dehydration, soft/liquid feces, scant/absent feces, ungroomed coat, urine-stained abdominal fur, and hunched posture, pronounced body-weight loss and marked reductions in food consumption. In the F1-generation the observed toxicity included increased pup mortality (at all doses, 44-100% pup losses on PND 1-18), reduced weights, signs of dehydration, coldness to touch, decreased motor activity, absence of milk band, absence of maternal nursing or nesting, emaciation, ungroomed coat and reduced serum IgG levels. The clinical toxicities seen in the rat pre- postnatal study are considered to be attributed to opportunistic infection, secondary to pharmacologically mediated immunosuppression. Collectively, pup mortality in these litters is consistent with compromised maternal care (nesting and/or nursing) and/or nutritional support (milk production); and is thus considered secondary to maternal toxicity (these findings were restricted to 3.8-9.6% dams in all treated groups). All pups showed signs of immunosuppression by reduced IgG levels, however this finding was not accompanied by any toxicity or signs of autoimmunity.

The toxicity of belatacept in juvenile animals has not been evaluated. However, the toxicity of abatacept (more active analogue in rodents) in juvenile animals was evaluated in a definitive study in juvenile rats administered abatacept parenterally from postnatal day 4 to 93. Two additional pivotal studies were conducted in juvenile and adult rats to further investigate the etiology of the findings observed in the initial juvenile rat study. The data show that abatacept has impact on the developing immune system as shown by increased bacterial infections and altered immune parameters. These animals also showed signs of autoimmunity (lymphocytic infiltration of the thyroid gland and pancreatic islets). Some of these findings were reversible over a 3-month treatment-free period. However, the infiltration of the pancreatic islet and thyroid gland increased in incidence and severity during the post dosing period. When administration was postponed to postnatal day 28, the amount of infections decreased but the immunological parameters and signs of pancreatic islets autoimmunity remained similar to animals administered on postnatal day 4. The lower incidence and severity of infections in this study, as compared to the first juvenile study, may be due to the conduct of the study under more microbiologically controlled conditions. In conclusion abatacept and most likely also belatacept show signs of potential juvenile secondary toxicity. The findings in these three studies have been described in 5.3 of the SPC. The data presented in these studies indicate a potential clinical risk when using belatacept during pregnancy. These risks include both an increased risk for infections (which most likely is attributed to the immunosuppressive action of belatacept), but also an increased risk for immune enhancement as shown by autoimmune reactions. Overall, the data show that belatacept has a negative impact on the developing immune system and should therefore not be used in later phases of pregnancy.

In local tolerance studies performed in rabbit reactions were mild to moderate at the site of belatacept administration. The reactions were in many cases similar in the belatacept and vehicle control groups. The results provide evidence for a good local tolerance of belatacept.

The Applicant refers to a combined belatacept safety and efficacy study in which selected organs were microscopically analyzed to assess and compare potential drug-related toxicities when the immunosuppressive compounds were administered simultaneously, relative to single-agent administration following renal transplantation in monkeys. Data show that efficacy (duration of graft survival) is improved by belatacept addition to MMF, and solumedrol. From a safety point of view belatacept does not contribute to any significant histopathological findings in the transplanted kidney.

A dedicated belatacept CNS study was conducted in monkeys with the intention to establish if belatacept crosses the blood-brain barrier and if belatacept has effects on the CNS immune cells expressing CD80 or CD86. Data show that belatacept does not cross the blood brain barrier in healthy monkeys.

No amino acid sequence comparison has been presented by the applicant in which all the parts of the belatacept constructs are aligned with corresponding amino acid sequences for the various species used in safety testing. When looking at the amino acid sequence within the CLTA-4 coding region rhesus monkeys and humans share all but one amino acid. As such this part of the construct is most likely less immunogenic in rhesus monkeys than in mice or rats which have a more heterogeneous sequence compared to humans. However, the amino acid sequence coding for the construct fusion regions will most likely be more immunogenic due to the formation of neoantigen. This is also true for humans. In addition, other amino acid species differences in the sequence will be immunogenic, for instance within the Ig domain. In the species tested, drug-directed antibodies appeared generally when belatacept serum levels had dropped below immunosuppressive levels. Taken the neo-antigenic nature of belatacept, it is a theoretical risk that this also could take place in humans at low serum levels, for instance after miss-dosing or after discontinuation of treatment (i.e. after graft rejection). In such events, retreatment with belatacept could be hampered by preformed drug-directed antibodies, for instance in case of retransplantation.

2.3.7. Conclusion on the non-clinical aspects

Overall the non-clinical program conducted by the Applicant meets the requirements and the data are acceptable. The initially raised concerns regarding the mode of action and the potential risk for enhanced immunity were adequately addressed by the Applicant hence this issue is resolved. As expected for this type of product there are potential risks associated with belatacept treatment during pregnancy, increased risks for infections and risks associated with tumour formation; these will need to be addressed with clinical data. The SmPC adequately reflects the non-clinical findings.

2.4. Clinical aspects

2.4.1. Introduction

The Phase 3 program was composed of two randomized, active-controlled, partially-blinded global studies in de novo renal transplant patients receiving allografts from a broad range of donor types. Both studies evaluated 2 belatacept dose regimens, which were compared to CsA. In the studies, belatacept was administered in conjunction with basiliximab induction, mycophenolate mofetil (MMF) and corticosteroids.

Scientific advice on the phase III program for belatacept was received from the EMEA in February 2005 (EMEA/CHMP/SAWP/44749/05) and resulted in the inclusion of acute rejection (AR) as a third primary endpoint in study IM103008.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Phase 2 and 3 clinical studies with belatacept in transplant recipients

Study Number	Objectives	Study Design (No. of Sites)	Type of Subjects	Dosage Regimen Background Therapy	Study Duration	No. Subjects[a]
Core Studies						
IM103008	Efficacy, safety, immunogenicity, PK	Phase 3, randomized, partially-blinded, active-controlled (100 sites)	De novo renal transplant, SCD	IV belatacept[b] (MI and LI) or CsA[b] Basiliximab induction, maintenance with MMF + corticosteroids	3 years	Bela MI: 219 Bela LI: 226 CsA: 221
IM103027	Efficacy, safety, immunogenicity, PK	Phase 3, randomized, partially-blinded, active-controlled (79 sites)	De novo renal transplant, ECD	IV belatacept[b] (MI and LI) or CsA[b] Basiliximab induction, maintenance with MMF + corticosteroids	3 years	Bela MI: 184 Bela LI: 175 CsA: 184
IM103100	Efficacy, safety, immunogenicity, PK Efficacy, safety	Phase 2, randomized, partially-blinded, active-controlled (41 sites) Long-term extension (20 sites)	De novo renal transplant	IV belatacept[c] (MI and LI) or CsA[c] Basiliximab induction, maintenance with MMF + corticosteroids Belatacept: 5 mg/kg every 4 or 8 wks IV; or CsA MMF or another approved IMPDH + corticosteroids (weaning/withdrawal permitted)	12 months Through Year 11 (Month 131)[d]	Bela MI: 74 Bela LI: 71 CsA: 73 Entered Year 2 Bela MI: 52 Bela LI: 50 CsA: 26
Other Phase 2 Studies						
IM103010	Efficacy, safety, immunogenicity, PK	Phase 2, randomized, open-label (34 sites)	Maintenance renal transplant	IV belatacept[e] or CNI MMF, MPA, SRL, or AZA ± corticosteroids	12 months	Bela: 84 CNI: 89
IM103034	Efficacy, safety, immunogenicity, PK	Phase 2, randomized, open-label (20 sites)	De novo renal transplant	IV belatacept MI[b] or TAC[f] All, thymoglobulin induction + MMF or SRL	12 months	Bela+MMF: 33 Bela+SRL: 26 TAC+MMF: 30

2.4.2. Pharmacokinetics

In total, 13 studies contributed to clinical pharmacology in healthy volunteers [IM103001, 3024, 3029, 3038, 3046], in renal transplant subjects [3010, 3034, 3047, 3100, 3100LTE, 3008, 3027], and in patients with Rheumatoid arthritis [3002].

Standard pharmacokinetic data analysis has been utilized. Both non-compartmental methods and nonlinear mixed effects modelling have been applied.

A total of three different bioanalytical methods (at two sites: BMS and PPD) were used for the determination of belatacept in serum (BMS Manual Method, BMS Automated Method and PPD Manual Method). The bioanalytical method seems adequately validated and the analyses at the two sites were cross-validated.

To characterize the PK of mycophenolic acid (MPA) in stable renal transplant patients receiving either a belatacept-based or a CsA-based regimen, a LC-MS/MS bioanalytical method was developed and validated.

Absorption

Belatacept is intended for iv administration hence bioavailability is by definition 100 %.

Three formulations, A, B and C, have been used during development due to the manufacturing process being changed twice. When comparing belatacept manufactured by process C and B, PK differ due to a reduction in CL with process C resulting in a 20 % higher AUC. This is not considered critical as the difference is small and most importantly, phase 3 was conducted with belatacept manufactured by process C. Regarding the comparison with process A, no definite conclusions can be drawn due to the comparison being done between studies. However, no marked difference between processes A, B and C in PK is expected based on the results.

Distribution

The typical reference volumes determined by POP-PK were 3.59 L and 5.11 L for the central compartment and the peripheral compartment (in total 8.7 L or 0.12 L/kg), respectively (reference body weight 75 kg).

The determination of volume of the central and peripheral compartments determined by the population analysis is consistent with the Vss determined by non-compartmental analysis (0.10 L/kg, 0.12 L/kg, 0.11 L/kg based on studies IM103024, IM103047, IM103100, respectively).

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. Preclinical brain distribution data further supports this statement.

Elimination

No studies of the metabolism of belatacept in humans were conducted. Like most therapeutic proteins, belatacept is not expected to be metabolized by CYP.

It is expected that the high molecular weight (approximately 90 kD) of belatacept precludes renal excretion as a route of elimination. There is limited data on renal excretion. In one study (IM103047), urine data was collected from 4 subjects with proteinuria. All subjects had low but measureable belatacept concentrations.

The elimination half-life in serum was about 8-10 days. Plasma clearance was about 0.5 ml/h/kg.

Overall in subjects receiving belatacept as a component of a 4-agent immunosuppressive regimen in the Phase 3 studies and the 4-week schedule of IM103100LTE, drug specific antibodies against belatacept were developed in 4.4 % (37/847) of the subjects during treatment. Based on the presented data, antibodies directed towards belatacept seem not to affect belatacept clearance, but the data are limited.

Dose proportionality and time dependencies

Data on dose proportionality is found in study IM103001. This was a randomized, double-blind, placebo-controlled, sequential escalating single dose study of belatacept (produced by Process A) administered intravenously over 1 hour in 40 healthy subjects. Groups of 8 subjects (6 subjects on belatacept and 2 subjects on placebo) each were assigned to one of five dose levels; 0.1, 1.0, 5.0, 10 or 20 mg/kg of belatacept or placebo. The data showed that belatacept seems to exhibit dose proportionality within 1-20 mg/kg. The population PK analysis did not include a formal analysis of time dependency but supported time invariant PK since the plots of conditional weighted residuals and weighted residual versus time after first dose revealed no trends.

Special populations

Intra- and inter-individual variability

In the final model, interindividual variability in CL, central volume of distribution and peripheral volume of distribution were 21.4%, 17.7% and 28.8% CV respectively. Interoccasion variability was estimated in the base model only and was about 9% for CL.

Impaired renal function

No formal renal impairment study has been performed. The pharmacokinetic profile of belatacept seems not to be affected by varying degrees of renal function. The proposed SPC text in section 4.2 is acceptable.

Impaired hepatic function

No specific study in patients with hepatic impairment was performed. It is generally accepted therapeutic proteins are eliminated by catabolism and/or receptor-mediated processes and not by hepatic metabolic clearance. The proposed SPC text in section 4.2 is acceptable.

Gender

Based on the POP-PK analysis, the effect of gender on the clearance of belatacept was not clinically relevant.

Race

Based on the POP-PK analysis, the effect of race on the clearance of belatacept was not clinically relevant.

Weight

The data show that the relation between the CL and V is not directly proportional to body weight therefore there is a slight increase in exposure with increasing body weight when dosed by body weight. Between 12 and 25% higher median Cmax and Cmin was observed in obese subjects compared with non-obese subjects was observed. Overall there is no strong indication that the increase in exposure in obese subjects is of relevance and hence the suggested dose by body weight is considered appropriate also for obese subjects from a pharmacokinetic point of view.

Elderly

Although the number of subjects above 75 years is not extensive there is no obvious trend of decreased clearance and the observed slight decrease in clearance with age is not clinically relevant.

Pharmacokinetic interaction studies

No i*n vitro* and i*n vivo* studies on the interaction potential of belatacept have been performed. The interaction potential for belatacept is likely low.

The applicant has investigated the interaction between CsA and mycophenolic acid. The Phase 3 program was composed of 2 randomized, active-controlled, partially-blinded global studies in de novo renal transplant patients receiving allografts from a broad range of donor types. Both studies evaluated 2 belatacept dose regimens, which were compared to CsA. In the studies, belatacept was administered in conjunction with basiliximab induction, mycophenolate mofetil (MMF) and corticosteroids. These adjunctive agents were also used in the comparator group. Dose normalised MPA, which is the active moiety of MMF, Cmax and AUC were approximately 22% and 41% higher, respectively, in subjects receiving belatacept compared to subjects receiving CsA.

In study IM103034 it was observed that belatacept concentrations were higher in the sirolimus group vs. the MPA group, but there were large overlaps in exposure and no relevant interaction between the agents was concluded.

2.4.3. Pharmacodynamics

Mechanism of action

Belatacept is a CD28-selective costimulation blocker. It is a fully human, soluble, recombinant fusion protein of the extracellular domains of CTLA-4 and a fragment of a modified F_c portion of human IgG. It is produced by recombinant DNA technology in a mammalian cell expression system. During the development program, belatacept was known as BMS-22481 and as LEA29Y.

T cells require at least 2 signals for full activation, an antigen-specific signal (*signal 1*) and a *costimulatory signal* (*signal 2*). *CD28* is a cell surface receptor that is constitutively expressed on T cells. It is a counter-receptor for the costimulatory molecules CD80 (B7-1) and CD86 (B7-2), which are expressed on APCs. Binding of CD28 to CD80 or CD86, along with the antigen-specific signal described above, triggers intracellular signalling pathways that result in the expansion of antigen-specific T cells. The CD28 costimulation lowers the threshold for T cell activation. Belatacept binds with high avidity to CD80 and CD86 receptors on APCs, thereby inhibiting the interaction of CD80/CD86 with CD28 and, thus, CD28-mediated costimulation of T cells.

Primary and Secondary pharmacology

Primary pharmacology

Belatacept's capacity to saturate its targets and to inhibit CD28-mediated T-cell costimulation, proliferation, and cytokine production in response to antigen was shown in several in vitro studies. Belatacept is a potent inhibitor of T-cell activation. These studies demonstrated that the 2 amino acid substitutions in belatacept not only enhance binding to CD80 and CD86 as compared to abatacept, but also result in a 5-10-fold increase in immunomodulatory activity in vitro. A number of in vitro experiments were performed to evaluate the effect of belatacept on T-cell responses stimulated by allogeneic monocyte-derived dendritic cells. In these models, approximately 10 µg/mL and above of belatacept was necessary for maximal inhibition of both cytokine production and T-cell proliferation in these dendritic cell-driven mixed lymphocyte response (MLR) assays. In some of these studies, belatacept's capacity to saturate CD80 and CD86 on the APCs was also evaluated. Concentrations of approximately 0.1 µg/mL belatacept maximally saturate CD80 molecules on the surface of APCs in whole blood, as well as on cultured dendritic cells in a MLR assay; however, these concentrations are insufficient for full inhibition of T-cell responses to allo-antigen. The concentration of belatacept required to maximally saturate CD86 is higher, at least 10 µg/ml. This is approximately the concentration of belatacept required to fully inhibit both IFNγ production and T-cell proliferation in these DC-driven MLRs. These data suggest that to fully inhibit T-cell proliferation and cytokine production, the interaction of both CD80 and CD86 with CD28 needs to be blocked by belatacept. Based on these in vitro data, the target concentration of belatacept in the clinic are greater than 0.1 µg/ml and thus would probably be sufficient to fully block CD80 at all times. The trough concentrations of belatacept observed clinically in the first month after the transplantation (C_{min} > 20 µg/ml) would be predicted to fully saturate CD86 and inhibit T cell responses (~90%) during this first period after transplantation when the risk of rejection is highest. As the dose of belatacept is attenuated during months 2-4, and again during the maintenance phase, the belatacept exposure is reduced, and therefore reduced CD86 saturation and T-cell inhibition during these periods could be predicted.

Additional assays were performed to evaluate the ability of belatacept to inhibit the proliferation and cytokine production by T cells in both a primary and secondary MLR assay in vitro. Belatacept was found to be 5 - 10-fold more potent at inhibiting these in vitro immune responses than abatacept.

Measurement of IL-2, IL-4 and IFNγ was performed on culture supernatants collected 24 hours post primary and secondary stimulation. In the primary MLR assay, only IL-2 was detectable and the EC50 of belatacept for inhibition of IL-2 production in the primary MLR was 0.04 µg/ml. In the secondary MLR IL-2, IL-4 and IFNγ were produced at detectable levels and it appeared that belatacept's EC50 for inhibition of IL-2, IL-4 and IFNγ production in the secondary MLR were 0.03 µg/ml, 0.20 µg/ml and 0.14 µg/ml respectively. The data suggests that belatacept is an inhibitor of both primary and secondary in vitro immune responses to allo-antigens.

Other *in vitro* experiments were also performed to evaluate the effect of belatacept on T-cell responses stimulated by allogeneic, monocyte-derived, DCs**.** The potency for inhibition of T-cell proliferation and cytokine production in the DC-driven MLR was confirmed in these experiments. The range of belatacept concentrations required to inhibit the proliferation of T cells in these MLR assays by 50% was 0.18 - 0.20 µg/ml and the range to inhibit cytokine production in these assays by 50% was 0.03 - 0.16 µg/ml. Belatacept also inhibited human memory responses to tetanus toxoid in vitro as measured by T-cell proliferation.

A concentration-dependent inhibition of proliferation was observed with belatacept achieving an IC50 of 0.40 µg/ml. The relationship between these results and the maintenance of an *in vivo* memory response to a pathogen is unclear. The effect of CD28 blockade *in vivo* on memory immune responses would depend on the nature of the protective memory immunity (e.g. antibody-mediated, CD8+ CTL-mediated etc), which would be pathogen specific. Belatacept effectively inhibited both primary and secondary T-cell responses to allogeneic antigen *in vitro*, confirming that the enhanced binding properties of belatacept resulted in high functional potency. Belatacept should therefore potently inhibit the T-cell responses against allogeneic antigen *in vivo*, which are induced following solid organ transplantation.

Selection of dose regimens: The LI and MI dosing regimens of belatacept investigated in the phase 2/3 studies were constructed using an integrated assessment of belatacept PK, PD and clinical efficacy and safety data from in vitro, nonclinical and clinical studies. In the dendritic cell-simulated mixed lymphocyte reaction (MLR) assay, the maximal inhibition of alloresponse by belatacept began to plateau around 10 µg/ml, concentrations that would result in maximal inhibition of CD80- and CD86-mediated costimulation or allogeneic antigen immune response of CD4+ T cell proliferation and maximal inhibition of production of cytokines IFNγ, IL-2 and TNF-α. Based on these data and on belatacept concentrations needed to inhibit the alloresponse, the belatacept concentrations were selected for the clinical studies, to provide maximal inhibition of the alloimmune response. The CD80/86 receptor occupancy assay was then established and the set target concentrations were shown to provide high degrees of CD80/86 receptor saturation.

From the biomarker data generated, the conclusion was drawn by the Applicant that the belatacept regimens studied provide a sufficient level of target saturation to inhibit immune responses to the graft, in combination with the co-administered other immunosuppressive drugs. These data was the basis for the selection of doses for the primate renal transplant study to achieve transplant efficacy. The selected target concentrations were ≈20 µg/ml for the first month followed by ≈7 µg/ml up to day 90 and then ≈2 µg/ml up to day 365. These concentrations provided approximately 80 % inhibition of the alloresponse during the first 3 months and approximately 50 % or greater inhibition of the alloresponse later. These concentrations were confirmed by the receptor occupancy assay to produce about 60 % CD86 receptor occupancy and complete CD80 receptor occupancy in vitro. With belatacept monotherapy in doses providing the target concentrations of belatacept, median survival time was 45 days compared to 6 days for the control treatment in the primate model. When basiliximab, MMF and steroids were coadministered with belatacept, survival time was prolonged to 112 days, while a

combination of basiliximab, MMF and steroids resulted in 22.5 days survival, and CsA plus steroids that resulted in a median survival time of 28 days in this primate model. There appeared to be a relationship between C_{min} of belatacept and prophylaxis of acute rejection in the primate transplant model. A belatacept C_{min} of 3 – 30 µg/ml seemed to be adequate during the engraftment phase and the initial phase post transplantation while a C_{min} of 0.005 – 1.5 µg/ml seemed appropriate during the maintenance phase to prevent acute rejection.

