SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

NULOJIX 250 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250 mg of belatacept.
After reconstitution, each ml of concentrate contains 25 mg belatacept.

Belatacept is a fusion protein produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipient with known effect
Each vial contains 0.55 mmol sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

The powder is a white to off-white whole or fragmented cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NULOJIX, in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for prophylaxis of graft rejection in adult recipients of a renal transplant (see section 5.1 for data on renal function).

4.2 Posology and method of administration

Treatment should be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and of renal transplant patients.

Belatacept has not been studied in patients with Panel Reactive Antibody (PRA) > 30% (who often require increased immunosuppression). Because of the risk of a high total burden of immunosuppression, belatacept should only be used in these patients after consideration of alternative therapy (see section 4.4).

Posology

Initiation at the time of transplantation

For transplant recipients receiving NULOJIX treatment from time of transplantation ("newly transplanted patients"), the addition of an interleukin-2 (IL-2) receptor antagonist is recommended.

The recommended dose is based on patient body weight (kg). The dose and treatment frequency is given below.

Table 1: Dose of belatacept for renal transplant recipients

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
Maintenance phase	**Dose**
Every 4 weeks (± 3 days), starting at the end of week 16 after transplantation	6 mg/kg

For more details on the dose calculation, see section 6.6.

Patients do not require pre-medication prior to administration of belatacept.

At the time of transplantation, NULOJIX should be administered in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. Corticosteroid tapering in patients taking belatacept should be implemented cautiously, particularly in patients with 4 to 6 human leukocyte antigen (HLA) mismatches (see sections 4.4 and 5.1).

Conversion from a calcineurin inhibitor (CNI)-based regimen at least 6 months post-transplantation

For conversion from a CNI based to a NULOJIX based maintenance regimen in patients at least 6 months post-transplant, a dose of 6 mg/kg of NULOJIX administered every 2 weeks is recommended for the first 8 weeks, followed by the same dose every 4 weeks thereafter. Following initiation of therapy with NULOJIX, the calcineurin inhibitor should be continued, in tapering doses, for at least 4 weeks after infusion of the initial dose of NULOJIX (see section 5.1). More frequent monitoring for acute rejection is recommended, per local

standard of care, for at least 6 months after conversion to NULOJIX (see section 4.4).

Infusion-related reactions have been reported with belatacept administration in clinical studies. If any serious allergic or anaphylactic reaction occurs, belatacept therapy should be discontinued immediately and appropriate therapy initiated (see section 4.4).

Therapeutic monitoring of belatacept is not required.

During clinical studies, there was no dose modification of belatacept for a change in body weight of less than 10%.

Special populations

Elderly patients
No dose adjustment is required (see sections 5.1 and 5.2).

Renal impairment
No dose adjustment is recommended in patients with renal impairment or undergoing dialysis (see section 5.2).

Hepatic impairment
No patients with hepatic impairment were studied in renal transplant protocols, therefore dose modification of belatacept in hepatic impairment can not be recommended.

Paediatric population
The safety and efficacy of belatacept in children and adolescents 0 to 18 years of age have not yet been established. No data are available.

Method of administration

NULOJIX is for intravenous use only.

The diluted solution must be administered as an intravenous infusion at a relatively constant rate over 30 minutes. Infusion of the first dose should be given in the immediate preoperative period or during surgery, but before completion of the transplant vascular anastomoses.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Transplant recipients who are Epstein-Barr virus (EBV) seronegative or serostatus unknown.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Post-transplant lymphoproliferative disorder (PTLD)

In Phase 2 and 3 studies (3 studies) in newly transplanted patients, 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.

Infections

Use of immunosuppressants, including belatacept, can increase susceptibility to infection, including fatal infections, opportunistic infections, tuberculosis, and herpes (see progressive multifocal leukoencephalopathy (PML) warning below and also section 4.8).

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.

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.

Progressive multifocal leukoencephalopathy

PML is a rare, often rapidly progressive and fatal, opportunistic infection of the CNS that is caused by the John Cunningham (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.

Malignancies

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.

Graft thrombosis

In clinical trials, an increased incidence of graft thrombosis was observed in the post-transplant period in recipients of extended criteria donor allografts. In postmarketing experience in patients with other predisposing risk factors for thrombosis of the renal allograft, renal allograft thrombosis has occurred when the initial dose of anti-thymocyte globulin, as immunosuppressive induction, was coadministered at the same or nearly the same time with the first dose of belatacept. (see section 4.8).

Conversion from a CNI-based maintenance regimen

Conversion of clinically stable patients receiving a CNI-based maintenance regimen to a belatacept-based regimen may initially increase the risk of acute rejection. Closer monitoring for acute rejection is recommended for at least 6 months following conversion to belatacept, as per local standard of care. There are no data on conversion in patients considered to be at higher immunological risk as these were excluded from the conversion studies based on protocol defined criteria related to their previous rejection history (see section 5.1). Such patients may initially be at further risk of acute rejection following conversion to belatacept than those who were actually studied. In subjects with high immunological risk, conversion should only be considered when the potential benefits are anticipated to outweigh the risks.

Liver transplantation

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).

Concomitant use with other immunosuppressive agents

Belatacept has been administered with the following immunosuppressive agents in clinical studies: basiliximab, an MPA and corticosteroids.

Lymphocyte Depleting Therapies and MPA: As the total burden of immunosuppression is a risk factor for malignancies and opportunistic infections, higher than the recommended doses of concomitant immunosuppressive agents should be avoided. Lymphocyte depleting therapies to treat acute rejection should be used cautiously.
Patients with high PRA often require increased immunosuppression. Belatacept has not been studied in patients with PRA > 30% (see section 4.2).

Corticosteroid Taper: Corticosteroid tapering in patients taking belatacept should be implemented cautiously, particularly in patients at high immunologic risk, such as those with 4 to 6 human leukocyte antigen (HLA) mismatches. In postmarketing experience, use of belatacept in conjunction with basiliximab induction, mycophenolate mofetil and corticosteroid taper to 5 mg/day by Week 6 post-transplant was associated with an increased rate of acute rejection, particularly Grade III rejection. These Grade III rejections occurred in patients with 4 to 6 HLA mismatches (see sections 4.2 and 5.1).

For patients who may be switched from belatacept to another immunosuppressant, physicians should be aware of the 9-10 day half-life of belatacept to avoid potential under- or over-immunosuppression following discontinuation of belatacept.

Allergic reactions

Infusion-related reactions have been reported with belatacept administration in the clinical studies. Patients are not required to be pre-treated to prevent allergic reactions (see section 4.8). Special caution should be exercised in patients with a history of allergic reactions to belatacept or to any of the excipients. Anaphylaxis has been reported during post marketing surveillance (see section 4.8). If any serious allergic or anaphylactic reaction occurs, NULOJIX therapy should be discontinued immediately and appropriate therapy initiated.

Vaccinations

Immunosuppressant therapy may affect response to vaccination. Therefore, during treatment with belatacept, vaccinations may be less effective although this has not been studied in clinical trials. The use of live vaccines should be avoided (see section 4.5).

Autoimmune process

There is a theoretical concern that treatment with belatacept might increase the risk of autoimmune processes (see section 4.8).

