22 April 2021
EMA/266477/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nulojix

International non-proprietary name: belatacept

Procedure No. EMEA/H/C/002098/II/0070

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibodies
AE	Adverse event
AR	Acute rejection
AZA	Azathioprine
BMS	Bristol-Myers Squibb
BPAR	Biopsy proven acute rejection
cGFR	Calculated glomerular filtration rate
CI	Confidence interval
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CNS	Central Nervous System
CsA	ciclosporin
CSR	Clinical Study Report
DBL	Database lock
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DSA	Anti-donor HLA antibodies
EBV	Epstein-Barr virus
EC-MPS	Enteric-coated mycophenolate sodium
ESRD	End-stage renal disease
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
HLA	Human leukocyte antigen
ICH	International Conference on Harmonization
ITT	Intent-to-treat
ITT-LT	Intent-to-treat long-term extension
ITT-SW	Intent-to-treat Switch from CNI to Belatacept
IV	intravenous
LI	Less intense
LTE	Long-term extension
MAA	marketing authorisation application
MDRD	Modification of diet in renal disease

MI	More intense
mITT	Modified intent-to-treat
MMF	Mycophenolate mofetil
MPS	Mycophenolate sodium
MTOR	mammalian Target of Rapamycin
MTSOSDS	Modified Transplant Symptom Occurrence and Symptom Distress Scale
NODM	New onset diabetes mellitus
OBF	O'Brien & Fleming
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PMS	post-marketing surveillance
PRA	Panel-reactive antibodies
PRO	Patient reported outcomes
PTLD	Post-transplant lymphoproliferative disorder
PY	Patient-years
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SCr	Serum creatinine
SD	Standard deviation
SF-36	Short form (36) health survey
SmPC	Summary of product characteristics
SRL	sirolimus
TAC	tacrolimus
TB	tuberculosis
TG	triglyceride
TMA	thrombotic microangiopathy
TSQM	Treatment satisfaction questionnaire for medication

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 28 July 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the use of belatacept in conversion from a calcineurin inhibitor - based regimen to a belatacept-based regimen post transplantation; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 18.0 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.1 and requirement on sodium excipients is added.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision P/0277/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	28 July 2020
Start of procedure:	15 August 2020
CHMP Rapporteur Assessment Report	07 October 2020
PRAC Rapporteur Assessment Report	07 October 2020
PRAC members comments	21 October 2020
PRAC Outcome	29 October 2020
CHMP members comments	03 November 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	05 November 2020
Request for supplementary information (RSI)	12 November 2020
CHMP Rapporteur Assessment Report	23 March 2021
PRAC Rapporteur Assessment Report	23 March 2021
PRAC members comments	12 April 2021
PRAC Outcome	09 April 2021
CHMP members comments	12 April 2021
Updated CHMP Rapporteur Assessment Report	15 April 2021
Opinion	22 April 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Renal transplantation, the most effective treatment for end-stage renal disease, requires lifelong immunosuppressive therapy to prevent immune-mediated allograft injury. However, the current standard of care immunosuppressive therapies, the calcineurin inhibitors (CNIs), ciclosporin (CsA) and tacrolimus (TAC), are known to be nephrotoxic, and may also contribute to the development or exacerbation of cardiovascular comorbidities, including hypertension, hypercholesterolemia, and diabetes mellitus. Attempts to replace CNIs with non-CNI regimens in maintenance renal transplant patients have been associated with mixed results. Therefore, there is an unmet medical need for immunosuppressive agents that can provide control of the alloimmune response comparable to CNIs without the renal and cardiovascular toxicities that may contribute to long-term graft loss and death.

2.1.2. About the product

Belatacept represents a class of selective co-stimulatory immunomodulators for prophylaxis of organ rejection in adult patients receiving renal transplants. Belatacept is a second-generation fusion protein consisting of the modified extracellular domain of human CTLA-4 (cytotoxic T lymphocyte-associated protein-4) fused to a fragment (hinge-CH2-CH3) of the Fc domain of human immunoglobulin G1 (IgG1); its mechanism of action involves blockade of the interaction between T-cell CD28 and the

B7.1, B7.2 (CD80, CD86) receptors on the surface of antigen presenting cells, a key step resulting in the generation of co-stimulatory signals required for naïve T-cell activation.