Thus, dose selection for phase 2 studies was based on the in vitro data, preclinical study data referred to above, data from phase 1 safety/tolerability study IM103001 in healthy subjects, plus a pilot dose ranging phase 2 clinical and safety study in subjects with RA (IM103002). No traditional sequential dose escalation study was undertaken. The doses selected for initial and maintenance phases following transplantation were 10 and 5 mg/kg IV, respectively. Study IM103100 formed part of the basis for selection of belatacept dosage schedules brought forward to the two pivotal studies IM103008 and IM103027.

Based on data from study IM103002 and also on data from PK modelling and simulation, it was concluded that the belatacept LI and MI dosing regimens with the 10 and 5 mg/kg doses would provide the targeted C_{min} concentrations. During the maintenance phase after transplantation, a 8 week versus a 4 week dosing schedule was evaluated to target maintenance C_{min} of 0.25 or 2 µg/ml, respectively. The rate of subclinical ARs and the immunogenicity was about 2-fold higher during the long-term extension when subjects were reallocated from the 4-week maintenance regimen to the 8-week maintenance schedule. Both LI and MI dosing regimens were carried forward to phase 3 studies as they were both considered to have shown acceptable efficacy and safety in phase 2. In clinical studies, approximately 90 % of the patients treated with the LI dosing regimen achieved target C_{min} of 20 µg/ml during month 1, 5 µg/ml during months 2 and 3, and 2 µg/ml thereafter during the maintenance phase.

Relationship between plasma concentration and effect: A time-to-event model was developed to characterise the E-R relationship between belatacept serum concentrations (as a time-varying variable) and time-to-first acute rejection (defined as central biopsy proven rejection that was either clinically suspected by protocol defined reasons or clinically suspected by other reasons and treated) up to 1 year after transplant in patients included in studies IM103008 and IM103027. The hazard (instantaneous probability) of acute rejection at a given time was assumed to be related to the serum concentration at that time. No time delay in effect was included. The analysis demonstrated that the hazard of acute rejection decreases with time, increases with baseline body weight and is higher in mismatched HLA (≥2 mismatched) and in North America and Europe (relative to South America, Asia and Africa) while belatacept serum concentration was not a significant predictor, i.e. there is insufficient evidence of a relationship between serum concentration and the risk of acute rejection.

Exploratory E-R analysis was performed by graphical examination of the relationship between observed trough belatacept serum concentrations and each of the following efficacy or safety endpoints: AR (up to 1 year after transplant), CMV infection, PTLD, PML detected up-to database lock (30/Jun/2008 for IM103027 and 21/Jul/2008 for IM103008) and cGFR measured within 1 year after transplant. There was no obvious relation between exposure and acute rejection or cGFR nor between exposure and CMV, PTLD or PML (very limited number).

Therapeutic Drug Monitoring (TDM): Dose was found to be a good predictor of belatacept exposure. Renal function is not a covariate of belatacept clearance, meaning that no dose reduction of belatacept is necessary during the period directly after renal transplantation even if renal function is impaired. Over a 1-year period, the overall mean variability for belatacept C_{max}, C_{avg}, and C_{min} was 15 %, 23 % and 47 %, respectively. On these grounds, the Applicant claims that therapeutic monitoring (TDM) of

belatacept is not necessary as the drug is not nephrotoxic, does not have a narrow therapeutic index and the risk of drug-drug interaction is low.

Secondary pharmacology

No clinical studies regarding secondary pharmacology. This is in concordance to non-clinical part of the application without experimental studies on secondary pharmacodynamics, since there is no evidence of off target biological effects with belatacept.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Across studies, belatacept exhibits a consistent PK profile with a low volume of distribution (similar to the vascular space) and a low clearance (leading to an elimination half-life of about 8-10 days). These characteristics are as expected given that belatacept is a large therapeutic protein including a domain of a human IgG1 antibody.

The lack of studies on protein binding and metabolism is acceptable as this is a therapeutic protein.

The POP-PK analysis was developed based on data in healthy subjects and renal transplant patients (studies IM103001, IM103008, IM103024, IM103027 and IM103100). A two-compartment model with linear elimination could adequately describe the data. No clinically relevant effect of age, race (caucasian subjects, black subjects, Asian/Pacific islander subjects), sex, renal function including dialysis, diabetes or dose level (5 or 10 mg/kg) was identified in the POP-PK. The only identified significant patient factor influencing belatacept pharmacokinetics is body weight. A body weight based dosing of belatacept was therefore used in phase 3. As the relation between the CL and V is not directly proportional to body weight, there is a slight increase in exposure with increasing body weight although dosed by body weight. The Applicant was asked to discuss degree of obesity in the population and the risk of overexposure with dosing by total body weight. A number of obese subjects were included in the population and the observed increase in exposure was relatively small in this group of patients. No difference between non-obese and obese was detected in the subgroup analysis for safety (see further discussion on safety below).

In one study (IM103047), urine data was collected from 4 subjects with proteinuria. All subjects had low but measureable belatacept concentrations. Proteinuria was rather frequent in phase 3 and therefore a graphical exploration of POP-PK data has been provided indicating a tendency toward higher clearance in subjects with proteinuria, but the effect appears limited.

The pharmacokinetic profile of belatacept seems not notably affected by varying degrees of renal function (calculated GFR). Analysis of Ctrough versus measured and calculated GFR at 12 months revealed no obvious effects and the data support that no dose adjustments are needed in patients with renal impairment.

No study in hepatically impaired subjects has been performed which is generally acceptable for this kind of therapeutic protein. The lack of data is reflected in the SmPC.

In the Phase 3 studies and with the 4-week schedule of IM103100LTE, 6 subjects had neutralizing antibodies. Graphical analyses of effects of antibodies (including specific analysis for neutralizing antibodies) on PK parameters have been submitted. No major effects on clearance could be identified but the data are very limited. Conclusions on the relationship between antibodies against belatacept (neutralising and/or non-neutralising) and efficacy or safety are not very robust due to the low numbers of patients with antibodies and more data are to be collected post-approval.

As there were remaining questions on the data presented by the Applicant on timing of infusional events in core studies, further assessment to rule out immunogenicity is needed and the Applicant has presented an appropriate program for postapproval further follow up of peri-infusional event.

The interaction potential for belatacept is considered low and the lack of interaction data is acceptable.

Regarding the interaction between CyA and MPA, it is difficult to determine the contribution of one drug or its exposure to the overall safety and efficacy of an immunosuppressant regimen. Accordingly, it is unclear whether the increased exposure to MPA has any clinically meaningful contribution to the efficacy and safety of a belatacept-based regimen. This was further discussed by the Applicant; the circumstance that patients on belatacept (and resulting higher MPA exposure), did not show an increase in MPA-related adverse events is an argument against a detrimental effect of this higher MPA exposure in belatacept treated subjects.

The Applicant discussed the possible benefits of therapeutic drug monitoring in order to avoid under- or over immunosuppression. In the response no new arguments have been put forward. No potential cut-offs for exposure response or safety has been identified. It is agreed that TDM is not warranted.

Pharmacodynamics

The mechanism of action for belatacept has not been clarified in all details and there is a theoretical possibility that different immunological mechanisms could be involved, depending on the dose administered. Receptor occupancy for belatacept is higher for CD80 than for CD86. The Applicant has discussed if this difference in binding could mean that low concentrations of belatacept could result in other types of immune modulation than those that seen with higher concentrations, (e. g. an altered balance between Th1 and Th2 cells and/or different lymphokine production). The Applicant has further discussed additional possible mechanisms of action, without the occurrence of new data that would influence the clinical safety perspective. The effects of CD80/86 blockade on host pathogen defense have been studied in several preclinical models. The Applicant has discussed how belatacept affects the human host pathogen defense against different classes of pathogens. The CD28 costimulation seems to be more important following initial exposure to a pathogen than in the chronic phase of a polyoma virus infection and the same is most likely true for exposure to mycobacteria while exposure to other kinds of pathogens do not exhibit the same difference between initial exposure and reexposure.

In the exposure-response analysis, no relation between belatacept serum concentration and efficacy (acute rejection and cGFR) or safety (CMV infection, PTLD or PML) has so far been identified. A direct relation between exposure and AR could not be verified. Although some minor trends were observed, no clear relations or cut-offs for potential monitoring and dose adjustments could be identified based on these analyses. In the graphical analysis, it was observed that the cGFR is constantly lower in the highest exposure quartile in study IM103008, and the Applicant was asked to discuss possible reasons for this. The Applicant provided some additional data on the exposure response. The presented number of acute rejections was rather different between the two studies IM103008 and IM103027. Separate graphical analysis for the two studies was provided for AR and safety measures. The separate graphical analysis was largely consistent with the pooled data. Possible reasons for the higher risk of acute rejections in subjects with high body weight and appropriateness of the body weight based dosing in obese was discussed but a relation between high dosing in the highest weight group and safety parameters could not be verified.

The Applicant provided reasonable explanations and sufficient data from in vitro studies, preclinical studies, and early clinical studies to justify the dosage used in phase 3 studies. The Applicant could satisfactorily justify why the 4 week maintenance dose schedule instead of the 8 week maintenance

dose schedule also investigated in study M103100 was selected, as more acute rejections were seen in the 8 week dosing group.

In light of the outcome of the phase III studies, a post hoc discussion on the adequacy of the targeted occupancy levels during the early post-transplantation period was provided by the Applicant, on request. Since the CD86 receptor occupancy in a clinical setting correlates well with belatacept serum concentration and since AR events do not correlate with belatacept serum concentration in the dose ranges studied, it is considered unlikely that receptor occupancy correlates with the AR events.

The possibility to optimize dosing using biomarkers in the entire target population or in any particular subset of patients e.g. IDO phenotype was explored by the Applicant. The only reliable biomarker for exposure pointed out was CD86 receptor occupancy.

Due to the nature and mechanism of action of belatacept, it is not expected to have pharmacodynamic interactions with other drugs.

2.4.5. Conclusions on clinical pharmacology

The Applicant has presented a comprehensive clinical pharmacology program. There are no outstanding issues on clinical pharmacology.

2.5. Clinical efficacy

2.5.1. Dose response study

No conventional dose finding study was undertaken.

Study IM103002 was a pilot study to evaluate the safety, preliminary clinical activity and immunogenicity of multiple doses of abatacept and belatacept to subjects with rheumatoid arthritis. In a substudy, the pharmacokinetics and pharmacodynamics of the two drugs in subjects with RA were investigated. Belatacept at doses of 0.5, 2, or 10 mg/kg was administered as a one-hour intravenous infusion on study days 1, 15, 29, and 57. At day 85, a positive dose-response was noted for both active treatments. A dose-effect relationship could be seen for belatacept, with the best effect on RA symptoms for the dose 10 mg/kg.

For additional information on the selection of dose regimens please also refer to section "Pharmacodynamics / Primary pharmacology".

2.5.2. Main studies

The two pivotal studies were IM103008 in patients receiving low risk transplants, and IM103027 in a higher risk patient population. Study treatments were the same in both these studies and study procedures were very similar.

Study IM103008: Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) in de novo renal transplant recipients who received grafts from standard criteria donors (SCD).

Methods

This study was a randomized, partially-blinded, active-controlled, parallel-group, multicenter clinical trial. Subjects were to be randomized in equal numbers to receive belatacept in a more intensive regimen (MI), belatacept in a less intensive regimen (LI), or CsA. All subjects also received a

background immunosuppressive regimen consisting of basiliximab induction therapy and mycophenolate mofetil (MMF) and corticosteroid maintenance therapy.

Study duration is 3 years with a subsequent 8-week follow-up period for safety evaluations. At the end of the 3-year treatment period, subjects may be eligible for a long-term extension study.

Study procedure

Protocol biopsies were performed at baseline and at the end of month 12. Biopsies were also performed for assessment of clinically suspected acute rejections.

GFR was assessed as *measured GFR*, at the end of months 3, 12 and 24 (and the early termination visit if applicable).

Anti-belatacept antibody testing was done at baseline and at weeks 12, 24, 52, 76, 104, 128, and 156.

The composite cardiorenal disease endpoint (death, graft loss, non-fatal myocardial infarction, and stroke) was assessed based upon the adjudication of these events at 12, 24, and 36 months.

Quality of Life (QoL) was assessed at baseline and at 6, 12, 24, and 36 months by questionnaires.

Mammograms were done at baseline and then yearly during the study for all female study subjects aged 40 or older, and for younger females who had a first line relative with a history of breast cancer.

The severity of acute rejections were diagnosed according to the Banff -97 classification.

Study Participants

Inclusion and exclusion criteria: de novo renal transplant recipients at least 18 years of age and receiving a graft from a standard criteria donor (SCD), a living donor or deceased donor with anticipated cold ischemic time <24 hours, were to be included. Subjects were excluded from study participation if receiving an extended criteria donor organ defined by donor age ≥60 years or donor age 50-59 years and two or more of the following: (1) Cerebrovascular accident; (2) Hypertension or (3) Serum creatinine ≥1.5 mg/dl or anticipated cold ischemia time ≥24 hours or donor with cardiac death (non-heart beating donor). The following categories of patients were also excluded: Subjects with previous graft loss due to acute rejection; HLA-identical donor-recipient pairs; and subjects with a history of panel-reactive antibodies greater than 20%.

Treatments

All study patients were to receive induction therapy with *basiliximab* (20 mg IV on days 1 and 5) plus a background maintenance immunosuppressive regimen of mycophenolate mofetil (MMF) and corticosteroids. An IV dose of 500 mg methylprednisolone was administered on day 1, 250 mg on day 2. Steroids were then administered orally and doses were to be gradually tapered to no less than 2.5 mg daily. The normal dose of MMF was 1 g twice daily. In subjects who had AEs related to MMF, the dose could be reduced to the maximally tolerated dose. Therapeutic drug monitoring (TDM) for MMF was not done in the study. All study subjects were required to receive at least 6 months of Pneumocystis carinii prophylaxis. CMV-negative recipients receiving a CMV-positive transplant received CMV prophylaxis for at least 3 months. In addition, subjects treated with T-cell depleting agents were treated with antiviral agents prophylactically.

CsA regimen: Subjects randomised to *CsA* received doses twice daily, designed to achieve a serum concentration of 150-300 ng/ml during the first month, and thereafter a target level of 100-250 ng/ml. The use of *lymphocyte depleting therapy (LDT)* was permitted but not required for subjects

randomised to CsA who experienced impaired renal allograft function and anticipated delayed graft function (DGF).

Belatacept treatment: On the day of transplantation (day 1), the first belatacept infusion was started before completion of the transplant vessel anastomoses. Study drug was administered over 30 minutes.

Belatacept MI regimen: Subjects received IV belatacept (10 mg/kg) on days 1 and 5, then every 2 weeks through month 3 (weeks 2, 4, 6, 8, 10, and 12), and then every 4 weeks through 6 months (weeks 16, 20, and 24). After 6 months, subjects in the MI treatment group received the maintenance dose of belatacept 5 mg/kg administered every 4 weeks until completion of the trial at 36 months.

Belatacept LI regimen: Subjects received IV belatacept (10 mg/kg) on days 1 and 5, and then every 2 weeks through month 1 (weeks 2 and 4), and every 4 weeks through month 3 (weeks 8 and 12). After 3 months, subjects in the LI treatment group received the maintenance dose of belatacept 5 mg/kg administered every 4 weeks until completion of the trial at month 36. The clinical program employed a new vial size (250 mg) of belatacept during the study. Clinical study sites could switch from the 100 mg to 250 mg vial of belatacept when IRB/EC approval had been obtained and all subjects had completed month 12.

Objectives

The primary study hypothesis was that treatment with belatacept will result in superior preservation of renal function, as compared to CsA, with similar rates of subject and graft survival and no clinically important increase in acute rejection by 12 months in subjects receiving a kidney transplant from a living or deceased donor with cold ischemia time (CIT) < 24 hours.

The key secondary hypotheses were: a) Belatacept-treated subjects will have superior measured GFR at 12 months as compared with CsA-treated subjects; b) Belatacept-treated subjects will have a lower incidence of chronic allograft nephropathy (CAN) by 12 months as compared with CsA-treated subjects. These two key secondary endpoints are separated from other secondary endpoints.

Outcomes/endpoints

This pivotal study had three co-primary endpoints:

(1) the composite of subject and graft survival by 12 months;

(2) the composite of measured glomerular filtration rate (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 (this endpoint was chosen in accordance with advice received from the FDA and from EMEA), and

(3) the incidence of acute rejection by 12 months

Key secondary endpoints were:

(1) mean GFR at 12 months**,** and

(2) incidence of biopsy-proven chronic allograft nephropathy (CAN) at 12 months.

Sample size

A sample size of 220 subjects per treatment arm was chosen, which afforded 93% power to detect one belatacept regimen that meets all co-primary endpoints with overall Type I error controlled at the 0.05 level.

Randomisation

After informed consent had been obtained, subjects were randomised, via an IVRS system, 1:1:1 to receive belatacept in either MI or LI regimen or to receive CsA. Randomisation was stratified by study site. Since treatment with belatacept was to be started before the implantation of the renal graft, a number of patients were randomised but not transplanted.

Blinding (masking)

Blinding was done between the two belatacept treatment groups but not for the CsA group due to the need for monitoring CsA blood levels and also the potential use of LDT in CsA-treated subjects. Fully blinded adjudication committees, a fully blinded central pathologist and a blinded central GFR laboratory were used in the study.

Statistical methods

Intent-to-Treat (ITT) population was defined as all randomised and transplanted subjects. The ITT population was used for primary efficacy and safety analyses. The *Per-Protocol population (PP)* was used for secondary efficacy analyses*:* all randomised and transplanted subjects who did not violate terms of the protocol that might affect the efficacy outcome. In the initial statistical analysis plan (SAP) patients who never received any study drug were excluded from the PP-analysis. Since the administration of CsA but not of betalacept was conditional of allograft function this might bias the PP analysis. The SAP was therefore amended to include these patients in the PP population. Bearing in mind the primary analyses concerning non-inferiority, it was questioned whether the PP-population defined by the Applicant was too generously defined to be a useful alternative to the ITT population. The PP population originally defined by the Applicant was later recalculated according to a more strict definition; the results of this recalculation did not significantly differ from the original analysis. *As-treated population:* All randomised and transplanted subjects who received at least 1 dose of CsA or belatacept. A non-inferiority margin of 10% for the co-primary endpoint of subject and graft survival was used. The treatment differences between each belatacept treatment group and CsA group was tested at the 0.027 significance level for efficacy endpoints including subject and graft survival (based on 10% non-inferiority margin), acute rejection (based on 20% non-inferiority margin), measured GFR, intensity of anti-hypertension medication, lipid parameters (and incidence of new onset diabetes mellitus (NODM).

Study IM103027: Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial - EXTended Criteria Donors (BENEFIT-EXT).

Methods

Randomized, partially-blinded, active-controlled, parallel-group, multicenter clinical study. Post-Month 12, subjects continued to receive their study treatment regimen: belatacept more intensive regimen (MI), less intensive regimen (LI), or CsA according to the randomization assigned at the beginning of the study.

Study duration is 3 years with a subsequent 8-week follow-up period for safety evaluations. At the end of the 3-year treatment period, subjects may be eligible for a long-term extension study.

Study procedure: Same as in study IM103008.

Study Participants

Inclusion and exclusion criteria: De novo renal transplant recipients at least 18 years of age who were receiving a kidney transplant from an extended criteria deceased donor (ECD) were included. The specific ECD criteria are based upon the 'expanded criteria' for organ donation issued by UNOS. Subjects at varying levels of immunological risk were eligible but subjects of greatest immunological risk (positive cross-match, panel reactive antibodies, PRA, of ≥30%, or those previously transplanted) were excluded from study participation.

Treatments

All study patients were to receive induction therapy with *basiliximab* plus a background maintenance immunosuppressive regimen of *MMF* and *corticosteroids*. Details of these medications were the same as in study IM103008. Study drug regimens were to be maintained until month 36.

All study subjects were required to receive at least 6 months of Pneumocystis carinii prophylaxis. CMV-negative recipients receiving a CMV-positive transplant received CMV prophylaxis for at least 3 months. In addition, subjects treated with T-cell depleting agents were treated with antiviral agents prophylactically.