Immunogenicity

Although there were few patients that developed antibodies and there was no apparent correlation of antibody development to clinical response or adverse events, the data are too limited to make a definitive assessment (see section 4.8). 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.

Sodium Content

This medicinal product contains 0.55 mmol or 13 mg sodium per vial, equivalent to 0.64% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be taken into consideration when treating patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Belatacept is a fusion protein that is not expected to be metabolised by the cytochrome P450 enzymes (CYPs) and UDP-glucuronosyltransferases (UGTs). Belatacept appears not to have any relevant direct effects on cytokine levels in liver

transplant recipients or in healthy volunteers. Belatacept is therefore not expected to affect cytochrome P450 enzymes via effects on cytokines.

Belatacept is not expected to interrupt the enterohepatic recirculation of MPA. At a given dose of MMF, MPA exposure is approximately 40% higher with belatacept coadministration than with ciclosporin coadministration.

Immunosuppressant therapy may affect response to vaccination. Therefore, during treatment with belatacept, vaccinations may be less effective although this has not been studied in clinical trials. The use of live vaccines should be avoided (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing 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.

Pregnancy

There are no adequate data from use of belatacept in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal development at doses up to 16-fold and 19-fold a human 10 mg/kg dose based on AUC. In a pre- and postnatal development study in rats, limited changes in immune function were observed at 19-fold a human 10 mg/kg dose based on AUC (see section 5.3). Belatacept should not be used in pregnant women unless clearly necessary.

Breast-feeding

Studies in rats have shown excretion of belatacept in milk. It is unknown whether belatacept is excreted in human milk (see section 5.3). Women should not breast-feed while on treatment with a belatacept-based regimen.

Fertility

There are no data on use of belatacept and effect on fertility in humans. In rats, belatacept had no undesirable effects on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Belatacept has a minor influence on the ability to drive and use machines since it may cause fatigue, malaise and/or nausea. Patients should be instructed that if they

experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The adverse reaction profile associated with immunosuppressive agents is often difficult to establish due to the underlying disease and the concurrent use of multiple medicinal products.

In trials conducted to support use in newly transplanted patients, the most common serious adverse reactions (≥ 2%) reported with belatacept in both regimens (more intensive [MI] and less intensive [LI]) cumulative up to Year 3 were urinary tract infection, CMV infection, pyrexia, increased blood creatinine, pyelonephritis, diarrhoea, gastroenteritis, graft dysfunction, leukopenia, pneumonia, basal cell carcinoma, anaemia, dehydration.

The most commonly reported adverse reactions (≥ 20%) among patients treated with both belatacept-based regimens (MI and LI) up to Year 3 are diarrhoea, anaemia, urinary tract infection, peripheral oedema, constipation, hypertension, pyrexia, nausea, graft dysfunction, cough, vomiting, leukopenia, hypophosphataemia, and headache.

Adverse reactions resulting in interruption or discontinuation of belatacept in ≥ 1% of patients up to Year 3 were renal vein thrombosis and CMV infection.

Tabulated list of adverse reactions

Presented in Table 2, by system organ classification and frequency categories, is the list of adverse reactions with at least a suspected causal relationship, reported in newly transplanted patient clinical trials cumulatively up to Year 3 and pooled for both belatacept regimens (MI and LI).

The frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100). Within each frequency category adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions in newly transplanted patient clinical trials

Infections and infestations	
Very Common	urinary tract infection, upper respiratory infection, cytomegalovirus infection*, bronchitis
Common	sepsis, pneumonia, influenza, gastroenteritis, herpes zoster, sinusitis, herpes simplex, oral candidiasis, pyelonephritis, onychomycosis, BK virus infection, respiratory tract infection, candidiasis, rhinitis, cellulitis, wound infection, localised infection, herpes virus infection, fungal infection, fungal skin infection
Uncommon	progressive multifocal leukoencephalopathy*, cerebral fungal infection, cytomegalovirus (CMV) colitis, polyomavirus-associated nephropathy, genital herpes, staphylococcal infection, endocarditis, tuberculosis*, bronchiectasis, osteomyelitis, strongyloidiasis, blastocystis infection, giardiasis, lymphangitis
Neoplasms, benign, malignant and unspecified (incl cysts and polyps)*	
Common	squamous cell carcinoma of skin, basal cell carcinoma, skin papilloma
Uncommon	EBV associated lymphoproliferative disorder**,lung cancer, rectal cancer, breast cancer, sarcoma, kaposi's sarcoma, prostate cancer, cervix carcinoma, laryngeal cancer, lymphoma, multiple myeloma, transitional cell carcinoma
Blood and lymphatic system disorders	
Very Common	anaemia, leukopenia
Common	thrombocytopenia, neutropenia, leukocytosis, polycythaemia, lymphopenia
Uncommon	monocytopenia, pure red cell aplasia, agranulocytosis, haemolysis, hypercoagulation
Immune system disorders	
Common	blood immunoglobulin G decreased, blood immunoglobulin M decreased
Uncommon	hypogammaglobulinaemia, seasonal allergy
Endocrine disorders	
Common	cushingoid
Uncommon	adrenal insufficiency
Metabolism and nutrition disorders	
Very Common	hypophosphataemia, hypokalaemia, dyslipidaemia, hyperkalaemia, hyperglycaemia, hypocalcaemia
Common	weight increase, diabetes mellitus, dehydration, weight decrease, acidosis, fluid retention, hypercalcaemia, hypoproteinaemia
Uncommon	diabetic ketoacidosis, diabetic foot, alkalosis, decreased appetite,

	vitamin D deficiency
Psychiatric disorders	
Very Common	insomnia, anxiety
Common	depression
Uncommon	abnormal dreams, mood swings, attention deficit/hyperactivity disorder, libido increased
Nervous system disorders	
Very Common	headache
Common	tremor, paraesthesia, cerebrovascular accident, dizziness, syncope, lethargy, neuropathy peripheral
Uncommon	encephalitis, Guillain-Barré syndrome*, brain oedema, intracranial pressure increased, encephalopathy, convulsion, hemiparesis, demyelination, facial palsy, dysgeusia, cognitive disorder, memory impairment, migraine, burning sensation, diabetic neuropathy, restless leg syndrome
Eye disorders	
Common	cataract, ocular hyperaemia, vision blurred
Uncommon	retinitis, conjunctivitis, eye inflammation, keratitis, photophobia, eyelid oedema
Ear and labyrinth disorders	
Common	vertigo, ear pain, tinnitus
Uncommon	hypoacusis
Cardiac disorders	
Common	tachycardia, bradycardia, atrial fibrillation, cardiac failure, angina pectoris, left ventricular hypertrophy
Uncommon	acute coronary syndrome, atrioventricular block second degree, aortic valve disease, arrhythmia supraventricular
Vascular disorders	
Very Common	hypertension, hypotension
Common	shock, infarction, haematoma, lymphocele, angiopathy, arterial fibrosis
Uncommon	venous thrombosis, arterial thrombosis, thrombophlebitis, arterial stenosis, intermittent claudication, flushing
Respiratory, thoracic and mediastinal disorders	
Very Common	dyspnoea, cough
Common	pulmonary oedema, wheezing, hypocapnea, orthopnoea, epistaxis, oropharyngeal pain
Uncommon	acute respiratory distress syndrome, pulmonary hypertension,