Subjects randomised to *CsA* received CsA according to the immunosuppressive schedule for the CsA arm in study IM 1003008. Target level for CsA trough level was 150-300 ng/ml during the first month after transplantation and thereafter it was 100-250 ng/ml.

The use of LDT was permitted but not required for subjects randomized to CsA who experienced impaired renal allograft function and anticipated DGF.

On the day of transplantation, the first belatacept infusion was started before completion of the transplant vessel anastomoses for subjects randomised to belatacept. Study drug was administered over 30 minutes.

a. The *belatacept more intensive (MI) regimen* was identical to the belatacept MI regimen in study IM103008
b. The *belatacept less intensive (LI) regimen* was identical to the belatacept LI regimen in study IM103008

Objectives

Primary hypothesis*:* Treatment with belatacept will result in superior preservation of renal function, as compared with CsA, with similar rates of subject and graft survival by 12 months in subjects receiving an extended criteria donor (ECD) kidney transplant from a deceased donor.

Key secondary hypotheses:

- Belatacept-treated subjects will have superior measured glomerular filtration rate (GFR) at 12 months as compared with CsA-treated subject
- Belatacept-treated subjects will have a lower incidence of chronic allograft nephropathy (CAN) at 12 months as compared with CsA-treated subjects.

Outcomes/endpoints

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

a) Composite endpoint of subject and graft survival by 12 months
b) 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.

Key secondary objectives were to evaluate the effects of belatacept, relative to CsA, on:

a. Measured GFR at 12 month, by iothalamate clearance method
b. Biopsy-proven CAN at 12 months

Sample size

A sample size of 180 subjects per treatment group which was chosen considered to afford at least 80% power to detect 1 belatacept regimen that meets both co-primary endpoints with overall Type I error controlled at the 0.05 significance level (Dunnett adjustment).

Randomisation

Same as in study IM103008.

Blinding (masking)

Same as in study IM103008.

Statistical methods

Intent-to-Treat (ITT) population: All randomized and transplanted subjects. The ITT population was used for primary efficacy and safety analyses.

Per-Protocol population, used for secondary efficacy analyses*:* all randomised and transplanted subjects who did not violate terms of the protocol that might affect the efficacy outcome.

As-treated population: all randomised and transplanted subjects who received at least 1 dose of CsA or belatacept.

The primary efficacy data set includes all randomised and transplanted subjects (ITT).

All safety analyses were performed on the data set that included all randomised and transplanted subjects. All available data from belatacept-treated subjects were included in analyses of PK and immunogenicity.

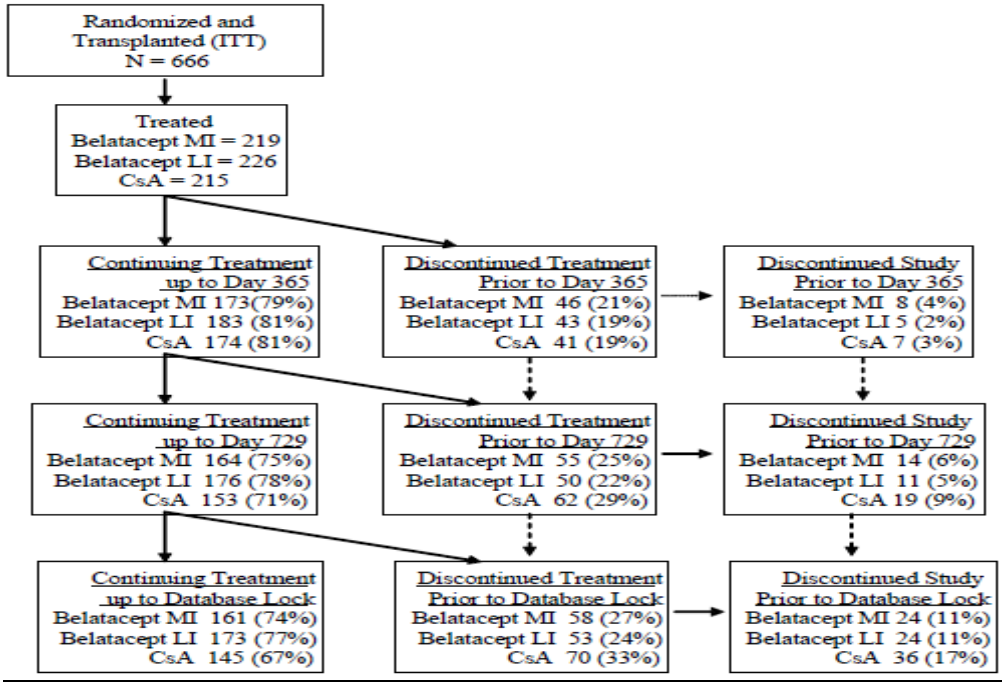
The co-primary and key secondary analyses include, in the order of hierarchy:

- assessment of the 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

Results

Study IM103008

Participant flow



Recruitment

Study recruitment was initiated in January 2006 and the study is still ongoing.

Conduct of the study

104 study sites enrolled subjects. Study sites were located in the US (34 sites), India (10 sites), South America, Australia, South Africa, Israel, Turkey, and Europe.

Protocol deviations were reported for 31 patients. However the conduct of the study does not indicate significant protocol deviations that could invalid the study results.

Baseline data

Table 3. Baseline patient demographics, study IM103008

Demographic Characteristic	Number (%) of Subjects Belatacept – MI N=219	Belatacept – LI N=226	Cyclosporine N=221	Total N=666
AGE (YEARS)				
N	219	226	221	666
MEAN (SD)	43.6 (14.6)	42.6 (13.4)	43.5 (14.3)	43.2 (14.1)
MEDIAN	45.0	44.0	46.0	45.0
MIN – MAX	18.0 – 77.0	18.0 – 71.0	18.0 – 75.0	18.0 – 77.0
Q1 – Q3	31.0 – 54.0	30.0 – 54.0	31.0 – 54.0	31.0 – 54.0
AGE CATEGORY, N (%)				
18-45	111 (50.7)	124 (54.9)	110 (49.8)	345 (51.8)
46-65	93 (42.5)	93 (41.2)	101 (45.7)	287 (43.1)
>65	15 (6.8)	9 (4.0)	10 (4.5)	34 (5.1)
GENDER, N (%)				
MALE	151 (68.9)	146 (64.6)	165 (74.7)	462 (69.4)
FEMALE	68 (31.1)	80 (35.4)	56 (25.3)	204 (30.6)
RACE, N (%)				
WHITE	132 (60.3)	133 (58.8)	139 (62.9)	404 (60.7)
BLACK OR AFRICAN AMERICAN	15 (6.8)	23 (10.2)	17 (7.7)	55 (8.3)
AMERICAN INDIAN/ALASKAN NATIVE	1 (0.5)	4 (1.8)	1 (0.5)	6 (0.9)
ASIAN	27 (12.3)	29 (12.8)	27 (12.2)	83 (12.5)
OTHER	44 (20.1)	37 (16.4)	37 (16.7)	118 (17.7)
ETHNICITY A				
US-HISPANIC OR LATINO	8 (3.7)	2 (0.9)	8 (3.6)	18 (2.7)
US-NOT HISPANIC OR LATINO	53 (24.2)	57 (25.2)	57 (25.8)	167 (25.1)
MISSING	158 (72.1)	167 (73.9)	156 (70.6)	481 (72.2)
GEOGRAPHIC REGION N (%)				
NORTH AMERICA	95 (43.4)	92 (40.7)	94 (42.5)	281 (42.2)
SOUTH AMERICA	35 (16.0)	36 (15.9)	33 (14.9)	104 (15.6)
EUROPE	55 (25.1)	64 (28.3)	58 (26.2)	177 (26.6)
ROW(ASIA/PACIFIC)	32 (14.6)	33 (14.6)	34 (15.4)	99 (14.9)
AFRICA	2 (0.9)	1 (0.4)	2 (0.9)	5 (0.8)
PREVIOUS # OF TRANSPLANT, N (%)				
0	210 (95.9)	218 (96.5)	208 (94.1)	636 (95.5)
1	5 (2.3)	5 (2.2)	9 (4.1)	19 (2.9)
2	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
MISSING	3 (1.4)	3 (1.3)	4 (1.8)	10 (1.5)

Table 4. Baseline disease characteristics of donors in study IM103008 ITT population

Demographic Characteristic	Number (%) of Subjects Belatacept – MI N=219	Belatacept – LI N=226	Cyclosporine N=221	Total N=666
PRIMARY CAUSE OF DEATH: N (%)				
TRAUMA	45 (20.5)	35 (15.5)	37 (16.7)	117 (17.6)
ANOXIA	7 (3.2)	8 (3.5)	10 (4.5)	25 (3.8)
CVA	28 (12.8)	46 (20.4)	35 (15.8)	109 (16.4)
MYOCARDIAL INFARCTION	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.3)
NOT APPLICABLE	126 (57.5)	124 (54.9)	121 (54.8)	371 (55.7)
OTHER	10 (4.6)	8 (3.5)	18 (8.1)	36 (5.4)
MISSING	3 (1.4)	3 (1.3)	0 (0.0)	6 (0.9)
COLD ISCHEMIC TIME (HOUR) OF LIVING TRANSPLANT				
N	128	127	121	376
MEAN (SD)	1.4 (1.9)	1.3 (1.6)	1.5 (2.8)	1.4 (2.2)
MEDIAN	0.9	1.0	0.9	0.9
MIN – MAX	0.0 – 18.0	0.0 – 15.2	0.0 – 22.5	0.0 – 22.5
Q1 – Q3	0.5 – 1.6	0.5 – 1.5	0.5 – 1.7	0.5 – 1.6
COLD ISCHEMIC TIME (HOUR) OF CADAVERIC TRANSPLANT				
N	87	97	97	281
MEAN (SD)	15.4 (6.4)	16.7 (6.4)	16.7 (5.7)	16.3 (6.1)
MEDIAN	15.2	16.5	16.5	16.1
MIN – MAX	0.0 – 27.8	0.5 – 38.1	3.0 – 31.0	0.0 – 38.1
Q1 – Q3	11.2 – 21.0	12.7 – 20.4	12.8 – 20.8	12.3 – 20.6
MOST RECENT SCR PRIOR TO ORGAN RETRIEVAL (MG/DL)				
< 0.5	10 (4.6)	8 (3.5)	7 (3.2)	25 (3.8)
0.5 - <1	132 (60.3)	150 (66.4)	140 (63.3)	422 (63.4)
1 - < 1.5	57 (26.0)	52 (23.0)	48 (21.7)	157 (23.6)
1.5 - <2	8 (3.7)	8 (3.5)	8 (3.6)	24 (3.6)
>= 2	4 (1.8)	3 (1.3)	9 (4.1)	16 (2.4)
MISSING	8 (3.7)	5 (2.2)	9 (4.1)	22 (3.3)
TYPE OF TRANSPLANT, N (%)				
LIVING-RELATED	91 (41.6)	99 (43.8)	91 (41.2)	281 (42.2)
LIVING-UNRELATED	41 (18.7)	30 (13.3)	33 (14.9)	104 (15.6)
CADAVERIC	87 (39.7)	97 (42.9)	97 (43.9)	281 (42.2)

Numbers analysed

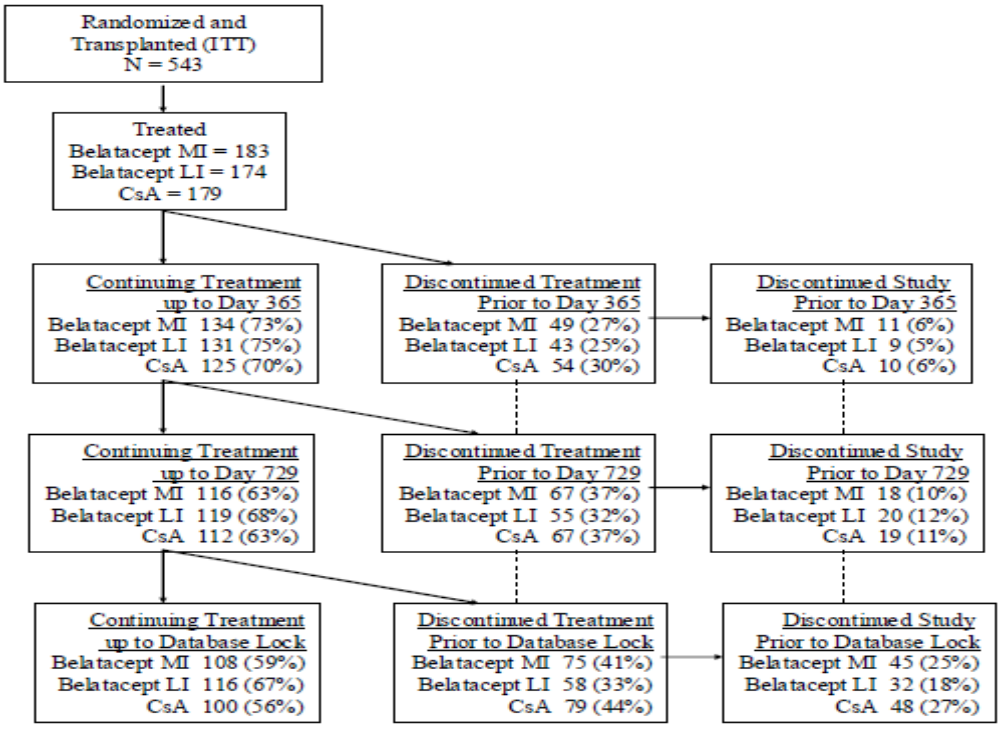
The ITT population used for primary efficacy and safety analyses consisted of 219, 226 and 221 patients in the MI, LI and CsA treatment arms, respectively.

The PP population analysed for secondary efficacy analyses was 217, 221 and 208 patients in the MI, LI and CsA treatment arms, respectively.

The as-treated population used for secondary efficacy analyses included all randomised subjects who received a renal transplant and at least one dose of study medication. This population consisted of 219, 226 and 215 patients in the MI, LI and CsA treatment arms, respectively.

Study IM103027

Participant flow



Recruitment

This study started to recruit patients in March 2005 and the study is still ongoing.

Conduct of the study

One hundred and eight study sites received study drug; only 79 sites enrolled subjects. Of these sites were 28 in the US, 9 in France, 6 in Brazil, 5 each in Germany, Argentina, and Spain, 4 in Canada, 3 in Italy, 2 each in Hungary, Austria, and Poland, 1 each in Belgium, Chile, Czech Republic, Norway, South Africa, Sweden, UK, and Australia.

Ten subjects had at least 1 relevant protocol deviation. These Protocol deviations detected do not invalided the study results.

Baseline data

Table 5. Baseline demographics of recipients, ITT population in study IM103027

Demographic Characteristic	Belatacept – MI N=184	Belatacept – LI N=175	Cyclosporine N=184	Total N=543
	Number (%) of Subjects			
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 (%)				
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)
a The information is collected for US recipients only.				
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 6. Baseline disease characteristics of donors in study IM103027 ITT population

Demographic Characteristic	Belatacept – MI N=184	Belatacept – LI N=175	Cyclosporine N=184	Total N=543
	Number (%) of Subjects			
AGE (YEARS)				
N	184	174	183	541
MEAN (SD)	56.9 (14.3)	55.9 (13.7)	57.6 (14.1)	56.8 (14.1)
MEDIAN	60.0	58.0	60.0	59.0
MIN – MAX	14.0 – 84.0	16.0 – 84.0	12.0 – 81.0	12.0 – 84.0
Q1 – Q3	51.0 – 66.0	51.0 – 65.0	52.0 – 68.0	52.0 – 66.0
AGE CATEGORY, N (%)				
< 18	7 (3.8)	3 (1.7)	1 (0.5)	11 (2.0)
18-45	21 (11.4)	27 (15.4)	31 (16.8)	79 (14.5)
46-65	107 (58.2)	104 (59.4)	91 (49.5)	302 (55.6)
>65	49 (26.6)	40 (22.9)	60 (32.6)	149 (27.4)
MISSING	0 (0.0)	1 (0.6)	1 (0.5)	2 (0.4)
GENDER, N (%)				
MALE	100 (54.3)	87 (49.7)	96 (52.2)	283 (52.1)
FEMALE	84 (45.7)	87 (49.7)	88 (47.8)	259 (47.7)
MISSING	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
RACE, N (%)				
WHITE	124 (67.4)	105 (60.0)	118 (64.1)	347 (63.9)
BLACK OR AFRICAN AMERICAN	4 (2.2)	13 (7.4)	10 (5.4)	27 (5.0)
AMERICAN INDIAN/ALASKAN NATIVE	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
ASIAN	1 (0.5)	2 (1.1)	1 (0.5)	4 (0.7)
OTHER	33 (17.9)	33 (18.9)	31 (16.8)	97 (17.9)
MISSING	22 (12.0)	21 (12.0)	24 (13.0)	67 (12.3)
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)				
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)

Numbers analysed

The ITT population used for primary efficacy and safety analyses consisted of 184, 175, and 184 patients in the MI, LI and CsA treatment arms, respectively.

The PP population analysed for secondary efficacy analyses was 180, 170 and 183 patients in the MI, LI and CsA treatment arms, respectively.

The as-treated population used for secondary efficacy analyses included all randomised subjects who received a transplant and at least one dose of study medication. This population consisted of 183, 174 and179 patients in the MI, LI and CsA treatment arms, respectively.

PP analyses were performed on the co-primary endpoint of subject and graft survival. It was also to be performed on the co-primary endpoint of measured GFR at month 12, only if >10% of the total number of subjects included into the ITT data set at month 12 had significant protocol violations/deviations and consequently would be excluded from the PP data set.

Outcomes and estimation

There were no major imbalances between treatment groups with respect to risk factors and concomitant treatment. Due to the different donor criteria there were obvious differences in risk factors between studies (Table 7). Subject and graft survival status was available for 663/666 patients in study IM103008 and month 12 biopsies were available from 79% of patients with functioning graft. In study IM103027, subject and graft survival status was available for 532/543 subjects and graft biopsies at 12 months were available for 70 – 75% of patients alive with a functioning graft. In both pivotal studies, measured and calculated GFR data collection rates were 81 – 91%.

Table 7. Selected comparative baseline demographic data in pivotal belatacept studies (compiled from core study reports)

Phase 3 pivotal study	**IM103008**	**IM103027**
Mean recipient age (yrs)	43.2	56.2
Mean donor age (yrs)	40	57
% Male recipients	69.4	67.0
% White recipients	60.7	76.1
% Black recipients	8.3	13.1
% Asian recipients	12.6	2.6
% First transplantation	95.5	100? (re-tx exclusion criterion)
CIT (hrs)	16.3	20
% Non heart beating donors	0? (exclusion criterion)	10
0-3 HLA mismatches (%)	56	47

The results for the primary and key secondary endpoints are given in Tables 8 - 10. In both phase 3 studies, the belatacept MI/LI immunosuppression regimen met the 10 % non-inferiority margin for the composite endpoint subject and graft survival. In both studies, the proportion of deaths up to month 12 was similar between treatment groups (2 – 3%, equally divided between cardiovascular and non-cardiovascular causes) and without any discernable pattern for any of the treatment groups. In IM103027 only, primary thrombosis as an adjudicated cause of graft loss was more frequent in both belatacept groups and accounted for approximately half of the graft losses in the belatacept groups (41% in the MI and 50% in the LI group) versus 10 % in the CsA group.

For the primary composite endpoint of renal function statistically significant differences in favour of the belatacept groups were seen in study IM103008 for both belatacept groups and for the MI group in IM103027, with a strong positive trend for the LI group. The differences were driven by the incidence of GFR<60 at 12 months. However, cumulative distribution plots of calculated GFR at month 36 in both pivotal studies showed better cGFRs in belatacept groups, almost irrespective of GFR cutoff level.

In study IM103008 there were significantly more acute reactions in the belatacept groups, mainly driven by a higher incidence of severe rejections (Table 9). Almost all cases of AR occurred during the first 12 months in the pivotal studies. About half of subjects experiencing an acute rejection episode in each group continued study drug at month 12. Most subjects who discontinued study drug after rejection were treated with tacrolimus. Higher AR rates were recorded in all treatment groups for subjects with 5 or 6 HLA mismatches compared to those with 0 – 2 mismatches. In IM103008, subjects with race other than white outside the US, Europe, and South America, and subjects with low pretransplant weight had lower AR rates. In study IM103027, subjects with race other than white, subjects from South America, non-diabetics, subjects receiving grafts without fibrosis or vasculopathy at baseline, subjects receiving a graft from a donor below 60 years of age and subjects with low pretransplant weight had lower rates of AR. HLA antibodies did not develop more often in belatacept-treated subjects than in CsA-treated subjects, irrespective of if the patient had a rejection or not. Delayed graft function (DGF) is associated with an increased risk of AR. There were however no differences in DGF incidence disfavouring the belatacept groups. The differences in rejection frequency did not seem to have any impact on subject and graft survival and the proportion of patients alive with a functioning graft was similar for patients with and without an acute rejection.