	pneumonitis, haemoptysis, bronchopneumopathy, painful respiration, pleural effusion, sleep apnoea syndrome, dysphonia, oropharyngeal blistering
Gastrointestinal disorders	
Very Common	diarrhoea, constipation, nausea, vomiting, abdominal pain
Common	dyspepsia, aphthous stomatitis, abdominal hernia
Uncommon	gastrointestinal disorder, pancreatitis, large intestinal ulcer, melaena, gastroduodenal ulcer, rectal haemorrhage, small intestinal obstruction, cheilitis, gingival hyperplasia, salivary gland pain, faeces discoloured
Hepatobiliary disorders	
Common	cytolytic hepatitis, liver function test abnormal
Uncommon	cholelithiasis, hepatic cyst, hepatic steatosis
Skin and subcutaneous tissue disorders	
Common	acne, pruritis, alopecia, skin lesion, rash, night sweats, hyperhidrosis
Uncommon	psoriasis, hair growth abnormal, onychoclasis, penile ulceration, swelling face, trichorrhexis
Musculoskeletal and connective tissue disorders	
Very Common	arthralgia, back pain, pain in extremity
Common	myalgia, muscular weakness, bone pain, joint swelling, intervertebral disc disorder, joint lock, muscle spasms, osteoarthritis
Uncommon	bone metabolism disorder, osteitis, osteolysis, synovitis
Renal and urinary disorders	
Very Common	proteinuria, blood creatinine increased, dysuria, haematuria
Common	renal tubular necrosis, renal vein thrombosis*, renal artery stenosis, glycosuria, hydronephrosis, vesicoureteric reflux, urinary incontinence, urinary retention, nocturia
Uncommon	renal artery thrombosis*, nephritis, nephrosclerosis, renal tubular atrophy, cystitis haemorrhagic, kidney fibrosis
Reproductive system and breast disorders	
Uncommon	epididymitis, priapism, cervical dysplasia, breast mass, testicular pain, vulval ulceration, atrophic vulvovaginitis, infertility, scrotal oedema
Congenital, familial and genetic disorders	
Common	hydrocele
Uncommon	hypophosphatasia

General disorders and administration site conditions	
Very Common	oedema peripheral, pyrexia
Common	chest pain, fatigue, malaise, impaired healing
Uncommon	infusion related reaction*, irritability, fibrosis, inflammation, disease recurrence, feeling hot, ulcer
Investigations	
Common	c-reactive protein increased, blood parathyroid hormone increased
Uncommon	pancreatic enzymes increased, troponin increased, electrolyte imbalance, prostate-specific antigen increased, blood uric acid increased, urine output decreased, blood glucose decreased, CD4 lymphocytes decreased
Injury, poisoning and procedural complications	
Very Common	graft dysfunction
Common	chronic allograft nephropathy (CAN), incisional hernia
Uncommon	transplant failure, transfusion reaction, wound dehiscence, fracture, tendon rupture, procedural hypotension, procedural hypertension, post-procedural haematoma, procedural pain, procedural headache, contusion

* See section "Description of selected adverse reactions".
** Includes all events reported over a median of 3.3 years in the newly transplanted patient Phase 3 studies, and a median of approximately 7 years in the newly transplanted patient Phase 2 study.

Long-term extension in Study 1 and Study 2
Of the 1209 randomised and newly transplanted patients in the two Phase 3 studies (see section 5.1), 761 patients continued after Year 3 in a long-term extension period for up to an additional 4 years and continued to receive the study drug according to their original treatment assignment. As compared to the results from the initial 3 years, no new adverse reactions or increasing incidence of adverse reactions (listed above from the initial 3-year period) were detected during the 4-year long-term open label extension.

Conversion Studies 1 and 2
The overall safety profile of belatacept in the two conversion studies was consistent with the known safety profile in the existing clinical population from the studies in newly transplanted patients presented in Table 2 above.

Description of selected adverse reactions

Malignancies and post-transplant lymphoproliferative disease
In the newly transplanted patient trials, Year 1 and 3 frequencies of malignancies are shown in Table 3, except for cases of PTLD which are presented at 1 year and > 3 years (median days of follow-up were 1,199 days for belatacept MI, 1,206 days for belatacept LI, and 1,139 days for ciclosporin). The Year 3 frequency of malignant neoplasms, excluding non-melanoma skin

cancers, was similar in the belatacept LI and ciclosporin groups and higher in the belatacept MI group. PTLD occurred at a higher rate in both belatacept treatment groups versus ciclosporin (see section 4.4). Non-melanoma skin cancers occurred less frequently with the belatacept LI regimen than with the ciclosporin or belatacept MI regimens.

Table 3: Malignancies occurring by treatment group (%)

	Up to Year 1			**Up to Year 3*,****		
	Belatacept MI N= 477	**Belatacept LI N= 472**	**Ciclosporin N= 476**	**Belatacept MI N= 477**	**Belatacept LI N= 472**	**Ciclosporin N= 476**
Any malignant neoplasm	3.4	1.9	3.4	8.6	5.7	7.1
Non-melanoma skin cancer	1.0	0.2	1.5	4.2	1.5	3.6
Malignant neoplasms excluding non-melanoma skin cancers	2.3	1.7	1.9	4.4	4.2	3.6
PTLD	0.8	0.8	0.2	1.7	1.3	0.6
Malignancies excluding non-melanoma skin cancer and PTLD	1.5	0.8	1.7	2.7	3.2	3.4

*Median follow-up excluding PTLD for pooled studies is 1,092 days for each treatment group.
**Median follow-up for PTLD for pooled studies is 1,199 days for MI, 1,206 days for LI, and 1,139 days for ciclosporin.

In the 3 newly transplanted patient studies (one Phase 2 and two Phase 3 studies, Study 1 and Study 2), the cumulative frequency of PTLD was higher in belatacept treated patients at the recommended dosing regimen (LI) (1.3%; 6/472) than in the ciclosporin group (0.6%; 3/476), and was highest in the

belatacept MI group (1.7%; 8/477). Nine of 14 cases of PTLD in belatacept-treated patients were located in the CNS; within the observation period, 8 of 14 cases were fatal (6 of the fatal cases involved the CNS). Of the 6 PTLD cases in the LI regimen, 3 involved the CNS and were fatal.

EBV seronegative patients receiving immunosuppressants are at a particularly increased risk for PTLD (see sections 4.3 and 4.4). In clinical studies, belatacept-treated transplant recipients with EBV seronegative status were at an increased risk for PTLD compared with those who were EBV positive (7.7%; 7/91 versus 0.7%; 6/810, respectively). At the recommended dosing regimen of belatacept there were 404 EBV positive recipients and 4 cases of PTLD occurred (1.0%); 2 of these presented in the CNS.

During the long-term extension period, malignancies (including PTLD) were reported in 10.3%, 8.4%, and 14.7% of patients in the belatacept MI, belatacept LI, and ciclosporin groups, respectively, in Study 1; and in 19.2%, 13.3% and 16.1% of patients in the belatacept MI, belatacept LI, and ciclosporin groups, respectively, in Study 2. Cases of PTLD varied by serostatus. In Study 1, one additional case of PTLD was reported in the ciclosporin group, in a patient who was EBV seropositive at the time of transplant. In Study 2, among patients who were EBV seropositive at the time of transplant, there was one case of PTLD in each of the three treatment groups. Among Study 2 patients who were EBV seronegative at the time of transplant (for whom use of belatacept is not recommended), there were three cases of PTLD in the belatacept LI group, and none in the belatacept MI and ciclosporin groups.