There was a clear overall pattern of less chronic allograft nephropathy (CAN) on belatacept treatment. This difference is mainly driven by a lesser prevalence of mild cases of chronic allograft nephropathy.

Table 8. Summary of key efficacy outcomes at month 12, study IM103008

	Belatacept MI N = 219	Belatacept LI N = 226	CsA N = 221
Subject and Graft Survival (n, %)[a]	**209 (95.4)**	**218 (96.5)**	**205 (92.8)**
Difference from CsA (97.3% CI)	2.7 (-2.5, 8.1)	3.7 (-1.1, 9.0)	-
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	2 (0.9)
Composite Endpoint for Measured GFR (mL/min/1.73 m^2): < 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 mL/min/1.73 m^2	**65.0 (30.0)**	**63.4 (27.7)**	**50.4 (18.7)**
Difference from CsA (97.3% CI)	14.6 (8.8, 20.3)	12.9 (7.2, 18.6)	-
P-Value	< 0.0001	< 0.0001	
Mean (SD) calculated GFR mL/min/1.73 m^2	**68.3 (19.2)**	**68.1 (19.0)**	**53.6 (16.9)**
Difference from CsA (97.3% CI)	14.7 (10.5, 18.9)	14.6 (10.4, 18.8)	-
Acute Rejection (n, %)[a,b]	**48 (21.9)**	**39 (17.3)**	**16 (7.2)**
Difference from CsA (97.3% CI)	14.7 (7.5, 22.2)[c]	10.0 (3.3, 17.1)	-
Prevalence of CAN (n, %)	**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, %)			
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] 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.

[c] Did not meet the 20% protocol-specified margin for non-inferiority to CsA

Table 9. Acute rejections (%) at month 12 by Banff severity in pivotal studies

IM103008	Belatacept MI	Belatacept LI	CsA
Grade I	4.6	5.3	3.7
Grade II-III	19.2	11.9	3.6
IM103027			
Grade I	3.3	3.4	2.2
Grade II-III	14.1	14.3	11.9

Table 10. Summary of key efficacy outcomes at month 12, study IM103027

	Belatacept MI N = 184	Belatacept LI N = 175	Cyclosporine N = 184
Subject and Graft Survival (n, %)[a]	**158 (85.9)**	**154 (88.0)**	**156 (84.8)**
Difference from CsA (97.3% CI)	1.1 (-7.2, 9.4)	3.2 (-5.0, 11.4)	-
Graft Loss (n, %)	17 (9.2)	15 (8.6)	19 (10.3)
Death (n, %)	8 (4.3)	4 (2.3)	8 (4.3)
Imputed as Graft Loss or Death	3 (1.6)	3 (1.7)	3 (1.6)
Composite Endpoint for Measured GFR (mL/min/1.73 m^2):			
< 60 or decr ≥ 10 from Month 3 to 12 (n, %)[a]	**124 (70.5)**	**129 (76.3)**	**151 (84.8)**
Difference from CsA (97.3% CI)	-14.4 (-24.0, -4.7)	-8.5 (-18.0, 0.9)	-
P-Value	0.0018	0.0616	-
Measured GFR < 60 mL/min/1.73 m^2 (n, %)	98 (55.7)	105 (62.1)	120 (67.4)
Decrease in measured GFR ≥ 10 mL/min/1.73 m^2 from Month 3 to Month 12 (n, %)	31 (17.6)	46 (27.2)	44 (24.7)
Mean (SD) measured GFR mL/min/1.73 m^2	**52.1 (21.9)**	**49.5 (25.4)**	**45.2 (21.1)**
Difference from CsA (97.3% CI)	6.9 (1.1, 12.7)	4.3 (-1.5, 10.1)	-
P-Value	0.0083	0.1039	-
Mean (SD) calculated GFR mL/min/1.73 m^2	**50.1 (17.2)**	**49.5 (16.7)**	**42.7 (15.9)**
Difference from CsA (97.3% CI)	7.4 (3.0, 11.8)	6.8 (2.4, 11.3)	
Acute Rejection (n, %)[b]	**32 (17.4)**	**31 (17.7)**	**26 (14.1)**
Difference from CsA (97.3% CI)	3.3 (-5.2, 11.8)	3.6 (-5.0, 12.3)	-
Prevalence of CAN (n, %)	**82 (44.8)**	**80 (46.0)**	**95 (51.6)**
Difference from CsA (97.3% CI)	-6.8 (-18.2, 4.7)	-5.7 (-17.2, 6.0)	-
Delayed Graft Function (n, %)	**87 (47.3)**	**83 (47.4)**	**90 (48.9)**

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] Acute Rejection = secondary endpoint, 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.

Composite endpoint of acute rejection, death or graft loss: By month 12, the proportion of subjects meeting the composite endpoint of AR, death or graft loss was 26%, 20%, and 14% in the belatacept MI, LI and CsA groups, respectively, in IM103008; and 29%, 27%, and 25%, respectively, in IM103027. Differences between treatment groups were primarily driven by the AR frequencies.

New onset diabetes mellitus (NODM): The proportion of subjects with NODM in each pivotal study at month 12 was lower in the belatacept groups compared with CsA groups, the differences were however not statistically significant.

Blood pressure (BP): Belatacept-treated subjects had lower BP and less anti-hypertensive medications than CsA-treated subjects. Subjects in both belatacept groups had clinically meaningful and statistically significant decreases in SBP and DBP and were treated with fewer antihypertensive drugs, relative to CsA. This effect was noted at month 12 and continued up to month 30.

Dyslipidemia: Belatacept-treated subjects tended to have lower non-HDL cholesterol and use less lipid lowering drugs than CsA-treated subjects. The effect on non-HDL was primarily driven by reduction of triglycerides.

Framingham risk score: At baseline, mean Framingham risk scores were similar across treatment groups in both studies and ranged from 2.9 to 5.8. In the pooled analysis (subjects pooled by

randomised treatment group across studies), the change from baseline to month 12 in Framingham risk score was lower for the belatacept MI (p=0.018) and LI (p<0.001) compared with CsA. A similar proportion of subjects in all 3 treatment groups met the composite cardiorenal and composite cardiovascular endpoints.

Quality of Life (QoL): At baseline, the SF-36 subscale and component summary scores for all subjects were substantially lower than the population norm. By month 12, both the belatacept and CsA treatment groups returned to physical and mental health functioning levels comparable to the general population with respect to all SF-36 scores. Greater improvements were seen in the physical domains than in the mental domains.

36 month data from pivotal studies

The Applicant submitted 36 month data from the pivotal studies. Patient and graft survival were not worse with belatacept than with ciclosporin at 36 months in any of the studies.

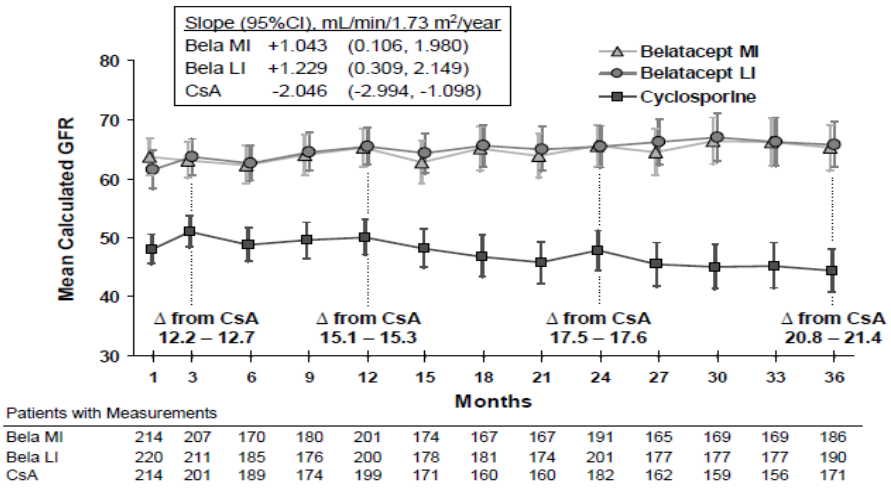
Table 11. Patient and Graft survival at 36 months in the ITT population

Patient and Graft Survival at 36 Months in the ITT Population

	Percent of Subjects					
	IM103008			IM103027		
	Bela MI N=219	Bela LI N=226	CsA N=221	Bela MI N=184	Bela LI N=175	CsA N=184
By Month 12	95.4	96.5	92.8	85.9	88.0	84.8
Diff. from CsA	2.2	3.2	---	1.1	3.2	---
(97.3% CI)	(-2.9, 7.5)	(-1.5, 8.4)	---	(-7.2, 9.4)	(-5.0, 11.4)	---
By Month 24	94.1	94.7	90.5	82.6	84.0	82.6
Diff. from CsA	3.6	4.2	---	0.0	1.4	---
(97.3% CI)	(-2.2, 9.6)	(-1.3, 10.1)	---	(-8.8, 8.8)	(-7.5, 10.2)	---
By Month 36	92.2	92.0	88.7	80.4	82.3	79.9
Diff. from CsA	3.5	3.3	---	0.5	2.4	---
(97.3% CI)	(-2.8, 10.0)	(-2.9, 9.8)	---	(-8.7, 9.8)	(-6.9, 11.6)	---

Renal function (although not equal between treatment groups at baseline), estimated as calculated GFR over time, was sustained during the 36 month study period in both belatacept treatment arms in both pivotal studies, although at different levels of GFR in the two studies.

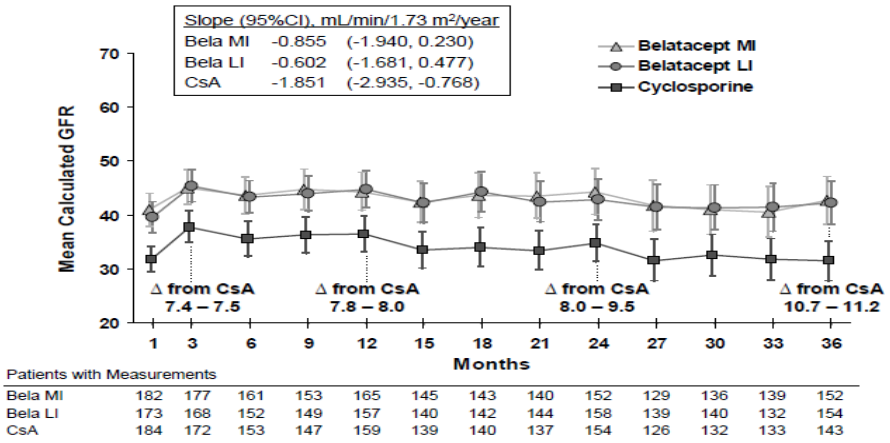
Figure 75.2: Calculated GFR over time - Study IM103008



Patients with Measurements

Bela MI	214	207	170	180	201	174	167	167	191	165	169	169	186
Bela LI	220	211	185	176	200	178	181	174	201	177	177	177	190
CsA	214	201	189	174	199	171	160	160	182	162	159	156	171

Calculated GFR over time - IM103027



Patients with Measurements

Bela MI	182	177	161	153	165	145	143	140	152	129	136	139	152
Bela LI	173	168	152	149	157	140	142	144	158	139	140	132	154
CsA	184	172	153	147	159	139	140	137	154	126	132	133	143

Ancillary analyses

Study IM103008

Subgroup analyses for subjects and graft survival, composite measured GFR, measured GFR, AR, and CAN were performed for the following baseline characteristics:

• Recipient age, gender, race, region, pre-transplant diabetes status, attributed cause of ESRD, weight, PRA, and without prior transplant

• Donor: fibrosis or vasculopathy in baseline biopsy, age, and donor condition

• Donor/Recipient HLA mismatch

Belatacept-treated subjects had a similar or, mostly, a lower proportion of subjects having CAN in most subgroups when compared with the CsA group.

The following subgroups tended to have worse outcomes for the composite endpoint of patient and graft survival at month 12 subgroup analyses: In the geographic region of South America, the belatacept MI group and the CsA group had worse outcome than the belatacept LI group. Patients with diabetes as cause of ESRD had worse outcomes when treated with CsA than with any of the belatacept regimens. Patients with 5-6 HLA mismatches also did worse for this primary endpoint when treated

with CsA than when treated with belatacept MI or LI regimen. CsA also tended to be less favourable than belatacept for this endpoint in patients who got their renal graft from a deceased donor.

This leads to the conclusion that CsA was less favourable for the composite endpoint of patient and graft survival in patient subpopulations with more baseline risk factors.

Study IM103027

Subgroup analyses for subject and graft survival, composite measured GFR, measured GFR, AR, and CAN were performed for the following baseline characteristics:

• Recipient: age, gender, race, region, pre-transplant diabetes status, attributed cause of end stage renal disease, pretransplant weight, and most recent PRA <20%

• Donor: fibrosis or vasculopathy in baseline biopsy, CIT, age, and donor condition

• Donor/Recipient: HLA mismatch

Subgroup analysis of the composite endpoint of subject and graft survival showed a tendency for lower rate in the CsA group in patients from the geographic region of South America *or* with 5-6 HLA mismatches *or* with pre-transplant diabetes. Otherwise rates were similar between treatment groups.

A similar or higher proportion of belatacept-treated subjects had AR than CsA-treated subjects in most subgroups. This difference was marked in patients from the geographic region of North America, in the group of patient who got a kidney from a donor younger than 50 years but with cardiovascular risk factors, and in the subgroup of patients with 5 - 6 HLA mismatch.

Consistent with the overall effect on CAN, belatacept-treated subjects had a similar or lower proportion of subjects having CAN in most subgroups compared with the CsA group. The difference between the CsA subgroup and the belatacept subgroups tended to be bigger in black subjects and in subjects with pretransplant diabetes (in particular if diabetes was the attributed cause of ESRD) or with heavy overweight.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12. Summary of Efficacy for trial IM103008

Title: Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT)		
Study identifier	Protocol Number: IM103008 IND Number: IND BB 9418 EUDRACT Number 2004-003635-31	
Design	Randomized, partially-blinded, active-controlled, parallel-group, multicenter clinical trial. Subjects were to be randomized in equal numbers (1:1:1) to receive belatacept in a more intensive regimen (MI), belatacept in a less intensive regimen (LI), or CsA. All subjects also received a background immunosuppressive regimen consisting of basiliximab induction therapy and mycophenolate mofetil (MMF) and corticosteroid maintenance therapy. Subjects receiving low risk transplants: de novo renal transplant recipients at least 18 years of age and receiving a graft from a standard criteria donor (SCD), a living donor or deceased donor with anticipated cold ischemic time <24 hours, were to be included. Subjects were excluded from study participation if receiving an extended criteria donor organ defined by donor age ≥60 years or donor age 50-59 years and two or more of the following: (1) Cerebrovascular accident; (2) Hypertension or (3) Serum creatinine ≥1.5 mg/dl or anticipated cold ischemia time ≥24 hours or donor with cardiac death (non-heart beating donor). The following categories of patients were also excluded: Subjects with previous graft loss due to acute rejection; HLA-identical donor-recipient pairs; and subjects with a history of panel-reactive antibodies greater than 20%.	
	Duration of main phase: Duration of Follow-up: Duration of Extension phase:	36 months 8 weeks 2 years
Hypothesis	Non-inferiority: for the primary composite endpoint of patient and graft survival.	
Treatments groups	Belatacept MI (More Intensive)	Treatment: 10 mg/kg IV on days 1 and 5, then every 2 weeks through month 3 (weeks 2, 4, 6, 8, 10, and 12), and then every 4 weeks through 6 months (weeks 16, 20, and 24). After 6 months, subjects in the MI treatment group received the maintenance dose of belatacept 5 mg/kg administered every 4 weeks until completion of the trial at 36 months. Duration:36 months Number randomized: 219
	Belatacept LI (Less Intensive)	Treatment: 10 mg/kg IV on days 1 and 5, and then every 2 weeks through month 1 (weeks 2 and 4), and every 4 weeks through month 3 (weeks 8 and 12). After 3 months, subjects in the LI treatment group received the maintenance dose of belatacept 5 mg/kg administered every 4 weeks until completion of the trial at month 36 Duration: 36 months Number randomized: 226

	CsA		Treatment: twice daily doses, designed to achieve a serum concentration of 150 - 300 ng/mL during the first month and thereafter 100 - 250 ng/mL Duration: 36 months Number randomized: 221
Endpoints and definitions	Primary endpoint	Subject and graft survival (n%)	Composite endpoint of subject and graft survival by 12 months
	Primary endpoint	Composite endpoint for measured GFR (mL/min/1.73 m^2)	Composite endpoint of measured glomerular filtration rate (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
	Primary endpoint	Acute rejection (n%)	Incidence of acute rejection (AR) by 12 months
	Secondary endpoint	Mean (SD) GFR measured (mL/min/1.73 m^2)	Mean GFR measured at 12 months
	Secondary endpoint	Mean (SD) GFR calculated (mL/min/1.73 m^2)	Mean GFR calculated at 12 months
	Secondary endpoint	Prevalence of CAN (n%)	Incidence of biopsy-proven chronic allograft nephropathy (CAN) at 12 months
Database lock	On going		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (ITT): all randomized and transplanted subjects. Per-protocol population (PP): all randomised and transplanted subjects who did not violate terms of the protocol that might affect the efficacy outcome. Secondary efficacy analyses.			
Descriptive statistics and estimate variability	Treatment group	Balatacept MI	Balatacept LI	CsA
	Number of subject	219	226	221
	Subject and graft survival (n%)	209 (95.4%)	218 (96.5%)	206 (93.2%)
	Composite endpoint for measured GFR (mL/min/1.73m^2)	115 (55.0%)	116 (54.2%)	166 (77.9%)
	Acute rejection (n%)	48 (21.9%)	39 (17.3%)	16 (7.2%)
	Mean (SD) GFR (mL/min/1.73m^2) measured	65.0 (30.0%)	63.4 (27.7%)	50.4 (18.7%)
	Mean (SD) GFR (mL/min/1.73m^2) calculated	68.3 (19.2%)	68.1 (19.0%)	53.6 (16.9%)

	Prevalence of CAN (n%)	40 (18.3%)	54 (23.9%)	71 (32.4%)

Effect estimate per comparison	Primary endpoint: Subject and graft survival (n%)	Comparison groups	Balatacept MI vs CsA
		Difference from CsA	2.7
		97.3% CI	(-2.5, 8.1)
		Comparison groups	Balatacept LI vs CsA
		Difference from CsA	3.7
		97.3% CI	(-1.1, 9.0)
	Primary endpoint: Composite endpoint for measured GFR (mL/min/1.73m2)	Comparison groups	Balatacept MI vs CsA
		Difference from CsA	-22.9
		97.3% CI	(-32.6, -12.9)
		P-value (ANOVA)	<0.0001
		Comparison groups	Balatacept LI vs CsA
		Difference from CsA	-23.7
		97.3% CI	(-33.3, -13.7)
		P-value (ANOVA)	<0.0001
	Primary endpoint: Acute rejection (n%)	Comparison groups	Balatacept MI vs CsA
		Difference from CsA	14.7
		97.3% CI	(7.5, 22.2)
		Comparison groups	Balatacept LI vs CsA
		Difference from CsA	10.0
		97.3% CI	(3.3, 17.1)
	Secondary endpoint: Mean (SD) GFR (mL/min/1.73m^2) measured	Comparison groups	Balatacept MI vs CsA
		Difference from CsA	14.6
		97.3% CI	(8.8, 20.3)
		P-value (ANOVA)	<0.0001
		Comparison groups	Balatacept LI vs CsA
		Difference from CsA	12.9
		97.3% CI	(7.2, 18.6)
		P-value (ANOVA)	<0.0001
	Secondary endpoint: Mean (SD) GFR (mL/min/1.73m^2) calculated	Comparison groups	Balatacept MI vs CsA
		Difference from CsA	14.7
		97.3% CI	(10.5, 18.9)
		Comparison groups	Balatacept LI vs CsA
		Difference from CsA	14.6
		97.3% CI	(10.4, 18.8)
	Secondary endpoint: Prevalence of CAN (n%)	Comparison groups	Balatacept MI vs CsA
		Difference from CsA	-14.2
		97.3% CI	(-23.2, -5.0)
		Comparison groups	Balatacept LI vs CsA
		Difference from CsA	-8.5
		97.3% CI	(-17.9, 0.9)
Notes			
Analysis description			

Table 13. Summary of Efficacy for trial IM103027

Title: Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial - EXTended Criteria Donors (BENEFITEXT)		
Study identifier	Protocol Number: IM103027 IND Number: IND BB 9418 EUDRACT Number 2004-002974-48	
Design	Randomized, partially-blinded, active-controlled, parallel-group, multicenter clinical trial. Subjects were to be randomized in equal numbers (1:1:1) to receive belatacept in a more intensive regimen (MI), belatacept in a less intensive regimen (LI), or CsA. All subjects also received a background immunosuppressive regimen consisting of basiliximab induction therapy and mycophenolate mofetil (MMF) and corticosteroid maintenance therapy. Subjects receiving high risk transplants: de novo renal transplant recipients at least 18 years of age who were receiving a kidney transplant from an extended criteria deceased donor (ECD) were included. The specific ECD criteria are based upon the 'expanded criteria' for organ donation issued by UNOS. Subjects at varying levels of immunological risk were eligible but subjects of greatest immunological risk (positive cross-match, panel reactive antibodies, PRA, of ≥30%, or those previously transplanted) were excluded from study participation.	
	Duration of main phase: Duration of Follow-up: Duration of Extension phase:	36 months 8 weeks 2 years
Hypothesis	Non-inferiority: for the primary composite endpoint of patient and graft survival	
Treatments groups	Belatacept MI (More Intensive)	Treatment: 10 mg/kg IV on days 1 and 5, then every 2 weeks through month 3 (weeks 2, 4, 6, 8, 10, and 12), and then every 4 weeks through 6 months (weeks 16, 20, and 24). After 6 months, subjects in the MI treatment group received the maintenance dose of belatacept 5 mg/kg administered every 4 weeks until completion of the trial at 36 months. Duration:36 months Number randomized: 184
	Belatacept LI (Less Intensive)	Treatment: 10 mg/kg IV on days 1 and 5, and then every 2 weeks through month 1 (weeks 2 and 4), and every 4 weeks through month 3 (weeks 8 and 12). After 3 months, subjects in the LI treatment group received the maintenance dose of belatacept 5 mg/kg administered every 4 weeks until completion of the trial at month 36 Duration: 36 months Number randomized: 175

	CsA		Treatment: twice daily doses, designed to achieve a serum concentration of 150 - 300 ng/mL during the first month and thereafter 100 - 250 ng/mL Duration: 36 months Number randomized: 184
Endpoints and definitions	Primary endpoint	Subject and graft survival (n%)	Composite endpoint of subject and graft survival by 12 months
	Primary endpoint	Composite endpoint for measured GFR (mL/min/1.73m^2)	Composite endpoint of measured glomerular filtration rate (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
	Primary endpoint	Acute rejection (n%)	Incidence of acute rejection (AR) by 12 months
	Secondary endpoint	Mean (SD) GFR measured (mL/min/1.73m^2)	Mean GFR measured at 12 months
	Secondary endpoint	Mean (SD) GFR calculated (mL/min/1.73m^2)	Mean GFR calculated at 12 months
	Secondary endpoint	Prevalence of CAN (n%)	Incidence of biopsy-proven chronic allograft nephropathy (CAN) at 12 months
Database lock	On going		

<u>Results and Analysis</u>

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (ITT): all randomized and transplanted subjects. Per-protocol population (PP): all randomised and transplanted subjects who did not violate terms of the protocol that might affect the efficacy outcome. Secondary efficacy analyses.			
Descriptive statistics and estimate variability	Treatment group	Balatacept MI	Balatacept LI	CsA
	Number of subject	184	175	184
	Subject and graft survival (n%)	158 (85.9%)	155 (88.6%)	157 (85.3%)
	Composite endpoint for measured GFR (mL/min/1.73m^2)	124 (70.5%)	131 (76.6%)	151 (84.8%)
	Acute rejection (n%)	32 (17.4%)	31 (17.7%)	26 (14.1%)
	Mean (SD) GFR (mL/min/1.73m^2) measured	52.1 (21.9%)	49.6 (25.8%)	45.2 (21.1%)

	Mean (SD) GFR (mL/min/1.73m^2) calculated	50.1 (17.2%)	49.5 (16.7%)	42.7 (15.9%)
	Prevalence of CAN (n%)	82 (44.8%)	80 (46.0%)	95 (51.6%)

Effect estimate per comparison	Primary endpoint: Subject and graft survival (n%)	Comparison groups	Belatacept MI vs CsA
		Difference from CsA	1.1
		97.3% CI	(-7.2, 9.4)
		Comparison groups	Belatacept LI vs CsA
		Difference from CsA	3.2
		97.3% CI	(-5.0, 11.4)
	Primary endpoint: Composite endpoint for measured GFR (mL/min/1.73m2)	Comparison groups	Belatacept MI vs CsA
		Difference from CsA	-14.4
		97.3% CI	(-24.0, -4.7)
		P-value (ANOVA)	0.0018
		Comparison groups	Belatacept LI vs CsA
		Difference from CsA	-8.5
		97.3% CI	(-18.0, 0.9)
		P-value (ANOVA)	0.0616
	Primary endpoint: Acute rejection (n%)	Comparison groups	Belatacept MI vs CsA
		Difference from CsA	3.3
		97.3% CI	(-5.2, 11.8)
		Comparison groups	Belatacept LI vs CsA
		Difference from CsA	3.6
		97.3% CI	(-5.0, 12.3)
	Secondary endpoint: Mean (SD) GFR (mL/min/1.73m^2) measured	Comparison groups	Belatacept MI vs CsA
		Difference from CsA	6.9
		97.3% CI	(1.1, 12.7)
		P-value (ANOVA)	0.0083
		Comparison groups	Belatacept LI vs CsA
		Difference from CsA	4.3
		97.3% CI	(-1.5, 10.1)
		P-value (ANOVA)	0.1039
	Secondary endpoint: Mean (SD) GFR (mL/min/1.73m^2) calculated	Comparison groups	Belatacept MI vs CsA
		Difference from CsA	7.4
		97.3% CI	(3.0, 11.8)
		Comparison groups	Belatacept LI vs CsA
		Difference from CsA	6.8
		97.3% CI	(2.4, 11.3)
	Secondary endpoint: Prevalence of CAN (n%)	Comparison groups	Belatacept MI vs CsA
		Difference from CsA	-6.8
		97.3% CI	(-18.2, 4.7)
		Comparison groups	Belatacept LI vs CsA
		Difference from CsA	-5.7
		97.3% CI	(-17.2, 6.0)

Notes	
Analysis description	

Clinical studies in special populations

Such studies have not been performed. There are no data in children or adolescents.

Supportive studies

Study IM103100 was an open-label randomised phase 2 controlled multiple-dose study of efficacy and safety of belatacept as part of a quadruple drug regimen in renal transplant recipients. The primary study objective was to assess the efficacy (prophylaxis of clinically-suspected and biopsy-proven acute rejection) at 6 months of belatacept vs CsA, when used in combination with MMF, corticosteroids, and basiliximab, using a non-inferiority design. Study M103100 formed part of the basis for selection of belatacept dosage schedules brought forward to the two pivotal studies. In this study, a belatacept LI regimen and a MI regimen were evaluated with either a 5 mg/kg q4week or a 5 mg/kg q8week maintenance schedule, starting at Month 4 for LI regimen and Month 6 for MI regimen. The Applicant has provided a thorough discussion on why the 4 week maintenance dose schedule instead of the 8 week maintenance dose schedule also investigated in this study was selected.

Study IM103010 was a phase 2 randomised open-label study of renal transplant subjects on a CNI-based regimen, randomised to treatment with either belatacept or continued CNI treatment. The primary objective was to assess the effects of a belatacept-based immunosuppressive regimen relative to a CNI regimen on the change in calculated GFR from baseline to 12 months post-randomisation.

Altogether 7.2 % of patients experienced an acute rejection after conversion to belatacept while none in the CNI continuation group; i.e. rather more rejections than what has been seen in other conversion studies. Graft and patient survival were not impaired in the belatacept group. A minor improvement of GFR was seen in the belatacept group. More AE, SAEs and treatment related SAEs were seen in the belatacept conversion group than in the CNI continuation group. In short, late conversion to belatacept from a CNI based regimen after renal transplantation was not advantageous in this study.

Study IM103034 was a 12 month phase 2 randomised open-label study of belatacept-based corticosteroid-free regimens in renal transplant recipients. The primary objective was to determine the rate of AR in different corticosteroid-avoiding, belatacept-based immunosuppressive regimens in *de novo* renal transplant subjects by 6 months post transplantation. Based on the PD it was concluded that the belatacept dosing regimen used in this study provided sufficient levels of drug to fully saturate the target site. It seemed as if a steroid-free and CNI-free belatacept-MMF therapy resulted in more rejections and more adverse events but better GFR at 12 months than steroid-free tacrolimus-MMF therapy in study IM103034. Significantly more rejections were seen in the belatacept-SRL treatment arm than in the other treatment arms. Subject and graft survival in the tacrolimus - MMF treatment arm were superior to the other two treatment arms. The composite of AR, death or graft loss by month 12 was significantly better in the tacrolimus-MMF arm than in belatacept arms. Calculated GFR was significantly better in both belatacept groups than in the tacrolimus-MMF group. More patients in the belatacept groups than in the tacrolimus-MMF group discontinued due to AEs.

Study IM103047 is an ongoing phase 2a open, multiple-dose study in de novo renal transplant subjects. All subjects are treated with the belatacept LI 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). The primary objective was the evaluation of the pharmacokinetics of belatacept in renal transplant subjects receiving i.v. infusions at

10 mg/kg and data were presented in the interim PK report. As request by the CHMP the synoptic report for IM103047 was provided by the Applicant.

Study IM103045 is a phase 2 randomised, partially-blinded (for belatacept dose only), active-controlled, parallel group study in de novo liver transplant subjects to study efficacy, safety, immunogenicity, and PK in this category of patients.

In the liver transplant, belatacept based regimens were less effective compared to standard of care regimen, tacrolimus **±** MMF + steroids. Two cases of PTLD and one case of PML occurred in belatacept treated patients.

Based on the results from study IM103045, a warning against the use of belatacept in the clinical liver transplantation has been introduced into section 4.4 of the Nulojix SmPC and a reference to a short information on the results from this study has been included in section 5.1 the SmPC.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The choice of CsA, rather than tacrolimus, as comparator in the pivotal studies is justified by the Applicant by stating that more long term data are available from studies that have been performed with CsA than with tacrolimus. Although this is true, a majority of renal transplant recipients are nowadays treated with tacrolimus as calcineurin inhibitor. As CsA (but not tacrolimus or sirolimus) interacts with MMF, a lower exposition to MMF can be foreseen in the CsA arm than in the belatacept treatment arms. This could mean that patients in the belatacept treatment arms have a greater contribution to their total immunosuppressive pressure from MMF than patients on the combination of CsA have. The expected difference in MMF exposure between CsA and belatacept groups was confirmed in a pharmacokinetic substudy. In pivotal studies, the use of lymphocyte depleting therapy, LDT, was permitted in the early posttransplant period in study subjects randomised to CsA only, but not to subjects randomised to belatacept. These differences with respect to MMF exposure and LDT are inherent properties of the immunosuppressive strategies that are compared and might be useful in explaining some of the findings, but should not question the overall comparison of the strategies. The Applicant demonstrated that the rate of MMF-related adverse events was not significantly higher in the belatacept treatment groups.

The CHMP advice given on this study was that, as the expected proportion of patients experiencing graft loss or death within one year in this low risk population would be low, the sensitivity of the primary endpoint needed to be increased, e. g. by using a composite of death, graft loss and biopsy proven acute rejection as the primary endpoint. The Applicant instead chose to include biopsy-proven acute rejection as a separate third primary endpoint. Although this approach is also informative, it leaves the problem with the lack of sensitivity in the primary endpoint unattended. Although not in detail identical to those recommended in the CHMP guideline on the clinical investigation of immunosuppressants for solid organ transplantation, the principal study objectives in this study are to a great extent in accordance with those recommended in the guideline.

Efficacy data and additional analyses

The young age of donors and recipients, the high percentage of living donors and the absence of donors with risk factors indicate that patients in IM103008 constitute a renal transplant population at an unusually low risk. Study IM103027 with older recipient and donor age, a majority of donors in IM103027 with cerebrovascular risk factors, no living donors in IM103027 but instead a considerable number of donors with cardiac death appears to be more relevant for European renal transplant recipients in general.

Numbers for death and graft loss are not remarkable but were generally higher in IM103008 than in IM103027. Although not significant, there were numerical differences in favour of belatacept with respect to subjects surviving with a functioning graft at 12 and 36 months in both studies. There was a remarkable difference in the incidence of graft thrombosis between belatacept and CsA treatment groups in study IM103027 only, without difference between treatment arms for other types of thromboembolic events. This difference was systematically explored by the Applicant but no clear explanation could be given. Graft thrombosis is considered as a potential risk in the RMP and information about the findings in study IM103027 is given in the SmPC.

With respect to renal function the difference between the belatacept LI group and the CsA group was less pronounced and did not reach formal statistical significance in study IM103027 in contrast to in study IM103008. It is difficult to find an obvious explanation to the difference in renal function between the two belatacept arms in IM103027 at 12 months, as the total number of acute rejections was not higher in the LI group than in the MI group and as the rate of more severe rejections did not significantly differ between the two belatacept groups in this study. A main difference between studies is of course the worse graft quality in IM103027. The difference in renal function between the belatacept treatment arms and the ciclosporin treatment groups was sustained through 36 months of treatment in both pivotal studies.

In study IM103008, patients in both belatacept groups had a much higher incidence of acute rejections, in particular more severe rejections, than patients in the CsA group. Of patients who experienced an acute rejection, more than half of patients in all treatment groups in both pivotal studies had returned to their baseline serum creatinine level at month 12, in belatacept as well as in CsA groups. Return to baseline creatinine after an acute rejection is considered to be a good prognostic sign for renal transplant recipients. Thus, it could be expected that a higher percentage of patients in the belatacept groups should have worse GFR at month 24. This was however not the case. Patients in study IM103008 who had not experienced an acute rejection developed more CAN in the CsA group than patients in any of the belatacept groups did while this difference between treatments was hardly discernable for study patients who had experienced a rejection. In study IM103027, there were no differences between treatment groups in the incidence or prevalence of CAN at 12 months, irrespective if patients had had a rejection or not. As expected, patients who had a biopsy finding of CAN at 12 months had worse GFR values, irrespective of treatment group. Belatacept treated patients tended to have a better GFR, irrespective of CAN status.

The differences in acute rejections do not seem to have an impact on subject and graft survival at 12 months, and the 36 month study data did not point to a significant deterioration with time up to 3 years after transplantation.

2.5.4. Conclusions on the clinical efficacy

Belatacept in a less intensive as well as in a more intensive dosing schedule was demonstrated to be noninferior to ciclosporin in a low risk as well as in a high risk population with respect to subject and graft survival at 12 months. Results from 12 and 24 months were sustained through 36 months.

For the second co-primary endpoint renal function, superiority was convincingly demonstrated for the applied low intensity dosage regimen in study IM103008 only. The results are driven by the incidence of patients with GFR< 60 at 12 months, however the results were later demonstrated to be applicable for different GFR levels, at least between 45 and 75 ml/min in study IM103008 and 35-65 ml/min in study IM103027 although much more pronounced in study IM1030008 with less donor and recipient risk factors.

A third co-primary endpoint of acute rejection was included in study IM103008 and showed significantly more acute rejections during the first 12 months in both belatacept study arms. This finding is not consistent with the results for other endpoints but does not seem to have an impact on subject and graft survival or renal function during the first 12 months. Although the excess of early acute rejections on belatacept treatment did not seem to have a detrimental impact on the overall patient and graft survival or on renal function at 36 months, it should be considered that it may increase the need for renal biopsies, hospital care and additional immunosuppressive treatment for patients treated with belatacept.

The patients in study IM103027 had more risk factors than patients in study IM103008, but they still achieved an approximately 35 % higher calculated GFR than patients in the CsA group (compared to an approximately 45 % higher calculated GFR for patients on belatacept, compared to CsA-treated patients, in study IM103008) which is considered as a clinically meaningful effect.

2.6. Clinical safety

Patient exposure

A total of 2347 subjects were enrolled in clinical studies of belatacept. Of these, 1495 subjects received belatacept. Within the 3 core studies, safety data are available for 1425 subjects (477, 472, and 476 subjects in the belatacept MI, LI, and CsA groups, respectively).

The safety analyses were performed using the ITT population for IM103008 and IM103027 and the as-treated population in IM103100. A total of 365 (77%), 369 (78%) and 350 (75%) subjects had at least 12 months of exposure to study medication, and 326 (68%), 339 (72%), and 288 (62%) subjects had at least 24 months of exposure in belatacept MI, LI, and CsA groups, respectively. The pooled median exposure was 864, 867, and 843 days in belatacept MI, LI, and CsA respectively. Approximately 8% (77/947) and 4% (42/947) of subjects had exposure to belatacept for at least 5 and 7 years, respectively. The median follow-up in the pooled core studies at the time of database lock was 894, 867, and 813 days in the belatacept MI, LI, and CsA groups, respectively. Safety data are below presented as pooled analyses on data from the pivotal studies + study IM103100, as these studies had similar study protocols and the same medication in the same three treatment groups.

Adverse events

The most frequently reported AEs among belatacept subjects were anemia, peripheral edema, constipation, diarrhea, and UTI. Overall, the majority of common AEs occurred within the first 3 months. Among the most common AEs (reported for ≥10% of subjects in any treatment group) up to month 12, those reported with at least a 2% increased frequency in the belatacept LI group compared with the CsA group included hypophosphatemia, hyperkalaemia, hypokalaemia, hypocalcamia, diarrhea, vomiting, procedural pain, pyrexia, proteinuria, hypotension, cough, and headache. These AEs were reported in the belatacept MI group at similar or lower frequencies compared with the belatacept LI group. Among the most common AEs up to month 12, those reported with at least a 2% increased frequency in the CsA group compared with the belatacept LI group included dyslipidemia, graft dysfunction, hirsutism, incision site pain, peripheral edema, leukopenia, renal tubular necrosis, hypertension, increased blood creatinine, dyspnea, tremor, and insomnia.

Malignancies: The total incidence of malignancy up to database lock in the core studies was 9.6 % in the MI group, 5.7 % in the LI group and 7.1 % in the CsA group. Narratives were submitted for all subjects who died or discontinued for a diagnosis of malignant neoplasm. All over, patients in the belatacept MI and CsA treatment arms tended to have more cancers than patients in the belatacept LI arm. Yearly incidence rates of malignancy stayed constant during the study period. Skin cancers, in

particular non-melanoma skin cancers, tended to be less common in the belatacept LI group than in the other two groups. 5 cases of breast cancer occurred in the belatacept MI group in the core studies, 1 in the LI group and one in the CsA group.

Post transplant lymphoproliferative disorder (PTLD): An increased frequency of this kind of malignant lymphoma was observed in the 3 core belatacept clinical studies and a comprehensive evaluation was therefore performed. The cumulative frequency of PTLD up to database lock was higher in the belatacept LI group compared with the CsA group, and lower in the belatacept LI compared with the MI group: 8 (1.7%), 5 (1.1%), and 2 (0.4%) cases in the belatacept MI, LI, and CsA groups, respectively. Up to database lock, the overall frequency of PTLD in combined belatacept MI and LI groups was 1.4% (13/949) compared with 0.4% (2/476) for the CsA group. All subjects with PTLD discontinued treatment following the event. Of the 15 subjects with PTLD, 9 died. Of the 8 PTLD cases with CNS localisation (6 from the MI and 2 from the LI group), 5 died. The risk of developing PTLD appears to be highest in the first 18 months and to decline thereafter. Median exposure to belatacept was 2.4 years in phase 3 and 6 years in phase 2 studies. The mean age for patient who developed PTLD was 41 - 53 years; the majority were males; 8 subjects had EBV-negative and 5 subjects had EBV-positive serologies at baseline, and in 2 subjects, EBV status was unknown. All but 1 of the 15 subjects with PTLD received CMV prophylaxis post transplant. There were no protocol-mandated specifications for the pathological assessment of the PTLD cases; histological characterisation was performed as per local guidelines and practice. Local pathology reports were available for all 15 cases. The predominant PTLD phenotype was of B cell origin, with the exception of one subject in the belatacept LI group who had a predominant T cell PTLD. A post-hoc evaluation was done by a blinded central pathologist for 13 of the 15 PTLD cases (6, 5, and 2 cases in the belatacept MI, LI, and CsA groups, respectively). Local histological data were completed on special case report forms by the sites on 14 of the 15 PTLD cases (7, 5, and 2 in the belatacept MI, LI, and CsA groups, respectively). Central and local pathology assessment was comparable for 11 of the 13 PTLD cases. Two centrally assessed cases were classified as not compatible with the diagnosis of PTLD. Both cases were in EBV positive recipients in the LI group and were diagnosed as PTLD in the renal allograft by the local pathologist. The central pathologist assessed one of the cases as acute rejection and the other as reactive T cell proliferation. Both subjects received treatment for PTLD based on local assessment and are alive with a functioning graft. The analyses related to PTLD presented here were based on all 15 cases of PTLD based on the local assessment of PTLD. A multivariate analysis suggested that the use of LDT, rather than BPAR, was associated with development of PTLD. The use of LDT was more strongly associated with increased risk in EBV-negative subjects compared to EBV-positive subjects; 3 out of 11 subjects who were EBV-negative and received LDT developed PTLD, whereas out of 102 subjects who were EBV positive and received LDT, only 1 developed PTLD. This subject also had an additional risk factor of CMV infection. The frequency of PTLD was higher in subjects with >1 risk factor in the belatacept MI group; this increase was not observed in the other 2 groups, but the numbers of subjects with >1 risk factor were small. A comparison concerning the incidence of PTLD was made between the belatacept pooled core study safety database and three large transplant databases: the Europe based CTS database (11000 transplants/year), the US based UNOS database (16000 transplants/year) and the US based USRDS database (6000 transplants/year). Comparisons were made for first single kidney transplants performed during the period 1995 – 2006, followed for 3 years after transplantation. In the clinical belatacept studies, PTLD commonly occurred in the CNS, while it typically involves the CNS in approximately 12% to 18% of cases in external databases. The 3-year incidence of PTLD in belatacept-treated subjects in these trials was high and manyfold higher than incidences reported from these transplant databases. 8/15 patients who developed PTLD were EBV-negative at the time of transplantation and EBV-status was unknown for 2. PTLD risk was 12-fold higher for EBV-negative patients than for EBV-positive patients in the core belatacept studies while in the external databases PTLD was 3 - 10 times higher in EBV-negative than in positive patients. Risk factors for PTLD were also

older age, a history of acute rejection, LDT treatment, posttransplant CMV infection, and belatacept MI regimen. The incidences of PTLD in CsA-treated subjects were comparable with those in the external databases.