Infections
In newly transplanted patient trials, Year 1 and Year 3 frequencies of infections occurring by treatment group are shown in Table 4. The overall occurrence of tuberculosis infections and non-serious herpes infections were higher for belatacept regimens than for the ciclosporin regimen. The majority of cases of tuberculosis occurred in patients who currently live or previously lived in countries with a high prevalence of tuberculosis (see section 4.4). Overall occurrences of polyoma virus infections and fungal infections were numerically lower in the belatacept LI group compared with the belatacept MI and ciclosporin groups.

Within the belatacept clinical program, there were 2 patients diagnosed with PML. One fatal case of PML was reported in a renal transplant recipient treated with belatacept MI regimen, an IL-2 receptor antagonist, MMF, and corticosteroids for 2 years in a Phase 3 trial. The other case of PML was reported in a liver transplant recipient in a Phase 2 trial who received 6 months of treatment with an augmented belatacept MI regimen, MMF at doses higher than the recommended dose and corticosteroids (see section 4.4).

Infections involving the CNS were more frequent in the belatacept MI group (8 cases, including the PML case discussed above; 1.7%) than the belatacept LI (2 cases, 0.4%) and ciclosporin (one case; 0.2%) groups. The most common CNS infection was cryptococcal meningitis.

Table 4: Infections occurring by treatment group in newly transplanted patient trials (%)

	Up to Year 1			Up to Year 3*		
	Belatacept MI N= 477	**Belatacept LI N= 472**	**Ciclosporin N= 476**	**Belatacept MI N= 477**	**Belatacept LI N= 472**	**Ciclosporin N= 476**
Infections and infestations	70.7	71.8	73.7	79.2	82.0	80.6
Serious infections	26.8	23.3	27.3	35.8	33.5	37.8
Viral infections	26.4	25.0	27.7	38.8	39.0	36.1
CMV	11.1	11.9	13.7	13.8	13.8	14.7
Polyomavirus	4.8	2.3	4.8	6.3	3.8	5.7
Herpes	8.0	6.6	6.1	15.5	14.2	10.7
Fungal infections	13.8	11.0	15.1	22.9	16.7	20.6
Tuberculosis	0.4	0.4	0.2	1.3	1.3	0.2

*Median exposure for pooled studies is 1,092 days for each treatment group.

During the long-term extension period in newly transplanted patient trials, serious infections occurred in 30.3% and 23.5% of patients in the belatacept MI and LI groups, respectively, and in 27.2% of patients in the ciclosporin group in Study 1; and in 35.6% and 38.1% of patients in the belatacept MI and LI groups, respectively, and in 37.9% of patients in the ciclosporin group in Study 2. There was one case of PML reported (Study 1) in the ciclosporin group at 82 months post-transplant (more than 56 days after discontinuing therapy).

Graft thrombosis

In a Phase 3 study in newly transplanted recipients of extended criteria donor (ECD) kidneys (Study 2), graft thrombosis occurred more frequently in the belatacept groups (4.3% and 5.1% for the MI and LI regimens respectively), versus 2.2% for ciclosporin. In another Phase 3 study in newly transplanted recipients of living donor and standard criteria deceased donor kidneys (Study 1), the incidence of graft thrombosis was 2.3% and 0.4% for the MI and LI regimens respectively, versus 1.8% for ciclosporin. In a Phase 2 study in newly transplanted patients, there were 2 cases of graft thrombosis, 1 each in MI and LI (incidence of 1.4% for both) versus 0 in the ciclosporin group. In general, these events occurred early and the majority resulted in graft loss. In postmarketing experience in patients with other predisposing risk factors for thrombosis of the renal allograft, renal allograft thrombosis has been reported when the initial dose of anti-thymocyte globulin was coadministered at the same or nearly the same time with the first dose of belatacept. (see section 4.4).

Infusion-related reactions

Anaphylaxis has been reported post marketing(see section 4.4).

In newly transplanted patient studies, acute infusion-related reactions (reactions occurring within one hour of infusion) occurred in 5.5% of patients in the belatacept MI group and 4.4% of patients in the belatacept LI group up to Year 3. The most frequently reported acute infusion-related reactions in

combined belatacept regimens were hypotension, hypertension, flushing and headache. Most events were not serious, were mild to moderate in intensity, and did not recur. When belatacept was compared to placebo infusions, there were no differences in event rates (placebo infusions were administered at Weeks 6 and 10 of the belatacept LI regimen to blind the MI and LI regimens).

Immunogenicity

Antibodies directed against the belatacept molecule were assessed in 796 kidney transplant recipients (551 of these treated for at least 3 years) in the two Phase 3 studies in newly transplanted patients. An additional 51 patients were treated for an average of 7 years in the long-term extension of a Phase 2 study in newly transplanted patients. Anti-belatacept antibody development was not associated with altered clearance of belatacept.

A total of 45 of 847 patients (5.3%) developed antibodies during treatment with belatacept. In the individual studies, the percentage of patients with antibodies ranged from 4.5% and 5.2% in the Phase 3 studies to 11.8% in the long-term extension of the Phase 2 study. However, immunogenicity rate normalised for duration of exposure was consistent at 2.0 to 2.1 per 100 patient years among the three studies. In 153 patients assessed for antibodies at least 56 days (approximately 6 half-lives) after discontinuation of belatacept, an additional 10 (6.5%) developed antibodies. In general, antibody titers were low, not usually persistent, and often became undetectable with continued treatment.

To assess for the presence of neutralising antibodies, samples from 29 patients with confirmed binding activity to the modified cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) region of the molecule were assessed by an in vitro assay; 8 (27.6%) patients were shown to possess neutralising antibodies. The clinical relevance of such antibodies is unclear.

Autoimmunity

In newly transplanted patient studies, the occurrence of autoimmune events across the core clinical studies was infrequent, occurring at rates of 1.7%, 1.7%, and 1.9% by Year 3 for the MI, LI, and ciclosporin groups respectively. One patient on belatacept MI regimen developed Guillian-Barré syndrome which led to treatment discontinuation and subsequently resolved. Overall, the few reports across clinical studies suggest that prolonged exposure to belatacept does not predispose patients to an increased risk of development of autoimmune events.

During the long-term extension period, autoimmune events occurred in 2.6% and 3.0% of patients in the belatacept MI and LI groups, respectively, and in 3.7% of patients in the ciclosporin group in Study 1; and in 5.8% and 3.5% of patients in the belatacept MI and LI groups, respectively, and in 0% of patients in ciclosporin group in Study 2.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance

of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Single doses up to 20 mg/kg have been administered without apparent toxic effect. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA28.

Belatacept, a selective costimulation blocker, is a soluble fusion protein consisting of a modified extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) fused to a portion (hinge-CH2-CH3 domains) of the Fc domain of a human immunoglobulin G1 antibody. Belatacept is produced by recombinant DNA technology in a mammalian cell expression system. Two amino acid substitutions (L104 to E; A29 to Y) were made in the ligand binding region of CTLA-4.