As a consequence of these analyses, the SmPC for belatacept contraindicates its use in patient negative for EBV or with unknown EBV status.

Thrombotic events: A greater number of graft losses independently adjudicated and attributed to graft thrombosis was seen in belatacept versus CsA subjects in study IM103027. In the combined core studies, results of this evaluation did not identify any increased risk of thrombosis with belatacept. In study IM103027, renal vein thrombosis was reported more frequently up to database lock in the belatacept LI group compared with the CsA group (1.1% vs. 0), and less frequently for belatacept LI compared with the belatacept MI group (1.1% vs. 3.3%). An independent adjudication committee reviewed all cases of allograft loss to determine the cause. Up to month 12, the frequency of primary allograft thrombosis as an adjudicated cause of allograft loss was reported for 7 (3.8%), 8 (4.6%), and 2 (1.0%) subjects in the belatacept MI, LI, and CsA groups, respectively, in IM103027; 1 (0.5%), 1 (0.4%), and 3 (1.3%) subjects, respectively, in IM103008; and 1 (1.4%), 1 (1.4%) and 2 (2.8%) subjects, respectively, in IM103100. The frequency of renal vein thrombosis alone reported for recipients of extended criteria donor kidneys in the USRDS database was 7.3%. The frequency of *all* thrombotic events was similar across the 3 treatment groups up to month 24 (9% in all groups), and up to database lock (10% in all groups). The cumulative frequency of thrombotic events up to database lock was higher in study IM103027 (14 - 15%) than in IM103008 (5% - 8%) or IM103100 (8% - 11%). Within studies, the frequency of thrombotic events was similar across treatment groups. In study IM103100, 2 patients in the CsA group lost their grafts due to venous thrombosis while 1 patient in each belatacept group suffered a graft thrombosis.

Infections: The incidence rates of infections per 100 patient years of exposure were higher in the first year versus cumulatively up to database lock. The frequency of serious infections up to database lock was for the belatacept LI group 32%, for the belatacept MI group 37% and for the CsA group 36%. Similar results were seen at the earlier time points. The frequency of serious viral infections was similar across treatment groups (13%, 10%, and 10% of subjects in the belatacept MI, LI, and CsA groups, respectively).

CMV infections: The frequency of CMV infections was similar across treatment groups during the study period and up to database lock for the belatacept MI, LI, and CsA groups, respectively. Adverse events of CMV infection (PT) led to discontinuation of study drug for 5 (1.0%), 5 (1.1%), and 0 subjects in the belatacept MI and LI, and CsA groups, respectively.

Polyoma virus infections: The frequency of polyoma virus infection was lower in the belatacept LI group compared with the belatacept MI and CsA groups. One subject who received belatacept MI, MMF and corticosteroids developed progressive multifocal leukoencephalopathy (PML) that was confirmed to be JC-virus positive in year 2. The frequency of polyoma virus infection was lower in the belatacept LI group compared with the belatacept MI and CsA groups up to month 12 (5%, 2%, and 5% in the belatacept MI, LI, and CsA groups, respectively), up to month 24 (6%, 3%, and 6% in the belatacept MI, LI, and CsA groups, respectively), and up to database lock (7%, 3%, and 6% in the belatacept MI, LI, and CsA groups. Serious polyoma virus infection was reported for 7 (1.5%), 2 (0.4%) and 4 (0.8%) subjects in the belatacept MI, LI, and CsA groups, respectively. AEs of polyoma virus infection led to discontinuation of study drug for 3 (0.6%), 3 (0.6%) and 1 (0.2%) subjects in the belatacept MI, LI, and CsA groups, respectively. Three subjects had polyoma virus infections with an outcome of death, 1 (0.2%) subject in the belatacept MI group and 2 (0.4%) subjects in the belatacept LI group. Polyoma virus infection was more frequent in IM103008 and IM103027 studies than in IM103100. Polyoma

virus-associated nephropathy was reported for 5 (1.0%), 3 (0.6%), 6 (1.3%) subjects in the belatacept MI, LI, and CsA groups, respectively. These events were reported as serious for 3 (0.6%), 1 (0.2%), and 2 (0.4%) subjects and led to discontinuation for 1 (0.2%), 2 (0.4%), and 1 (0.2%) subject in the belatacept MI, LI, and CsA groups, respectively. In addition, 1 (0.2%), 3 (0.6%), and 0 additional subjects in the belatacept MI, LI, and CsA groups, respectively, had polyoma virus-associated nephropathy beyond 56 days after the last dose date; all of these events were serious. Including these events, a total of 6 (1.3%), 6 (1.3%), and 6 (1.3%) subjects in the belatacept MI, LI, and CsA groups had polyoma virus associated nephropathy. Five of these subjects experienced graft loss (1 MI, 4 LI and 0 CsA), and in all but one of these cases, graft loss was attributed to polyoma virus associated nephropathy. Three subjects with polyoma virus-associated nephropathy died; (1 MI, 2 LI); the primary cause of death in these subjects was B-cell lymphoma and sepsis in the subject in the belatacept MI group and disseminated tuberculosis and polyoma virus infection, respectively, in the 2 subjects in the belatacept LI group.

Herpes virus infections: The frequency of all herpes virus infections up to database lock was higher in the belatacept LI and MI groups than in the CsA group, due to an increased frequency of herpes simplex virus infections. Herpes zoster frequency was similar between the belatacept LI and CsA groups but higher in the belatacept MI group. Most herpes infections were not serious and only 1 led to discontinuation. The majority of subjects had received anti-viral prophylaxis. Up to month 12, the frequency of herpes infections was similar across treatment groups (8%, 7%, and 6% in the belatacept MI, LI, and CsA groups, respectively). The frequency of herpes infection was similar in the belatacept MI and LI groups and higher in both belatacept groups compared with the CsA group up to month 24 (14%, 11%, and 9% in the belatacept MI, LI, and CsA groups, respectively) and up to database lock (15%, 13%, and 10% in the belatacept MI, LI, and CsA groups, respectively). The most common herpes virus infections in all 3 treatment groups were herpes zoster and oral herpes. Herpes infections were reported as serious in few subjects. The frequency of serious herpes virus infection was lower in the belatacept LI group compared with the belatacept MI group and was similar in the belatacept LI and CsA groups: 11 (2.3%), 5 (1.1%), and 4 (0.8%) subjects in the belatacept MI, LI, and CsA groups, respectively. Serious herpes zoster was reported for 8 (1.7%), 4 (0.8%), and 3 (0.6%) subjects in the belatacept MI, LI, and CsA groups, respectively. Oral herpes led to discontinuation of 1 subject in the belatacept LI group; no other subjects with herpes infections discontinued. No herpes or herpes associated events were reported with the outcome of death.

CNS infections

Progressive Multifocal Leukoencephalopathy (PML): This mostly lethal condition is caused by JC virus. A case of serious PML was reported for a belatacept MI subject in study IM103027. The patient was a 65-year old white female who received a kidney from a deceased donor and was treated with basiliximab, belatacept MI, MMF and steroids. She experienced left homonymous hemianopsia on day 689 (~23 months post transplant). A CT scan on day 705 was negative for intracranial bleeding or other acute pathology. The cerebral spinal fluid (CSF) examination showed JC virus. Magnetic resonance imaging revealed a white matter lesion primarily in the right occipital lobe extending into the posterior right temporal lobe, consistent with PML. The patient was hospitalised on day 730 for progressive neurological deterioration and further evaluation. Study drug was discontinued on day 704. She died on day 754. The investigator-assigned cause of death was PML probably related to belatacept. A second lethal case of PML in the belatacept clinical program in a subject receiving an augmented belatacept MI regimen was reported after database lock in the liver transplant study IM103045.

In addition, *CNS PTLD* was reported more frequently in belatacept subjects than in CsA subjects. In response to these reports, a post-hoc evaluation of all potential CNS infections was done. In total, 11 subjects across all 3 treatment groups were identified as potentially having a CNS infection. Following review of these cases, 2 were not considered to be true CNS infections: One subject (CsA group) had

toxic encephalitis due to imipenem (leading to death), and one subject in belatacept LI group had suspected Lyme disease which was not confirmed (the event was reported as a nonserious AE and the patient continued on study drug). Excluding these 2 cases, the frequency of CNS infections was higher in the belatacept MI group than in the belatacept LI and CsA groups: 7 (1.5%), 1 (0.2%), and 1 (0.2%), respectively. CNS infections led to discontinuation in 4 subjects, all in the belatacept MI group, and an outcome of death in 2 subjects, both in the belatacept MI group.

Fungal infections: Fungal infections were reported less frequently in the belatacept LI group than in the CsA and belatacept MI groups. The frequency of fungal infections was lower in the belatacept LI group compared with the belatacept MI and CsA groups up to month 12 (14%, 11%, and 15% in the belatacept MI, LI, and CsA groups, respectively), up to month 24 (20%, 16%, and 19% in the belatacept MI, LI, and CsA groups, respectively), and up to database lock (22%, 17%, and 21% in the belatacept MI, LI, and CsA groups, respectively). The most common fungal infections were oral candidiasis, onychomycosis, and candidiasis not otherwise specified. Fungal infections were reported as serious for 10 (2.1%), 5 (1.1%), and 7 (1.5%) subjects in the belatacept MI, LI, and CsA groups. The most common serious fungal infections were Pneumocystis jirovecii pneumonia and cryptococcal meningitis. Fungal infections led to discontinuation of study drug in 2 subjects in the belatacept MI group (cerebral aspergillosis and cryptococcal meningitis) and 1 subject in the belatacept LI group (cryptococcosis). Fungal infections with the outcome of death were reported for 1 subject in the belatacept MI group, (bronchopulmonary aspergillosis) and for 1 subject in the belatacept LI group, (cryptococcosis), and 1 subject in the CsA group died on day 1473 from severe mucormycosis infection.

Pneumocystis jirovecii (carinii) pneumonia (PCP): The frequency of this disease was similar in all 3 treatment groups over time. Up to month 12, PCP was reported across studies for 2 (0.4%) 1 (0.2%), and 0 subjects, respectively. Up to month 24, PCP was reported for 3 (0.6%), 1 (0.2%), and 2 (0.4%) subjects in the belatacept MI, LI, and CsA groups, respectively. PCP was reported for 3 (0.6%), 1 (0.2%), and 2 (0.4%) subjects in the belatacept MI, LI, and CsA groups, respectively. The study protocols required PCP prophylaxis for 6 months following transplant. All subjects with PCP had received prophylaxis with trimethoprim/ sulfamethoxazole except 2 subjects; 1 each in belatacept MI and CsA group. All 6 cases of PCP reported up to database lock were serious. Two cases of PCP (1 each in the belatacept MI and LI groups) were judged by the investigator to be related to study drug. None of the PCP infections led to treatment discontinuation. One subject in the belatacept LI group who experienced PCP died due to myocardial infarction.

Tuberculosis: Tuberculosis (TB) was reported for a total of 10 subjects across the 3 core studies. More cases were reported in the belatacept groups compared with the CsA group. Nearly all cases of TB were reported in subjects who currently or previously resided in endemic areas. Up to month 12, TB was reported for 2 (0.4%), 2 (0.4%), and 1 (0.2%) in the belatacept MI, LI, and CsA groups, respectively. Tuberculosis was more frequently reported in the belatacept groups compared with the CsA group up to month 24: 5 (1.0%) subjects, 3 (0.6%) subjects, and 1 (0.2%) subject in the belatacept MI, LI, and CsA groups, respectively. and up to database lock: 5 (1.0%) subjects, 4 (0.8%) subjects, and 1 (0.2%) subject in the belatacept MI, LI, and CsA groups, respectively. Of the 9 cases of TB in belatacept subjects, 4 cases were pulmonary, 3 were extra-pulmonary and 2 were disseminated.

All 10 cases of TB were reported as serious. Eight of the 10 subjects with SAEs of TB lived in endemic areas at the time of onset of the event (4 in Brazil, 4 in India); 2 lived in France and one of these 2 had lived in Mali previously. All subjects in the core studies were screened for TB pre-transplant according to local guidelines. None had a previous history of TB. History of BCG vaccination in the past was positive for 4, negative for 3, and unknown for 3 subjects. The majority of subjects were treated with 3 - 4 drug anti-tuberculosis therapy. The event resolved in 7 subjects. Of the 3 events of TB that

did not resolve, 1 was in the belatacept MI group (resolution unknown) and 2 were in the belatacept LI group. TB infection led to discontinuation in 3 subjects: 1 in the belatacept MI group and 2 in the LI group. Two subjects had TB with fatal outcome. The primary cause of death as assigned by the investigator was septic shock, bronchopneumonia, and lower digestive hemorrhage in one subject and cardiac arrest in one subject.

Serious adverse event and deaths

Deaths

Overall, the total number of deaths in the core studies up to database lock was lower in the belatacept LI group than in the belatacept MI and CsA groups.

AEs with the outcome of death were reported for 21 (4.4%), 16 (3.4%), and 28 (5.9%) of subjects in the belatacept MI, LI, and CsA groups, respectively, up to month 24. The causes of death did not significantly differ between the 3 treatment groups. Infections and cardiac disorders were the leading causes of death in all 3 treatment groups. Death rate during the study period was lower in the belatacept LI group than in the two other treatment groups. Infections and infestations accounted for the majority of deaths in all treatment groups. In the CsA group, deaths due to cardiac disorders were more common than in any of the belatacept treatment groups. During the first year of treatment, the frequency of SAEs was lower in the belatacept LI group than in the belatacept MI and CsA groups. Infections were the most common SAEs across all 3 treatment groups. Up to month 12, the frequency of treatment-related AEs (TEAEs) was lower in the belatacept MI and LI groups (53% and 54%, respectively) than in the CsA group (72%) in the pooled analysis. The rate of TEAEs of infection was lowest in the LI group and the total number of subjects with a TEAE was also lowest in the LI group. TEAEs were less common in the LI group than in the other groups. More subjects in the CsA group than in any of the belatacept groups discontinued study drug due to an AE.

Contrary to what is found in most other studies with new immunosuppressives, discontinuations as well as discontinuations due to AEs were more common in the comparator arm than in any of the belatacept study arms. Discontinuation due to AEs was less common in the MI group than in the LI group which is also noteworthy as the MI group as a whole had more rejections and more SAEs than the LI group.

Laboratory findings

Clinical laboratory test results were evaluated at a central laboratory. For haematological parameters, there were no clinically significant differences between treatment arms for haemoglobin or leukocyte counts. Electrolyte values were similar between treatment groups. The proportion of patients for whom high bilirubin levels were reported at any time was higher in the CsA treatment groups in clinical studies, e. g. in study IM103027, the proportion of subjects with high bilirubin levels up to month 24 was 0.6%, 4.1%, and 5.5% for belatacept MI, LI, and CsA groups, respectively. In the belatacept MI, LI and CsA groups, hypocalcaemia was reported as an AE in 9.4%, 11.0%, and 8.8%, respectively up to month 12. The cumulative frequencies of hypophosphatemia reported as an AE up to month 24 were 17%, 21%, and 13% in belatacept MI, LI, and CsA groups, respectively. The majority of these AEs occurred 0 - 3 months post transplant. No events were serious and none led to discontinuation. The proportions of subjects taking phosphates as concomitant medications were similar across treatment groups. In studies IM103008 and IM103027, proteinuria was defined as central laboratory determined, 2+ urine protein for at least 2 consecutive visit dates. Up to 36 months, the proportion of subjects with proteinuria was 2 to 3 % higher in subjects on belatacept. This difference was primarily due to a slight excess of belatacept subjects with urine protein 2+ or greater at month 1. The urine protein profile was similar after month 3 across all groups. Urinary protein excretion was not quantified.

Immunoglobulins (IgG, IgM, and IgA) were assessed at baseline and at months 6, 12, 18, and 24 in studies IM103008 and IM103027. A greater reduction in mean immunoglobulin was observed from baseline to month 24 in belatacept treated subjects compared with CsA treated subjects. No association was seen between low immunoglobulin levels and the frequency of serious infections.

Vital signs: ECG assessments were based upon local evaluations of ECG. As nonclinical studies did not detect QTc interval changes, non-standardised locally read ECG assessments only were made in phase 3 studies. Overall, belatacept had no effect on the QTc interval.

Blood pressure: The mean systolic and diastolic blood pressure values were lower in the belatacept groups than in the CsA group at all time points.

Heart rate and *body temperature* were similar among groups and remained within normal range over time.

Mean *body weight* increased from baseline to database lock in all three study groups (to month 24 in IM103008: ~4 to 6 kg; IM103027: ~3 to 4 kg).

Safety in special populations

Subgroup analyses for SAEs and AEs for individual studies IM103008 and IM103027 were performed for the following baseline characteristics: Recipient age, gender, race, pre-transplant diabetes status, attributed cause of ESRD, pretransplant weight, most PRA, and without prior transplant; *Donor* fibrosis or vasculopathy in baseline biopsy, age, and donor condition; *HLA mismatch* donor/recipient.

The Applicant states that subgroup analyses demonstrated similar frequencies among each of the treatment groups that were consistent with the rates for the overall population in each study.

The frequency of overall infections and serious infections was higher in subjects with AR than in subjects without AR in both the LI and CsA groups but lower in the MI group. In subjects with AR, the frequency of infections was similar or lower in the LI group compared with the CsA group.

Safety in liver transplantation

In the liver transplant study IM103045, recipients of liver transplants from cadaveric donor were randomised into 5 treatment groups: Group 1) Basiliximab + Belatacept MI + Mycophenolate mofetil (MMF); Group 2) Belatacept (MI) + MMF; Group 3) Belatacept LI + MMF; Group 4) Tacrolimus (TAC) + MMF; Group 5) TAC. Dropout rate was highest in the belatacept LI + MMF group. Significantly more deaths occurred in the belatacept LI + MMF treatment groups than in the other groups. Key safety results at 12 months were the following:

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

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

AE = adverse event; SAE = serious adverse event.

More patients in the belatacept LI + MMF and tacrolimus treatment groups discontinued study due to AEs than patients in the other 3 treatment groups did. HCV recurrence was more common in the belatacept MI + basiliximab + MMF group and TAC+ MMF groups than in the other groups. Higher rates of viral and fungal infections were reported in the belatacept LI group. One case of progressive multifocal leukoencephalopathy (PML) occurred in the belatacept MI + MMF group. Two cases of PTLD occurred, one in the belatacept LI + MMF group and the other in the basiliximab+belatacept MI+MMF group. More thromboembolic events were reported in the belatacept LI 0 MMF and tacrolimus + MMF groups than in the other groups.

On the 10th January 2011, the Data Monitoring Committee (DMC) for this study recommended the study to be terminated in a non-urgent but timely manner. The primary reason for this recommendation was that there was an observed increase in the number of deaths and graft loss in 2 of the 3 belatacept treatment groups, which became more evident in the follow-up period extending beyond one-year post-transplant.

Review by the DMC of these individual events did not reveal evidence of a clear causal relationship between these events and the use of belatacept. There were also increased numbers of viral and fungal infections in patients in the belatacept arms. In addition, due to the large number of discontinuations, the number of ongoing subjects in each treatment group is quite small.

On the 24th of January, the Applicant communicated to the EMA and the CHMP the premature closure of the long time extension of study IM103045.

The patient population as well as the immunosuppressive regimens in study IM103045 were different from those used in pivotal studies with belatacept for the renal transplantation indication applied for, and the doses of belatacept in the liver study were higher. Since mortality in belatacept treatment groups in the renal transplant phase 3 studies was not increased in 36 month data, the findings from the liver transplant study is not considered at this stage to be important for evaluation of renal transplantation safety data. The MAH committed to submit for evaluation complete study data from the extension of the liver transplantation study IM103045 as soon as they are available.

Pregnancies: Only one woman became pregnant during belatacept treatment in a clinical trial. A 31-year-old woman in IM103100 became pregnant after 7 years of treatment with belatacept; she had an induced abortion without complications. Two healthy volunteers became pregnant at 12 months and 15 months, respectively, after a single dose of subcutaneous belatacept. These pregnancies resulted in normal births. All other pregnancies in the renal trials were in partners of subjects with a total of 15 pregnancies in 12 partners on belatacept (8 normal births, 2 spontaneous abortions, and 5

without neonatal outcomes reported). There were a total of 6 pregnancies in 6 subjects in the CsA treatment group (1 normal birth, 1 normal birth with neonatal jaundice, and 4 without neonatal outcome available).

Immunological events

Belatacept antibodies: Overall in subjects receiving belatacept as a component of a 4-agent immunosuppressive regimen in the phase 3 studies and the 4-week schedule of IM103100LTE, drug specific antibodies against belatacept were developed in 4.4 % (37/847) of the subjects during treatment. A total of 6 subjects had neutralising antibodies. Few seropositive subjects experienced events that might represent loss of efficacy or a safety issue related to development of antibodies to belatacept in the phase 3 studies or the long-term extension of IM103100. Immunogenicity appeared also to have no impact on elimination of belatacept. In IM103008 and IM103027, 31/796 (3.9%) subjects were seropositive during treatment (up to 56 days following the last dose) and approximately equal numbers of these seropositive subjects had transient or persistent antibodies. An additional 8/132 (6%) subjects seroconverted after discontinuation of belatacept for ≥56 days. The 56 day period was chosen because it represents approximately 7 half lives of belatacept. Samples positive to the modified CTLA4 portion of the molecule were analysed by bioassay in vitro for the presence of neutralising antibodies (NAb). Of the 53 subjects in the core renal transplant studies who were seropositive, 24 had antibodies against the CTLA4 portion of the molecule. Of these, 6/24 (25%) subjects were NAb positive. In IM103008 and IM103100 LTE, no seropositive subject died or experienced graft loss. There were 4 seropositive subjects in IM103027 having graft loss during year 1; all cases of graft loss occurred within 8 days of transplant with the cause being either technical or primary graft thrombosis. The occurrence of AR was generally comparable among seropositive, seronegative or indeterminate subjects. One seropositive subject developed Guillain-Barré syndrome. Antibodies to belatacept appeared only after event onset, and a causal relationship was deemed unlikely. Comparison of trough levels of belatacept in individual subjects as well as Bayesian predicted clearance of belatacept from population PK analysis in seronegative and seropositive subjects suggested that there was no appreciable effect of antibodies on the clearance of belatacept. During the initial posttransplantation period, relatively high proportions of subjects with indeterminate antibody status occurred due to concentrations of belatacept that exceeded the range of assay validation.

In the *healthy volunteer studies*, on the other hand, development of antibodies to belatacept seemed very frequent (80-100 %). Relevant data on antibody formation in healthy volunteers may only be extracted from studies IM103029 and IM103046 as these studies were the only healthy volunteer studies utilising the same (and most recent) method for detection of antibodies as in the phase 3 studies and the 4-week schedule of IM103100LTE. *Study IM103029* was a single dose SC study in 30 healthy subjects. A total of 23 belatacept-treated subjects developed antibodies to belatacept and a total of 13 of the seropositive belatacept-treated subjects were positive for neutralizing antibodies.

Study IM103029 was a single dose SC and IV study in 41 healthy subjects. Thirty-one subjects received a single SC dose (50-250 mg) and 10 subjects received 125 mg as an IV infusion. Between 80% and 100% of the subjects who received a SC dose and 100% subjects who received the IV infusion developed antibodies to belatacept. Among the 39 subjects who developed antibodies against the modified CTLA4 region of belatacept, 32 developed neutralising antibodies.

Hypersensitivty reactions: Those events that occurred within one hour after infusion were defined as *acute infusional events*. Up to database lock, 6 % in the MI group and 4% in the LI group experienced acute infusional events (e. g. hypotension, hypertension, flushing, headache). Across all 3 studies, 3 acute infusional events were reported as SAEs in the MI group, none in the LI group. These events resolved on the same day and the subjects continued in the study. No events of anaphylaxis occurred.

Those hypersensitivity reactions occurring later but no more than 24 hours post infusion were defined as *peri-infusional events*. Approximately 49% of subjects in the MI group and 50% in the LI group reported peri-infusional events up to month 24. The most commonly reported events were hypertension, nausea, hypotension, cough, and headache. Serious peri-infusional events were reported for 1.5% and 2.1% of patients in MI and LI groups, respectively. These SAEs included pyrexia, hypotension, and vomiting. There was no association between these events and belatacept antibodies. One patient in each of the belatacept groups discontinued due to hypotension. No events lead to death. There were no differences in frequency of acute or peri-infusional events between belatacept groups and CsA group on days 1 and 5 when all patients received basiliximab.

Autoimmune events: The frequency of autoimmune events through the studies was similar for the 3 treatment groups: 8 (1.7%), 9 (1.9%), and 10 (2.1%) in the belatacept MI, LI, and CsA groups, respectively. New onset diabetes mellitus occurred with similar frequency in all 3 treatment groups. The predominant autoimmune disorder reported in belatacept subjects was psoriasis: 3 (0.6%) subjects each in the belatacept MI and LI groups. The most common autoimmune disorder in CsA subjects was hyperthyroidism: 3 (0.6%) subjects). Few autoimmune events were serious: 2 (0.4%), 1 (0.2%), and 5 (1.1%) subjects in belatacept MI, LI, and CsA groups, respectively, or led to discontinuation: (2 (0.4%), 0, and 0 subjects in belatacept MI, LI, and CsA groups, respectively. Fewer autoimmune events were reported in IM103008 and IM103100 than in IM103027. No deaths were reported to be related to autoimmune events. One case of Guillain-Barre syndrome was reported in IM103027: a 25-year old white male in the MI group developed this complication about posttransplant day 200. The patient discontinued the study and underwent plasmapheresis treatment and thereafter recovered completely. He had no belatacept antibodies at the time of the event but became seropositive after discontinuation (d 380 and onwards). The investigator did not consider the event to be treatment related.

Safety related to drug-drug interactions and other interactions

MPA levels in subjects who were also taking MMF in IM103008 and IM103027 were assessed. MPA exposure was approximately 41% higher with belatacept than with CsA. The explanation to this is that CsA inhibits the enterohepatic recirculation of MPA.

Table 14. AEs commonly related to MPA toxicity up to database lock in IM103008 and IM103027

	Number (%) of Subjects					
	IM103008			IM103027		
	MI N =219	LI N =226	CsA N =221	MI N =184	LI N =175	CsA N =184
Diarrhoea	81 (37.0)	77 (34.1)	76 (34.4)	84 (45.7)	76 (43.4)	60 (32.6)
Nausea	52 (23.7)	56 (24.8)	63 (28.5)	47 (25.5)	39 (22.3)	46 (25.0)
Vomiting	33 (15.1)	44 (19.5)	40 (18.1)	30 (16.3)	44 (25.1)	36 (19.6)
Anemia	73 (33.3)	87 (38.5)	72 (32.6)	94 (51.1)	90 (51.4)	98 (53.3)
Leukopenia	38 (17.4)	43 (19.0)	39 (17.6)	50 (27.2)	36 (20.6)	51 (27.7)
Neutropenia	9 (4.1)	14 (6.2)	10 (4.5)	13 (7.1)	10 (5.7)	12 (6.5)
Infections/ Infestations SOC	173 (79.0)	181 (80.1)	175 (79.2)	148 (80.4)	143 (81.7)	148 (80.4)
Serious infections	60 (27.4)	64 (28.3)	65 (29.4)	87 (47.3)	69 (39.4)	81 (44.0)

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

Discontinuation due to adverse events

Discontinuation due to AEs was more common in the CsA group than in the belatacept groups. Study discontinuation due to an AE of infection was more common in the belatacept groups than in the CsA group but did not differ between the two belatacept groups. Discontinuation due to malignancy was most common in the MI group and least common in the CsA group. Study withdrawal due to gastrointestinal disorders was more common in the CsA group than in the belatacept groups. Several patients in the CsA group discontinued because of hirsutism; none in the belatacept groups did so.

Safety data to 36 months were submitted; these additional data did not change any safety conclusions.

Post marketing experience

No post marketing data is available.

2.6.1. Discussion on clinical safety

The total number of patients exposed to belatacept (734 for at least 1 year, 665 for at least 2 years, 77 for at least 5 years and 42 for at least 7 years is considered acceptable for this application from a safety point of view, in accordance with the ICH guideline CPMP/ICH/375/95. Since the belatacept MI and LI as well as the CsA treatment arms are identical in the 3 core studies in renal transplantation, pooling of data from these studies for safety analyses is justified

Patients in the belatacept MI and CsA treatment arms tended to have a higher incidence of malignancy as compared to the patients in the belatacept LI arm.

The 3-year incidence of PTLD in belatacept-treated subjects in the performed trials was high and many fold higher than incidences reported from three great transplant databases CTS, UNOS and USRDS. Of specific concern was that CNS involvement was unexpectedly common. PTLD located in the CNS usually has a severe prognosis. Six cases of PTLD in the belatacept MI group were situated in the CNS while only two of the cases in the LI group and none in the CsA group had this extremely uncommon localisation. The reason for this high incidence of PTLD with CNS localisation was discussed by the Applicant from a mechanistic point of view and in the light of experimental studies, but no definite reason emerged. Eight of the 15 patients who developed PTLD were EBV-negative at the time of transplantation and EBV-status was unknown for two resulting in an estimated PTLD risk that was 12-fold higher for EBV-negative patients than for EBV-positive patients. Because of this, the Applicant suggests that EBV-negative serostatus or serostatus for EBV unknown should be contraindications for belatacept which seems reasonable; poatapproval studies are also proposed. These precautionary measures are believed to be sufficient to reduce the risk for PTLD to an acceptable level, in level with database findings.

In the pivotal studies, mammograms were done at study inclusion and then yearly. The rationale for this routine is probably explained by the finding of breast tumours in a belatacept mouse study. No increase incidence of breast cancer was however seen in any of the belatacept and recommendations have been updated to follow local guidelines for breast cancer screening also for women on belatacept treatment.

Transplant thrombosis was significantly more common in belatacept groups than in CsA groups in study IM103027 only, and these thromboses were seen more frequently in the MI group than in the LI group. An obvious explanation is the fact that donors as well as recipients had more risk factors in this study than in IM103008. As these background factors were the same in all three treatment groups, the fact that so many more graft thromboses occurred in the belatacept treatment groups can however not be explained by baseline factors in this study. The Applicant has extensively discussed possible

mechanisms for an increased thrombogenicity in the transplant situation with belatacept, and provided preclinical and clinical data that did not suggest any mechanism for a connection belatacept and activation of coagulation mechanisms in the early posttransplant situation. Information on transplant thrombosis is however now given in sections 4.4 and 5.2 of the SmPC, and is an important possible risk in the RMP.

During the first year after transplantation, *SAEs of infection* were less common in the LI group than in the MI and CsA groups. The same was true also for herpes virus infections, polyoma virus infections and fungal infections. Polyoma virus infections in the kidney transplant can cause severe harm to the transplant as nephropathy is commonly associated with the infection; the increased incidence of polyoma virus infections in the MI group could be a sign of overimmunosuppression in this group. The increased rate of herpes virus infection in both belatacept groups could also be a sign of impaired resistance to viral infectious agents. Herpes infections tended to be more common in the MI group than in the LI group. The Applicant discussed, from a mechanistic point of view, the increased susceptibility to certain viral infections during belatacept treatment in the pivotal studies.

CNS infections were reported more frequently in the belatacept MI group than in the belatacept LI and CsA groups. Of particular concern are the two lethal cases of PML among the betalacept treated patients. A warning has been included in the SmPC regarding PML. This risk is also addressed in the RMP.

Tuberculosis was more common in both belatacept groups than in the CsA group. Based on the data provided by the Applicant, it is concluded that CD28 costimulation seems to be more important following initial exposure to a pathogen than in the chronic phase of a polyoma virus infection and the same is most likely true for the special case of exposure to mycobacteria. Section 4.4 in the SmPC has been strengthened with regard to the risk for tuberculosis.

In subgroup safety analyses, the results on the impact of an acute rejection for risk of malignancies and infections are complex. As could be expected, the overall rate of infections and of serious infections was in all groups higher in patients who had been treated for an acute rejection. By dosing by body weight, the Applicant was asked to discuss the potential risk of overexposure in obese patients. The exposure is predicted to be somewhat higher in obese subjects and the Applicant submitted safety subgroup analyses for weight and BMI. These subgroup analyses did not reveal a systematic increase of adverse events in the highest weight/BMI categories in the belatacept groups.

Belatacept is a potent immunosuppressive agent and could impair the development of the immune system in the fetus if administered to *pregnant women*. The wording on pregnancies in the SmPC has been amended to provide this information.

In study IM103045, a phase II 12 month study in liver transplantation, there was an increased mortality in all three belatacept treatment arms and the long time extension of the study was therefore prematurely terminated. The Applicant has subsequently submitted all available data on the deaths in the study. There were a wide variety of causes of death. The presence of 2 cases of PTLD and 1 case of PML in belatacept treated subjects, together with an increased incidence of viral and fungal infections in the belatacept treatment groups are however suggestive of overimmunosuppression in these treatment arms. It is noted that one or two more belatacept doses were given in the early posttransplant course in this liver study than in the renal transplant studies, which is unexpected as liver transplant recipients in general are considered to have less need for immunosuppression than renal transplant recipients. The section 4.4 of the SmPC has been updated with a warning against the use of belatacept in liver transplantation and a short information on the liver study results has been introduced into section 5.1. Furthermore, off label use is identified as a potential risk in the RMP and follow-up queries will be sent on spontaneous reports of off-label use and off label use will be studied in two planned pharmacoepidemiology studies.

Antibody formation against belatacept seems to be very frequent in healthy volunteers. For belatacept, only limited data from healthy subjects is available for the IV route but data indicate a large potential for development of antibodies directed against belatacept (also neutralising). The large difference in antibody formation between healthy volunteers and patients is likely a consequence of the absence of immunosuppression in healthy subjects. Few seropositive subjects experienced events that might represent loss of efficacy or a safety risk related to belatacept antibodies in the phase 3 studies or the long-term extension of IM103100. However, conclusions on the relationship between antibodies against belatacept (neutralising and/or non-neutralising) and efficacy or safety are not very robust due to the low numbers of patients with antibodies. This problem was discussed by the Applicant. More data will be collected postapproval. Based on the data from healthy volunteers, one would expect a higher risk of developing antibodies, and also neutralising antibodies, against belatacept in stable transplant recipients on a low level of maintenance immunosuppression in the late posttransplant phase. Especially in a situation when belatacept therapy is temporarily stopped and then resumed (as could e.g. be the case if a patient becomes pregnant), one could fear that the risk of developing antibelatacept antibodies could be considerable.

Thus, there are insufficient data on the correlation between antibodies and efficacy or safety and no data on the development of antibodies in patients on a low level of immunosuppression or after resuming belatacept after an interruption of belatacept therapy. These safety concerns have been adequately addressed in the RMP. In addition, adequate information on the risk of developing antibodies to belatacept has been included in the section 4.4 of the SmPC.

Six percent of patients developed belatacept antibodies after discontinuation of belatacept. The Applicant has proposed the updates in RMP with a plan designed to improve the understanding of the relationship between antibody development and peri-infusional events within the clinical trials.

Autoimmunity: There is a theoretical concern that treatment with belatacept might increase the risk of autoimmune processes and the risk for autoimmunity should be considered. Belatacept treated patients in the pivotal studies did not have an increased incidence of autoimmune conditions but autoimmunity is identified as an important potential risk in the Risk Management plan and enhanced pharmacovigilance, with targeted questionnaires for autoimmunity will be used postapproval.

New case of PTLD: On 5 April, the Applicant informed the CHMP about a new case of PTLD in the long-term extension phase of study IM103027. The investigator reported that a 60-year-old black male was hospitalized on 21-Feb-2011 with fever and nausea. Work-up revealed that the patient had PTLD. This patient underwent kidney transplantation on 19-Jul-2006 and was randomized to the less intensive dosing regimen of belatacept. His medical history included Type II diabetes mellitus (1985) progressing to insulindependency (2000), diabetic retinopathy, hypertension (Oct-2000), dyslipidaemia, gastrointestinal haemorrhage, colonic polyp, gangrene of toes with toe amputation (04-Aug-2010-04-Sep-2010), end stage renal disease (Oct-2000), nephrolithiasis (1977), sinusitis, glaucoma, cataract, arteriovenous grafts (four-with the last in Feb-2002), gastric mucosal tear (2005) and shoulder reconstruction (1992). At the time of transplantation, the recipient was CMV positive and EBV negative. The donor was CMV positive and EBV unknown. The patient had been receiving oral valganciclovir 450 mg daily since 20-Jul-2006 for CMV prophylaxis. The week-52 renal allograft biopsy (18-Jul-2007) showed no acute rejection. EBV serologies performed on 21-Dec-2009 showed that the patient had seroconverted, and quantitative EBV viral load by PCR was 100 copies/ml. On repeat assessment 1 year later (21-Dec-2010), EBV viral load by PCR remained at 100 copies/ml. The patient did not experience AR, LDT use or CMV infection. Following presentation with fever and nausea on 21 Feb 2011, a positron emission tomography (PET) scan showed an enlarged transplant kidney. PTLD was diagnosed by open kidney graft biopsy on 21-Mar-2011 (study day 1707). A subsequent EBV viral load by PCR showed that it was positive but levels were too low to quantify. Belatacept and MMF were both withdrawn following diagnosis of PTLD and the patient was started on sirolimus 1 mg daily and

prednisone 20 mg daily. The fever and nausea resolved on 22-Mar-2011 and the patient was discharged from the hospital that day. Serum creatinine was 1.5 mg/dL at the time of discharge. Cytogenetic study results are currently pending.

All transplant recipients, irrespective of immunosuppressive therapy, are at increased risk of PTLD, particularly during the first 2 years after transplantation. The absolute size of risk increase for PTLD is closely related to the total burden of immunosuppression, and to serostatus for EBV (seronegative patients being at increased risk).

This second case of PTLD reported after the 36 month study period in the belatacept pivotal study. The patient in this case had only one risk factor for PTLD, but that was the most important risk factor negative EBV status at transplantation. Nulojix is not recommended for patients with a negative or unknown EBV serostatus at transplantation.

The CHMP therefore concluded that this newly reported case of PTLD is not considered to evoke any new concerns about the use of belatacept in renal transplant recipients, and is not considered to alter the positive total benefit risk balance of the drug. The contraindication for the use of belatacept in patients without a confirmed EBV-positive EBV serostatus, together with the measures undertaken in the Risk Management Plan, is considered to be adequate to control the risk for posttransplant PTLD during belatacept treatment.

2.6.2. Conclusions on the clinical safety

The risk profile for belatacept is to a great extent similar to what is seen with other immunosuppressive agent, especially risks of developing infections and malignancies. The mechanism of action is not completely clarified. There may be specific risks linked to this drug as it has a different mechanism of action to the calcineurin inhibitors, namely specific blockade of the co-stimulatory signal. Of specific concern is the number of patients that developed posttransplant lymphopfoliferative disease which unexpectedly was located in the CNS in several cases. Therefore, a contraindication in EBV-negative subjects and in addition an amended RMP is warranted. An important safety issue is also the two cases of lethal progressive multifocal leukoencephalopathy in patients on betalacept based regimens. Tuberculosis, infections with viruses of the herpes virus family, and polyoma virus infections was also seen in increased frequency in belatacept treated patients. The increased number of graft thromboses in belatacept treated patients in the high risk transplant population is also notable.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAH submitted a risk management plan, which included a risk minimisation plan.