Mechanism of action

Belatacept binds to CD80 and CD86 on antigen presenting cells. As a result, belatacept blocks CD28 mediated co-stimulation of T cells inhibiting their activation.
Activated T cells are the predominant mediators of immunologic response to the transplanted kidney. Belatacept, a modified form of CTLA4-Ig, binds CD80 and CD86 more avidly than the parent CTLA4-Ig molecule from which it is derived. This increased avidity provides a level of immunosuppression that is necessary for preventing immune-mediated allograft failure and dysfunction.

Pharmacodynamic effects

In a clinical study, approximately 90% saturation of CD86 receptors on the surface of antigen-presenting cells in the peripheral blood was observed following the initial administration of belatacept. During the first month post-transplantation, 85% saturation of CD86 was maintained. Up to month 3 post-transplantation with the recommended dosing regimen, the level of CD86 saturation was maintained at approximately 70% and at month 12, approximately 65%.

Clinical efficacy and safety

Study 1 and 2: Phase 3 studies in newly transplanted patients
The safety and efficacy of belatacept as part of an immunosuppressive regimen following renal transplantation were assessed in two randomised, partially-blinded, multicentre, 3 year studies with the primary endpoint specified at Year 1. These studies compared two dose regimens of belatacept (MI and LI) with ciclosporin in recipients of standard criteria (Study 1) or extended criteria (Study 2) donor organs. All patients received basiliximab, MMF, and corticosteroids. The more intensive (MI) regimen, which included higher and more frequent dosing during the first 6 months post transplant, resulted in 2-fold higher exposure to belatacept than the less intensive (LI) regimen during Months 2 through 7 post transplant. Efficacy was similar between MI and LI while the overall safety profile was better for the LI. Therefore, the recommended dose of belatacept is the LI dosage regimen.

Study 1: Recipients of Living Donor and Standard Criteria Deceased Donor Kidneys
Standard criteria donor organs were defined as organs from a living donor, or a deceased donor with anticipated cold ischemia time of < 24 hours and not meeting the definition of extended criteria donor organs. Study 1 excluded (1) recipients undergoing a first transplant whose current PRA were ≥50%; (2) recipients undergoing a retransplantation whose current PRA were ≥30%; (3) recipients when previous graft loss was due to acute rejection and in case of a positive T-cell lymphocytotoxic cross match.

In this study, 666 patients were enrolled, randomised, and transplanted; 219 to belatacept MI, 226 to belatacept LI, and 221 to ciclosporin. The median age was 45 years; 58% of donor organs were from living patients; 3% were re-transplanted; 69% of the study population was male; 61% of patients were white, 8% were black/African-American, 31% were categorised as of other races; 16% had PRA 10%; and 41% had 4 to 6 HLA mismatches.

The dose of corticosteroids used in all treatment groups was tapered during the first 6 months following transplantation. The median corticosteroid doses administered with the belatacept-recommended regimen up to months 1, 3, and 6 were 20 mg, 12 mg and 10 mg, respectively.

Study 2: Recipients of Extended Criteria Donor Kidneys
Extended criteria donors were defined as deceased donors with at least one of the following: (1) donor age ≥ 60 years; (2) donor age ≥ 50 years and other donor comorbidities (≥ 2 of the following: stroke, hypertension, serum creatinine > 1.5 mg/dl); (3) donation after cardiac death or (4) anticipated cold ischemia time of ≥ 24 hours. Study 2 excluded recipients with a current PRA ≥ 30%, re-transplanted patients, and in case of a positive T-cell lymphocytotoxic cross match.

In this study, 543 patients were enrolled, randomised, and transplanted; 184 to belatacept MI, 175 to belatacept LI, and 184 to ciclosporin. The median age was 58 years; 67% of the study population was male; 75% of patients were white, 13% were black/African-American, 12% were categorised as of other races; 3% had PRA ≥ 10%; and 53% had 4 to 6 HLA mismatches.

The dose of corticosteroids used in all treatment groups was tapered during the first 6 months following transplantation. The median corticosteroid doses administered with the belatacept-recommended regimen up to months 1, 3, and 6 were 21 mg, 13 mg and 10 mg, respectively.

Table 5 summarises results for belatacept LI compared with ciclosporin for the co-primary efficacy endpoints of death and graft loss, composite renal impairment, and acute rejection (defined as clinically suspected biopsy proven acute rejection). Patient and graft survival were similar between belatacept and ciclosporin. Fewer patients met the composite renal impairment endpoint and mean GFR was higher with belatacept compared to ciclosporin.

Acute rejection (AR) occurred more frequently with belatacept versus ciclosporin in Study 1 and with similar frequency with belatacept versus ciclosporin in Study 2. Approximately 80% of AR episodes occurred by Month 3 and were infrequent after Month 6. In Study 1, 11/39 belatacept and 3/21 ciclosporin acute rejections were Banff 97 grade ≥ IIb by Year 3. In Study 2, 9/33 belatacept and 5/29 ciclosporin acute rejections were Banff 97 grade ≥ IIb by Year 3. AR was treated more often with lymphocyte depleting therapy (a risk factor for PTLD; see section 4.4) in the belatacept group than the ciclosporin group. In both studies, in patients with AR by Year 2, donor-specific antibodies, one of the criteria for diagnosis of antibody-mediated rejection, were present in 6% (2/32, Study 2)-8% (3/39, Study 1) and 20% (4/20, Study 1)-26% (7/27, Study 2) in the belatacept and ciclosporin groups by year 3, respectively. By Year 3 recurrent AR was similar across groups (< 3%) and subclinical AR identified on the 1 year protocol biopsy was 5% in both groups. In Study 1, 5/39 belatacept patients versus 1/21 ciclosporin patients with AR had experienced graft loss, and 5/39 belatacept patients and no ciclosporin patients with AR had died by Year 3. In Study 2, 5/33 belatacept patients versus 6/29 ciclosporin patients with AR had experienced graft loss, and 5/33 belatacept patients versus 5/29 ciclosporin patients with AR had died by Year 3. In both studies, mean GFR following AR was similar in belatacept and ciclosporin-treated patients.

Table 5: Key efficacy outcomes at years 1 and 3

	Study 1: living and standard criteria deceased donors		**Study 2: extended criteria donors**	
Parameter	**Belatacept LI**	**Ciclosporin**	**Belatacept LI**	**Ciclosporin**
	N = 226	**N = 221**	**N = 175**	**N = 184**
Patient and Graft Survival (%)				
Year 1	96.5	93.2	88.6	85.3
[95% CI]	[94.1-98.9]	[89.9-96.5]	[83.9-93.3]	[80.2-90.4]

Year 3 [95% CI]	92.0 [88.5-95.6]	88.7 [84.5-92.9]	82.3 [76.6-87.9]	79.9 [74.1-85.7]
Death (%) Year 1	1.8	3.2	2.9	4.3
Year 3	4.4	6.8	8.6	9.2
Graft Loss (%) Year 1 Year 3	2.2 4.0	3.6 4.5	9.1 12.0	10.9 12.5
% of Patients meeting Composite renal impairment endpoint at Year 1[a]	54.2	77.9	76.6	84.8
P-value	< 0.0001	-	< 0.07	-
AR (%) Year 1 (%) [95% CI]	17.3 [12.3-22.2]	7.2 [3.8-10.7]	17.7 [12.1-23.4]	14.1 [9.1-19.2]
Year 3 (%) [95% CI]	17.3 [12.3-22.2]	9.5 [5.6-13.4]	18.9 [13.1-24.7]	15.8 [10.5-21.0]
Mean Measured GFR[b] *ml/min/1.73 m²* Year 1	63.4	50.4	49.6	45.2
Year 2	67.9	50.5	49.7	45.0
Mean Calculated GFR[c] ***ml/min/1.73 m²*** Month 1 Year 1 Year 2 Year 3	 61.5 65.4 65.4 65.8	 48.1 50.1 47.9 44.4	 39.6 44.5 42.8 42.2	 31.8 36.5 34.9 31.5

[a]Proportion of Patients with Measured GFR < 60 ml/min/1.73 m^2 or with a Decrease in Measured GFR ≥ 10 ml/min/1.73 m^2 from Month 3 to Month 12.
[b] Measured GFR was assessed by iothalamate at Year 1 and 2 only
[c] Calculated GFR was assessed by MDRD formula at Month 1, Years 1, 2, and 3

Progression of Chronic Kidney Disease (CKD) Staging
In Study 1 by Year 3, mean calculated GFR was 21 ml/min/1.73 m^2 higher with belatacept, and 10% and 20% of patients reached CKD stage 4/5 (GFR < 30 ml/min/1.73 m^2) with belatacept versus ciclosporin, respectively. In Study 2 by Year 3, mean calculated GFR was 11 ml/min/1.73 m^2 higher with belatacept, and 27% and 44% of patients reached CKD stage 4/5 (GFR < 30 ml/min/1.73 m^2) with belatacept versus ciclosporin, respectively.

Chronic Allograft Nephropathy/Interstitial Fibrosis and Tubular Atrophy (IFTA)
The prevalence of CAN/IFTA at Year 1 in Studies 1 and 2, was numerically lower with belatacept than ciclosporin (~ 9.4% and 5%, respectively).

New Onset Diabetes Mellitus and Blood Pressure
In a prespecified pooled analysis of Studies 1 and 2 at Year 1, the incidence of new onset diabetes mellitus (NODM), defined as use of an antidiabetic agent for ≥ 30 days or ≥ 2 fasting plasma glucose values > 126 mg/dl (7.0 mmol/l) post-transplantation, was 5% with belatacept and 10% with ciclosporin. At Year 3, the incidence of NODM was 8% with belatacept and 10% with ciclosporin.

For Studies 1 and 2 at Years 1 and 3, belatacept was associated with 6 to 9 mmHg lower mean systolic blood pressure, approximately 2 to 4 mmHg lower mean diastolic blood pressure, and less use of antihypertensive medicinal products than ciclosporin.

Long-term extension in Study 1 and Study 2
A total of 321 belatacept (MI: 155 and LI: 166) and 136 ciclosporin patients completed 3 years of treatment in Study 1 and entered the 4-year long-term open label extension period (up to 7 years in total). More patients discontinued in the ciclosporin group (32.4%) versus each belatacept group (17.4% and 18.1% in MI and LI groups, respectively) during the long-term extension period. A total of 217 belatacept (MI: 104 and LI: 113) and 87 ciclosporin patients completed 3 years of treatment in Study 2 and entered the 4-year long-term open label extension period (up to 7 years in total). More patients discontinued in the ciclosporin group (34.5%) versus each belatacept group (28.8% and 25.7% for MI and LI groups, respectively) during the long-term extension period.

As compared to ciclosporin and assessed by the hazard ratio (HR) estimates (for death or graft loss) from an ad hoc Cox regression analysis, overall patient and graft survival was higher for belatacept-treated patients in Study 1, HR 0.588 (95% CI: 0.356-0.972) for the MI group and HR 0.585 (95% CI: 0.356-0.961) for the LI group, and comparable across treatment groups in Study 2, HR 0.932 (95% CI: 0.635-1.367) for the MI group and HR 0.944 (95% CI: 0.644-1.383) for the LI group. The overall proportion of patients with death or graft loss was lower in belatacept-treated patients (MI: 11.4%, LI: 11.9%) as compared to ciclosporin-treated patients (17.6%) in Study 1. The overall proportion of patients with death or graft loss was comparable across treatment groups (29.3%, 30.9%, and 28.3% for MI, LI and ciclosporin, respectively) in Study 2. In Study 1, in the MI, LI, and ciclosporin groups, respectively, death occurred in 7.8%, 7.5%, and 11.3% of patients, and graft loss occurred in 4.6%, 4.9%, and 7.7% of patients. In Study 2, in the MI, LI, and ciclosporin groups, respectively, death occurred in 20.1%, 21.1%, and 15.8% of patients, and graft loss occurred in 11.4%, 13.1%, and 15.8% of patients. The higher proportion of deaths in the LI group in Study 2 was mainly due to neoplasms (MI: 3.8%, LI: 7.1%, ciclosporin: 2.3%).

The higher calculated GFR observed in belatacept-treated patients relative to ciclosporin-treated patients during the first 3 years was maintained over the long-term

extension period. In Study 1, mean calculated GFR at 7 years was 74.0, 77.9 and 50.7 mL/min/1.73 m² in the belatacept MI, belatacept LI and ciclosporin groups, respectively. In Study 2, mean calculated GFR at 7 years was 57.6, 59.1 and 44.6 mL/min/1.73 m², in the same groups, respectively. The time to death, graft loss, or GFR <30 mL/min/1.73 m² was analyzed over the 7-year period: in Study 1, approximately 60% reduction in the risk of death, graft loss, or GFR <30 mL/min/1.73 m² was observed among patients in the belatacept groups as compared with those assigned to ciclosporin. In Study 2, approximately 40% reduction in this risk was observed among patients in the belatacept groups as compared with those assigned to ciclosporin.

Conversion from calcineurin inhibitor (CNI)-based to belatacept-based regimen
Conversion Study 1:
A total of 173 kidney transplant recipients on a CNI-based maintenance regimen (ciclosporin; CsA: 76 patients or tacrolimus; TAC: 97 patients), who had received a renal allograft from a living or deceased donor at 6 to 36 months prior to study participation, were enrolled in a multicentre, prospective, randomised, open-label trial. Patients with a history of treatment for biopsy proven acute rejection (BPAR) within 3 months prior to study participation, recurrent BPAR, Banff grade IIA or higher cellular rejection, or antibody mediated rejection with the current allograft; loss of a previous allograft due to BPAR; or a positive T-cell lymphocytotoxicity cross match at the time of the current transplant were considered to be at higher immunological risk and were excluded from the study. Patients were randomised 1:1 to either continue on their CNI-based regimen or convert to a belatacept-based regimen. During the conversion phase, a maintenance dose of belatacept was administered on Day 1 and every two weeks for the first 8 weeks (see Section 4.2). The CNI dose was gradually tapered between Day 1 and Day 29: On day 1 patients received 100% of CNI dose, followed by 40-60% on day 15, 20-30% on day 23, and none on day 29. Following the initial, 8-week conversion phase, a maintenance dose of belatacept was administered every 4 weeks thereafter, beginning at 12 weeks after the first dose (see Section 4.2). The study duration was 12 months, with a long-term extension (LTE) period from Month 12 to Month 36. The primary (descriptive) endpoint was renal function (change in eGFR from baseline) at 12 months.