Table 15 Summary of the risk management plan

Safety concern	Proposed Pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important Identified Risks:		
Important Identified Risk 1 - PTLD with preponderance of CNS location	• Routine PV including- targeted questionnaire for PTLD and supplemental case report forms for clinical studies • Additional PV - post-marketing pharmacoepidemiology studies (protocols IM103089 and IM103075)	• Contraindications in patients who are EBV-negative or serostatus unknown. (Section 4.3 of SPC) (additional). • Special Warnings and Precautions for Use (Section 4.4 of SPC) (routine). *In the Phase 2 and 3 studies (3 studies), the incidence of PTLD was higher in belatacept treated patients than in ciclosporin treated patients (see section 4.8). Belatacept-treated transplant recipients who are EBV seronegative are at an increased risk for PTLD compared with those who are EBV positive (see section 4.8). EBV serology should be ascertained before starting administration of belatacept. Transplant recipients who are EBV seronegative or serostatus unknown should not receive belatacept (see section 4.3).* *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 section 5.1).* *PTLD in belatacept 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.* • Undesirable Effects (Section 4.8 of the SPC) (routine). • Patient Alert Card (additional).
Important Identified Risk 2- Infections Serious infections	• Routine PV including targeted questionnaire for select infections • Additional PV - post-marketing pharmacoepidemiology study (protocol IM103089)	• Special Warnings and Precautions for Use (Section 4.4 of SPC) (routine). *Use of immunosuppressants including belatacept, can increase susceptibility to infection, including fatal infections, opportunistic infections, tuberculosis, and herpes (see Progressive multifocal leukoencephalopathy (PML) warning).* • Undesirable Effects (Section 4.8 of the SPC) (routine). • Patient Alert Card (additional).
Serious viral infection	• Routine PV • Additional PV - postmarketing pharmacoepidemiology study (protocol IM103089)	• Special Warnings and Precautions for Use (Section 4.4 of the SPC) (routine). Refer to Serious Infections. • Undesirable Effects (Section 4.8 of the SPC) (routine). • Patient Alert Card (additional).
Serious herpes infections	• Routine PV • Additional PV - postmarketing pharmacoepidemiology study (protocol IM103089)	• Special Warnings and Precautions for Use (Section 4.4 of the SPC) (routine) Refer to Serious Infections. • Undesirable Effects (Section 4.8 of the SPC) (routine). • Patient Alert Card (additional).
Serious CMV infections	• Routine PV • Additional PV - postmarketing pharmacoepidemiology study (protocol IM103089)	• Special Warnings and Precautions for Use (Section 4.4 of the SPC) (routine). Refer to Serious Infections. *CMV prophylaxis is recommended for at least*

		3 months after transplantation, particularly for patients at increased risk for CMV infection. Pneumocystis pneumonia prophylaxis is recommended for at least 6 months following transplantation. • Undesirable Effects (Section 4.8 of the SPC) (routine). • Patient Alert Card (additional).
Serious polyoma infections	• Routine PV	• Special Warnings and precautions for Use (Section 4.4 of the SPC) (routine). Refer to Serious Infections. • Undesirable Effects (Section 4.8 of the SPC) (routine). • Patient Alert Card (additional).
CNS infections	• Routine PV including - targeted questionnaire for infections and supplemental case report forms for clinical studies	• Special Warnings and Precautions for Use (Section 4.4 of the SPC) (routine). Refer to Serious Infections. • Undesirable Effects (Section 4.8 of the SPC) (routine). • Patient Alert Card (additional).
Serious fungal infections	• Routine PV • Additional PV - postmarketing pharmacoepidemiology study (protocol IM103089)	• Special Warnings and Precautions for Use (Section 4.4 of the SPC) (routine). Refer to Serious Infections. • Undesirable Effects (Section 4.8 of the SPC) (routine). • Patient Alert Card (additional).
Tuberculosis	• Routine PV including - targeted questionnaire for infections and supplemental case report forms for clinical studies • Additional PV - postmarketing pharmacoepidemiology study (protocol IM103089)	• Special Warnings and Precautions for Use (Section 4.4 of the SPC) (routine). Refer to Serious Infections. *Tuberculosis was more frequently observed in patients receiving belatacept than ciclosporin in clinical studies (see section 4.8). 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 belatacept. Adequate treatment of latent tuberculosis infection should be instituted prior to belatacept use.* • Undesirable Effects (Section 4.8 of the SPC) (routine). • Patient Alert Card (additional).
Important Identified Risk 3 -PML	• Routine PV including - targeted questionnaire for select infections and supplemental case report forms for clinical studies for select infections • Additional PV - post-marketing pharmacoepidemiology study (protocol IM103089)	• Special Warnings and Precautions for Use (Section 4.4 of the SPC) (routine). *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 belatacept, 2 cases of PML were reported in patients receiving belatacept at doses higher than the recommended regimen. In the renal transplant studies of belatacept, 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. As an increased risk of PML and of other infections has been associated with high levels of overall immunosuppression, the recommended doses of belatacept and concomitant immunosuppressives, including MMF or MPA, should not be exceeded (see section 4.5).* *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 neurologist 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 removal of belatacept.* • Undesirable Effects (Section 4.8 of the SPC) (routine). • Patient Alert Card (additional).
Important Potential Risks:		
Important Potential Risk 1 - Malignancies (other than PTLD), including non-melanoma skin cancers	• Routine PV • Additional PV - post-marketing pharmacoepidemiology studies (protocol IM103089)	• Special Warnings and Precautions for Use (Section 4.4 of the SPC) (routine). • Undesirable Effects (Section 4.8 of the SPC) (routine). *In addition to PTLD, patients receiving immunosuppressive regimens, including belatacept, are at increased risk of malignancies, including skin cancer (see section 4.8). Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.*
Important Potential Risk 2 - Autoimmunity	• Routine PV including - targeted questionnaire for autoimmunity	• Special Warnings and Precautions for Use (Section 4.4 of SPC) (routine). *There is a theoretical concern that treatment with belatacept might increase the risk of autoimmune processes.* • Undesirable Effects in Section 4.8 of the SPC (routine).
Important Potential Risk 3 - Immunogenicity	• Routine PV - Monitored in ongoing Phase 3 clinical trials • Additional PV - monthly collection of immunogenicity samples prior to infusion during the first year of new clinical trials	• Special Warnings and Precautions for Use (Section 4.4 of SPC) (routine). *The safety and efficacy of retreatment with belatacept has not been studied. The potential impact of pre-existing antibodies to belatacept should be taken into account when considering retreatment with belatacept following prolonged discontinuation, particularly in patients who have not received continuous immunosuppression.* • Undesirable Effects in Section 4.8 of the SPC (routine).
Important Potential Risk 4 - Infusion-related reactions	• Routine PV including - targeted questionnaire for hypersensitivity/ infusion related reactions and module for enhanced collection of patient reported events 48 hours post infusion (immunogenicity sample collected at the time of every infusion in year 1)	• Special Warnings and Precautions for Use (Section 4.4 of SPC) (routine). *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.*

		• Undesirable Effects (Section 4.8) (routine).
Important Potential Risk 5 - Off-label use	• Routine PV • Additional PV - postmarketing pharmacoepidemiology studies (protocol IM103077 and IM103074) will capture off label use, including use in liver transplant recipients and pediatric populations	• Contraindications (Section 4.3 of SPC) Contraindication in patients who are EBV negative or serostatus unknown (additional) and Therapeutic Indications (Section 4.1) in adults receiving a kidney transplant (routine). • Special Wanings and Precautions for Use (Section 4.4 of SPC) (routine). *The safety and efficacy of belatacept have not been established in liver 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 section 5.1).* • Posology and Method of Administration (Section 4.2 of SPC) stating the lack of data in children and adolescents (routine).
Important Potential Risk 6 - Venous thrombosis of the allograft	• Routine PV • including - targeted questionnaire for allograft thrombosis	• Special Warnings and Precautions for Use (Section 4.4 of SPC) (routine). *An increased incidence of graft thrombosis was observed in the post-transplant period in recipients of extended criteria donor allografts.* • Undesirable effects (Section 4.8) (routine).
Important Missing Information:		
Pregnancy and lactation	• Routine PV including - surveillance form for pregnancy and supplemental case report forms for clinical studies • Additional PV - Post-marketing pharmacoepidemiology study in the US protocol IM103061)	• Warnings and risk information related to pregnancy in Fertility, Pregnancy, and Lactation (Section 4.6) (routine). *Women of child bearing potential should use effective contraception during treatment with belatacept and up to 8 weeks after the last dose of treatment since the potential risk to embryonic/foetal development is unknown.*
Children and adolescents < 18 years old	• Routine PV • Additional PV - post-marketing pharmacoepidemiology study (protocol IM103089, IM103077 and IM103074) • Pediatric investigational plan (PIP) was submitted for review by the PDCO in the EU. The plan was accepted (EMEA decision P/99/2008) on 03-Nov-2008. The PIP compliance check was completed on 24 July 2009.	• Posology and Method of Administration (Section 4.2 of SPC) stating the lack of data in children and adolescents (routine).
Patients with hepatic impairment	• Routine PV	• Posology and Method of Administration (Section 4.2 of SPC) (routine). *No patients with hepatic impairment were studied in renal transplant protocols, therefore dose modification of belatacept in hepatic impairment can not be recommended.* • Pharmacokinetic properties (Section 5.2 of SPC) (routine). *There is no data available in patients with hepatic impairment.*

Retreatment after prolonged discontinuation	• Routine PV	• Special Wanings and Precautions for Use (Section 4.4 of SPC) (routine). *The safety and efficacy of retreatment with belatacept has not been studied. The potential impact of pre-existing antibodies to belatacept should be taken into account when considering retreatment with belatacept following prolonged discontinuation, particularly in patients who have not received continuous immunosuppression.*

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

- Alert Card that refers to SmPC and PL for the important identified risks, raises awareness for non-specialists of transplant surgery that a patient is on belatacept and of the time for next treatment.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

Belatacept represents a new therapeutic principle for basal immunosuppression, co-stimulatory blockade, in the prevention of graft rejection after renal transplantation. It lacks the nephrotoxic adverse effects of calcineurin inhibitors that are now the cornerstones of short time as well as long time immunosuppression after organ transplantation. Consequently, belatacept could potentially provide better long time transplant function, measured as glomerular filtration rate and, in a prolonged time perspective, give less chronic allograft nephropathy and thereby also a better long time renal graft survival. As it is a protein, a fusion of a modified Fc domain of human IgG1to the extracellular domain of human CTLA-4, it does not seem to interact with any of the enzyme systems of the liver, making pharmacokinetic interaction less probable.

As belatacept is administered intravenously once a month, it gives possibilities for a better control of patient adherence to therapy. Another benefit is that therapeutic drug monitoring does not seem to be required.

To establish the clinical value of a new immunosuppressive agent with properties hypothesised for belatacept, clinically relevant superiority in renal function relative to the existing alternatives without a detrimental effect of subject and graft survival should be demonstrated.

In pivotal clinical studies, belatacept in the applied low intensity dosing regimen was shown to be non-inferior to ciclosporin for the primary composite endpoint of patient and graft survival at 12 months, in a low risk transplant population (96.5% vs 92.8% subject or graft survival for belatacept and CsA, respectively, 97.3% CI: -1.1; 9.0) as well as in a high risk transplant population (88.0% vs 84.8%, 97.3% CI: -5.0; 11.4). At 36 months, the results for patient and graft survival the belatacept treated

groups remained non-inferior to ciclosporin in the low risk study population (92.2%, 92.0%, and 88.7%), as well as in the high risk study population (80.4%, 82.3%, and 79.9”, respectively).

In the low risk transplant population, belatacept was significantly superior to ciclosporin for the composite co-primary endpoint proportion of patients with GFR <60 at 12 months or a decrease in GFR>10 between month 3 and 12 (54.2% vs 77.9%, 97.3 CI: -33.3; -13.7)), while in a high risk transplant population the effect was less pronounced and did not reach formal statistical significance for the applied low intensive belatacept regimen (76.3% vs 84.8, 97.3% CI: -18.0; 0.9). However, in both studies the mean difference in calculated GFR tended to increase during the 36 month follow-up. The positive effects on renal function were shown to be sustained up to 36 months in both pivotal studies. Both belatacept treatment arms had better results for GFR than patients in the ciclosporin treatment arm in the low risk patient study IM103008, the difference between treatment arms was independent of where the cutoff point was applied, between 45 and 75 ml/min. The difference between treatments, in favour of belatacept, was also seen in the high risk patient study IM103027 but this difference was much less between treatment arms in the latter study.

A trend towards a lower prevalence of chronic allograft nephropathy (CAN) was demonstrated in the low risk study (23.9% vs 32.4%, 97.3% CI: -17.9; 0.9) and in the high risk study, although less pronounced, (46.0% vs 51.6%, 97.3% CI: -17.2; 6.0).

- Uncertainty in the knowledge about the beneficial effects

Non-inferiority was demonstrated for the composite endpoint of patient and graft survival in both pivotal studies, in spite of more episodes of acute rejection with belatacept treatment.

With respect to renal function, convincing positive effects on glomerular filtration rate and prevalence of chronic allograft nephropathy were observed in the low risk study only while no significant effects in the high risk study with patients and donors more representative for renal transplant centres in general. The effects were sustained during a 36 month study period but was more evident in a low risk patient population than in a high risk patient population. Nevertheless, patients in study IM103027 still achieved an approximately 35% higher calculated GFR than patients in the CsA group (compared to an approximately 45% higher calculated GFR for patients on belatacept as compared to CsA-treated patients, in study low risk study IM103008). Even the smaller difference between treatment groups in study IM103027 is considered as a clinically meaningful difference.

Whether the better renal function at 3 years this will also translate into a better all over survival time of renal transplants on belatacept in the very long run remains to be proven.

There were more acute rejections on belatacept treatment during the first 12 months, especially in the low risk study. Although the excess of early acute rejections on belatacept treatment did not seem to have a detrimental impact on the overall patient and graft survival or on renal function at 36 months, it should be considered that it may increase the need for renal biopsies, hospital care and additional immunosuppressive treatment for patients treated with belatacept.

Results from pivotal studies hint that the cardiovascular risk profile of belatacept seems to be better than that of calcineurin inhibitors but a final evaluation of a possible advantage in this area will have to await larger and more targeted long-term studies.

Risks

- Unfavourable effects

Major deficiencies were identified in the documentation supporting the proposed system for in-process control of the drug substance and further documentation was provided to assure that comparability between commercial product and product used in clinical studies.

The selection of these tests is generally considered appropriate, as they cover most of the observed or expected variability. There were, however, concerns raised on the performance of some of the analytical methods. In process of this procedure, the control in performance of analytical methods has been improved and is largely considered acceptable. However, some concerns remain related to the B7 bioassay and the SDS-PAGE analysis. Although these analyses are considered acceptable for confirmation of consistency in production using the currently established and validated process, they do not hold acceptable standard for analytical procedures to be used for demonstration of comparability of product in conjunction with future introduction of major changes in the commercial production process. The applicant is therefore requested to perform optimisation/validation studies to further improve the control of biological activity and purity in analysis by the B7 bioassay and the SDS-PAGE analysis.

The size of the safety data base and the exposure over time is acceptable for an application for a new immunosuppressive regimen in renal transplantation.

Belatacept, like other immunosuppressives, increases the risk of malignancies and infections (these risks are addressed in the SmPC and in the RMP). However there are clear indications that the belatacept based regimens are associated with some specific safety issues that warrant further evaluation and discussion. Posttransplant lymphoproliferative disease, PTLD, was significantly more common with belatacept than with ciclosporin, especially in EBV-negative graft recipients, and these cases have a bad prognosis with high mortality. A remarkable proportion of the PTLDs were localised in the CNS, a localisation otherwise very rare for this kind of disease. The mechanism behind this unusual localisation is unknown, as there are no data making plausible that belatacept should be able to cross the blood brain barrier. The risk of PTLD is addressed in the SmPC and the RMP. In clinical studies there were two cases of the very rare and lethal disease of PML (this risk is addressed in the SmPC and the RMP).

Other infections that were more common in belatacept treated patients than in the control group patients were infections with viruses from the herpes virus family, polyoma virus infections and tuberculosis. These risks are addressed in the SmPC and in the RMP.

Furthermore, graft thromboses were more common with the belatacept based regimens than with cyclosporine in one of the pivotal studies with high risk recipients and high risk donors.

In a phase 2 liver transplantation study, with immunosuppressive regimens different from those used in pivotal studies with belatacept for the renal transplantation indication applied for, and with a higher dose of belatacept, an increased incidence of infections and an increased mortality was seen. This is in contrast to renal transplant studies, where there was no increased mortality in belatacept treatment groups at 36 months in pivotal studies. The increased mortality on belatacept in the liver transplant study is most likely due to overimmunosuppression. A warning against the use of belatacept in liver transplantation has been introduced to section 4.4 of the SPC, information on the liver transplant study has been amended to section 5.1, and the RMP has been updated with respect to off label use of belatacept in liver transplantation. Complete study data from the extension of the liver transplantation study IM103045 will be submitted for evaluation as soon as they are available.

- Uncertainty in the knowledge about the unfavourable effects

The CHMP initially raised the potential of belatacept to block the inhibitory receptor CTLA-4 thereby enhancing the immune response. This has been adequately addressed through re-assessment of the available *in vivo* or clinical data hence the potential issue of immune enhancement was considered

resolved. Autoimmunity is identified as an important potential risk in the RMP, with enhanced pharmacovigilance activities.

As antibody formation, also of neutralising antibodies, was very frequent in healthy volunteers, there is a fear that antibodies to belatacept could be more common in patients on a low basal immunosuppression or in patients resuming belatacept therapy after a prolonged pause between infusions. Such antibodies could possibly cause allergic reactions or autoimmunity and possibly impair the therapeutic effect of belatacept. From aspects of immunogenicity and antibody development, efficacy and safety of belatacept in the retreatment situation have not been fully clarified, especially in the situation when belatacept is restarted after a prolonged period of time, with or without continued other immunosuppression. Therefore, a warning against retreatment has been added to section 4.4 of the SmPC and these safety concerns have been adequately addressed in the RMP.

Further assessment to rule out immunogenicity is needed and the RMP has been updated with a plan designed to improve the understanding of the relationship between antibody development and peri-infusional events within the clinical trials.

In addition, preclinical data shows that belatacept has a negative impact on the developing immune system and should therefore not be used in later phases of pregnancy. Thus, pregnancy would lead to a recommendation to change to another treatment regimen. It is not clear how to handle a woman that becomes pregnant during belatacept treatment and whether belatacept treatment can safely be resumed after pregnancy and childbirth or not. Therefore, a warning related to pregnancy and lactation has been added to section 4.4 of the SmPC and this safety concern has been addressed in the RMP.

Even if EBV-negative or unknown transplant recipient status is a contraindication for belatacept, PTLD remains as a risk in the Risk Management Plan and will be monitored in postapproval studies.

Benefit-risk balance

- Importance of favourable and unfavourable effects

The need for new effective immunosuppressant lacking the adverse nephrotoxic and cardiovascular effects of calcineurin inhibitors is great. Therefore, the positive effects of belatacept in terms of 1- and 3-year patient and graft survival and of renal function at 1, 2 and 3 years are important.

The increased number of acute rejections with belatacept did not impair the efficacy or safety of in a 36 month perspective and is therefore considered not to have a severe impact on the risk benefit balance for the product.

The observed increased incidence of posttransplant lymphoproliferative disease with severe prognosis and often lethal outcome is a safety concern as are the PML cases. These observations could indicate increased risks that are carefully dealt with in the SmPC and in the RMP. Belatacept is contraindicated in EBV-negative patients. The observed increased risk for other infections such as herpes virus and polyoma virus infections and tuberculosis will be managed with appropriate risk minimisation activities.

Further assessment to rule out immunogenicity is needed and the RMP has been updated with a plan designed to improve the understanding of the relationship between antibody development and peri-infusional events within the clinical trials.

Safety findings from the phase 2 liver transplantation study are at this stage considered to be confined to liver transplantation, as no increased mortality with belatacept was seen up to 36 months in the renal transplant studies. The total immunosuppressive burden in the liver transplant study was heavier than in the renal transplant studies. Liver transplantation patients are subjected to more complicated

and extensive surgery than renal transplant patient but in general have less need for immunosuppression than the renal transplant population.

- Benefit-risk balance

The overall benefit of belatacept has been sufficiently demonstrated up to 36 months. The demonstrated benefits are considered to outweigh the identified and potential risks. The overall benefit-risk balance of Nulojix is positive.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of 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" was favourable and therefore recommended the granting of the marketing authorisation .