At Month 12, all of 84 patients (100%) in the belatacept conversion group and 98.9% (88/89) patients in the CNI continuation group had survived with a functioning graft. BPAR was reported in 7.1% (6/84) patients in the belatacept conversion group and none in the CNI continuation group. Of the 81 patients in each group who entered the LTE period (ITT-LT subpopulation), 97% (79/81) in the belatacept conversion and 98.8% (80/81) in the CNI continuation group had survived with a functioning graft by Month 36. One case of BPAR was reported in the belatacept conversion group and three cases of BPAR were reported in the CNI continuation group during the LTE period; in the ITT-LT subpopulation up to 36 months, BPAR was reported in 6.2% (5/81) vs 3.7% (3/81) of patients in the belatacept conversion vs CNI continuation groups, respectively. None of the BPAR events was of Banff grade III severity. One patient in each group with BPAR experienced subsequent graft loss. At Month 12, the mean (SD) change in cGFR from baseline was +7.0 (12.0) mL/min/1.73 m^2 in the belatacept conversion group (N=84) as compared

to +2.1 (10.3) mL/min/1.73 m^2 in the CNI continuation group (N=89). By Month 36, the mean change from baseline cGFR was +8.2 (16.1) mL/min/1.73 m^2 in the belatacept conversion group (N=72) and +1.4 (16.9) mL/min/1.73 m^2 in the CNI continuation group (N=69).

Conversion Study 2:

A total of 446 kidney transplant patients on a CNI-based maintenance regimen (CsA: 48 patients or TAC: 398 patients), who had received a renal allograft from a living or deceased donor at 6 to 60 months prior to study participation, were enrolled in a multicentre, prospective, randomised, open-label trial. Patients with a history of treatment for biopsy proven acute rejection (BPAR) within 3 months prior to study participation, recurrent BPAR, Banff grade IIA or higher cellular rejection, or antibody mediated rejection with the current allograft; loss of a previous allograft due to BPAR; or a positive T-cell lymphocytotoxicity cross match at the time of the current transplant were considered to be at higher immunological risk and were excluded from the study. Patients were randomised 1:1 to either continue on their CNI-based regimen or convert to a belatacept-based regimen. The CNI tapering and belatacept conversion phase followed a similar regimen as Conversion Study 1 (see above). The study duration was 24 months. The primary (descriptive) composite endpoint was the proportion of subjects who survived with a functioning graft at Month 24.

The proportion of patients surviving with a functioning graft was similar in the belatacept conversion (98.2%; 219/223) and CNI continuation (97.3%; 217/223) groups at Month 24. Four patients (1.8%) in each group had died and two (0.9%) in the CNI continuation group had lost a graft. At Month 12, BPAR was reported for 18/223 patients (8.1%) in the belatacept conversion group and 4/223 patients (1.8%) in the CNI continuation group. At Month 24, there were no further cases of BPAR in the belatacept conversion group, but 5 additional cases were reported in the CNI continuation group (total of 9/223 (4%) at Month 24). The majority of the BPAR cases reported in the belatacept conversion group occurred during the first 6 months; all were successfully treated with no subsequent graft loss. The overall severity of BPAR events was greater following belatacept conversion compared to those in the CNI continuation group. When analysed with imputation to zero for death and graft loss, values for adjusted mean cGFR at Month 24 were 55.5 and 48.5 mL/min/1.73 m^2 in the belatacept conversion and CNI continuation groups, respectively. The corresponding adjusted change from baseline cGFR values were +5.2 and -1.9 mL/min/1.73 m^2, respectively.

Phase 2 liver transplant study

A single, randomised, multi-centre, controlled Phase 2 trial of belatacept in *de novo* orthotopic liver transplant recipients was conducted. A total of 250 subjects were randomised to 1 of 5 treatment groups (3 belatacept and 2 tacrolimus groups). The belatacept dosing used in this liver study was higher in all 3 belatacept arms than the belatacept dosing used in the Phase 2 and 3 renal transplant studies.

An excess in mortality and graft loss was observed in the belatatacept LI + MMF group and an excess in mortality was observed in the belatacept MI + MMF group. No pattern was identified in the causes of death. There was an increase in viral and fungal

infections in the belatacept groups versus the tacrolimus groups, however overall frequency of serious infections was not different among all treatment groups (see section 4.4).

Elderly

Two hundred seventeen (217) patients 65 years and older received belatacept across one Phase 2 and two Phase 3 renal studies.
Elderly patients demonstrated consistency with the overall study population for safety and efficacy as assessed by patient and graft survival, renal function, and acute rejection.

Paediatric population

The licensing authority has deferred the obligation to submit the results of studies with belatacept in one or more subsets of the paediatric population in renal transplantation (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of belatacept in renal transplant patients and healthy subjects appeared to be comparable. The pharmacokinetics of belatacept was linear and the exposure to belatacept increased proportionally in healthy subjects after a single intravenous infusion dose of 1 to 20 mg/kg. The geometric mean (CV%) pharmacokinetic parameters of belatacept after multiple intravenous infusions at doses of 6 mg/kg in renal transplant subjects simulated from the population pharmacokinetic model were: terminal half-life 9.6 (27) days, systemic clearance 0.59 (22) ml/h/kg, and distribution volume at steady state, 0.15 (21) l/kg. At the recommended dosing regimen, serum concentration generally reached steady-state by Week 8 in the initial phase following transplantation and by Month 6 during the maintenance phase. At Month 1, 4, and 6 post-transplant, the geometric mean (CV%) of predicted trough concentrations of belatacept were 24 (31), 5.3 (50), and 3.1(49) μg/ml, respectively.

Distribution

Based on population pharmacokinetic analysis of 944 renal transplant patients up to 1 year post-transplant, the pharmacokinetics of belatacept were similar at different time periods post-transplant. The trough concentration of belatacept was consistently maintained up to 5 years post-transplant. Population pharmacokinetic analysis of renal transplant patients was used to determine systemic accumulation of belatacept upon multiple infusions of 6 or 10 mg/kg doses every 4 weeks. Minimal systemic accumulation occurred, with an accumulation index at steady state of 1.1.

Elimination

Population pharmacokinetic analyses in renal transplant patients revealed that there was a trend toward higher clearance of belatacept with increasing body weight. No clinically relevant effects of age, gender, race, renal function (calculated GFR), diabetes, or concomitant dialysis on clearance of belatacept was identified.

There is no data available in patients with hepatic impairment.

5.3 Preclinical safety data

Belatacept has less activity in rodents than abatacept, a fusion protein that differs from belatacept by two amino acids in the CD80/86 binding domains. Because of abatacept's similarity to belatacept in structure and mechanism of action and its higher activity in rodents, abatacept was used as a more active homolog for belatacept in rodents. Therefore, preclinical studies conducted with abatacept have been used to support the safety of belatacept in addition to the studies conducted with belatacept.

No mutagenicity or clastogenicity was observed with abatacept in a battery of *in vitro* studies. In a mouse carcinogenicity study, increases in the incidence of malignant lymphomas and mammary tumours (in females) occurred. The increased incidence of lymphomas and mammary tumours observed in mice treated with abatacept may have been associated with decreased control of murine leukaemia virus and mouse mammary tumour virus, respectively, in the presence of long-term immunomodulation. In a six-month and one-year toxicity study in cynomolgus monkeys with belatacept and abatacept, respectively, no significant toxicity was observed. Reversible pharmacological effects consisted of minimal decreases in serum IgG and minimal to severe lymphoid depletion of germinal centres in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphologic changes was observed in either study. This was despite the presence in the abatacept study of a virus, lymphocryptovirus, known to cause these lesions in immunosuppressed monkeys within the time frame of these studies. The viral status was not determined in the belatacept study but, as this virus is prevalent in monkeys, it was likely present in these monkeys as well.
In rats, belatacept had no undesirable effects on male or female fertility. Belatacept was not teratogenic when administered to pregnant rats and rabbits at doses up to 200 mg/kg and 100 mg/kg daily, respectively, representing approximately 16 and 19 times the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg based on AUC. Belatacept administered to female rats daily during gestation and throughout the lactation period was associated with infections in a small percentage of dams at all doses ($\geq$ 20 mg/kg, $\geq$ 3 times the MRHD exposure based on AUC), and produced no adverse effects in offspring at doses up to 200 mg/kg representing 19 times the MRHD exposure based on AUC. Belatacept was shown to cross the placenta in rats and rabbits. Abatacept administered to female rats every three days during gestation and throughout the lactation period, produced no adverse effects in offspring at doses up to 45 mg/kg, representing 3 times the exposure associated with the MRHD of 10 mg/kg based on AUC. However, at 200 mg/kg, 11 times the MRHD exposure, alterations in immune function were observed consisting of a 9-fold increase in T-cell dependent antibody response in female pups and thyroid inflammation in one female pup. It is not known whether these findings indicate a risk for development of autoimmune diseases in humans exposed *in utero* to abatacept or belatacept.

Studies in rats exposed to abatacept have shown immune system abnormalities including a low incidence of infections leading to death (juvenile rats) as well as inflammation of the thyroid and pancreas (both juvenile and adult rats). Studies in adult mice and monkeys have not demonstrated similar findings. It is likely that the increased susceptibility to opportunistic

infections observed in juvenile rats is associated with the exposure to abatacept before development of memory responses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium dihydrogen phosphate monohydrate
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

NULOJIX should not be used with siliconised syringes in order to avoid aggregate formation (see section 6.6).

6.3 Shelf life

Unopened vials

3 years

After reconstitution

The reconstituted solution should be transferred from the vial to the infusion bag or bottle immediately.

After dilution

Chemical and physical in-use stability of the solution for infusion has been demonstrated for 24 hours when stored in a refrigerator (2 °C – 8 °C). From a microbiological point of view, the product should be used immediately. If not used immediately, the solution for infusion may be stored in a refrigerator (2 °C – 8 °C) for up to 24 hours. Out of these 24 hours, the solution for infusion may be stored below 25 °C for a maximum of 4 hours. Do not freeze.

The NULOJIX infusion must be completed within 24 hours of reconstitution of the powder.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Store in the original package in order to protect from light.
For storage conditions after reconstitution or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

NULOJIX is supplied in a type I flint glass vial with a stopper (grey butyl rubber) and flip off seal (aluminum). Each vial is co-packaged with a disposable polypropylene syringe.

Pack sizes: 1 vial and 1 syringe or 2 vials and 2 syringes.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

- Use aseptic technique to reconstitute the vials and dilute the solution for administration.
- Use the silicone-free disposable syringe provided to make up the vials and to add the solution to the infusion. This will avoid aggregate formation (see section 6.2).
- Do not shake the vials. This will avoid foam formation.
- The solution for infusion is to be used in conjunction with a sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm).

<u>Dose selection and reconstitution of the vials</u>

Calculate the dose and number of NULOJIX vials required. Each NULOJIX vial provides 250 mg of belatacept.

- Total dose of belatacept in mg equals the patient weight in kg times the belatacept dose in mg/kg (6 or 10 mg/kg, see section 4.2).
- Dose modification of NULOJIX is not recommended for a change in body weight of less than 10%.
- Number of vials required equals the belatacept dose in mg divided by 250 rounded up to the next full number of vials.
- Make up each vial with 10.5 ml reconstitution solution.
- Volume of the reconstituted solution required (ml) equals total belatacept dose in mg divided by 25.

Practical details on the reconstitution of vials

Using aseptic technique, make up each vial with 10.5 ml of one of the following solvents (sterile water for injections, sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution for injection), using the co-packed disposable syringe (necessary to avoid aggregate formation) and an 18-21 gauge needle. Syringes are marked in units of 0.5 ml; therefore, the calculated dose should be rounded to the nearest 0.5 ml.

Remove the flip off seal from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper. Direct the stream of fluid to the glass wall of the vial and not into the powder. Remove the syringe and needle after 10.5 ml of reconstitution fluid has been added to the vial.

To minimize foam formation, gently swirl and invert the vial for at least 30 seconds or until the powder is completely dissolved. Do not shake. Although some foam may remain on the surface of the reconstituted solution, a sufficient excess of belatacept is included in each vial to account for withdrawal losses. Thus, 10 ml of a 25 mg/ml belatacept solution can be withdrawn from each vial.

The reconstituted solution should be clear to slightly opalescent and colourless to pale yellow. Do not use if opaque particles, discolouration or other foreign particles are present. It is recommended to tranfer the reconstituted solution from the vial to the infusion bag or bottle immediately.

Practical details on the preparation of the solution for infusion

After reconstitution, dilute the product to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution for injection. From a 100 ml infusion bag or bottle (typically, an infusion volume of 100 ml will be appropriate for most patients and doses, but total infusion volume ranging from 50 ml to 250 ml may be used), withdraw a volume of sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution for injection equal to the volume (ml equals total dose in mg divided by 25) of the reconstituted belatacept solution required to provide the dose and discard it. Slowly add the required amount of reconstituted belatacept solution from each vial to the infusion bag or bottle using the same disposable syringe used for reconstitution of the powder. Gently mix the infusion container. The concentration of belatacept in the infusion should be between 2 mg and 10 mg belatacept per ml solution.

Any unused portion in the vials must be discarded in accordance with local requirements.

Administration

When reconstitution and dilution are performed under aseptic conditions, the NULOJIX infusion should be started immediately or must be completed within 24 hours of reconstitution of the powder. If not used immediately, the solution

for infusion may be stored in the refrigerator (2 °C – 8 °C) for up to 24 hours. Do not freeze. The solution for infusion may be stored for a maximum of 4 hours of the total 24 hours below 25 °C. Infusion must be completed within 24 hours of reconstitution of the powder. Prior to administration, the solution for infusion should be inspected visually for particulate matter or discolouration. Discard the solution if any particulate matter or discolouration is observed. The entire, fully diluted infusion should be administered over a period of 30 minutes and must be administered with an infusion set and a sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 μm to 1.2 μm). Following administration, it is recommended that the intravenous line be flushed with infusion fluid to ensure administration of the complete dose.
Do not store any unused portion of the solution for infusion for reuse.

NULOJIX should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of NULOJIX with other agents.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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