Belatacept was first approved in the European Union (EU) in 2011 for prophylaxis of graft rejection in adults receiving a renal transplant, i.e., treatment with belatacept should be initiated in immediate association to renal transplantation. However, according to the MAH, it is currently estimated that approximately 80% belatacept in clinical practice is used in conversion from a CNI-based therapy to belatacept, months to years after the transplantation. The purpose of this submission is to provide efficacy and safety data from two clinical studies of conversion of maintenance renal transplant patients from CNI- to belatacept-based immunosuppression: a pivotal phase 3b study (IM103116) and a supportive phase 2 study (IM103010). The MAH proposes a modification to the current indication statement in section 4.1 of the SmPC to cover the conversion use and make a clear distinction for the recommendation to administer an interleukin-2 (IL)-2 receptor antagonist during induction therapy specific to *de novo* transplantation.

Approved indication at time of submission of the extension indication:

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.

Proposed indication by the MAH at time of submission of the extension indication (amendment in strikethrough/bold):

Nulojix, in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for prophylaxis of graft rejection in adult~~s receiving~~ **recipients** of 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.**~~ **For induction therapy in de novo renal transplant recipients, the addition of an interleukin-2 (IL-2) receptor antagonist to this Nulojix based regimen is recommended.**

A separate posology recommendation for conversion use has also been proposed in section 4.2 of the SmPC: 5 mg/kg every 2 weeks for the first 8 weeks, followed by the same dose every 4 weeks thereafter.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

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. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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.

Table 1 Tabular overview of clinical studies in conversion of maintenance renal transplant patients from CNI- to belatacept based immunosuppression (IM103010 and IM103116)

Study/ Number of Study Centers/ Locations	Study Design/ Duration/ Status	Patient Population	Treatment groups/ Background Therapy	No. Subjects Randomized (ITT Population)	Efficacy Endpoints
IM103010 (Phase 2) 34 sites worldwide	Randomized, open-label, active-controlled, parallel-group comparison of conversion to belatacept-based immunosuppression to continuation of CNI-based immunosuppression in renal transplant patients. Duration: 12 months and subsequent 8-week follow up with optional LTE. Status: completed	Recipients (ages 18 to 75 years, inclusive) of a renal allograft from a living donor or a deceased donor at least 6 months, but not longer than 36 months, prior to randomization.	Belatacept[a]: 5 mg/kg IV on Days 1, 15, 29, 43, 57 then every 28 days or CNI: dosed twice daily to achieve trough serum concentrations of 100-250 ng/mL (CsA) or 5 - 10 ng/mL (TAC) Maintenance with 1 of: MMF or MPA, SRL, or AZA with optional adjunctive corticosteroids	12-months: Belatacept: 84 CNI: 89 LTE Belatacept: 81 CNI: 81	Primary: cGFR from baseline to 12 months Secondary: AR, incidence of death and graft loss, change in SCr, incidence of NODM, incidence of HLA antibodies, QoL Tertiary: measures of hypertension, measures of dyslipidemia, urinary albumin to creatinine ratio
IM103116 (Phase 3b) 85 sites worldwide	Randomized, open-label, active-controlled, parallel-group comparison of conversion to belatacept-based immunosuppression to continuation of CNI-based immunosuppression in renal transplant patients. Duration: 24 months with subsequent 8-week follow up Status: completed	Recipients (ages 18 to 75 years, inclusive) of a renal allograft from a living donor or a deceased (standard criteria and extended criteria) donor transplanted at least 6 months, but not longer than 60 months prior to enrollment.	Belatacept[b]: 5 mg/kg IV on Days 1, 15, 29, 43, 57, and every 28 days thereafter or CNI: doses targeted to achieve trough serum concentrations (C0 levels) of 50 - 250 ng/mL (CsA) or 4 - 11 ng/mL (TAC). Maintenance with: MMF or EC-MPS, with adjunctive, daily corticosteroids	Belatacept: 223 CNI: 223	Primary: patient and functional graft survival (24 months) Secondary: patient and functional graft survival (12 months), incidence and severity of BPAR, renal function (mean change in cGFR, slopes of cGFR and 1/serum creatinine, proportion of subjects with >5% and > 10% improvement over baseline cGFR, UPCR), mean change in SBP, DBP, and intensity of anti-hypertensive treatment regimen, proportion of subjects with DSA, symptom occurrence and distress.

[a] Subjects randomly assigned to receive belatacept were to reduce their dose of CNIs to 40%-60% of the baseline dose on Day 15, 20%-30% of the baseline dose on Day 22, and were to discontinue CNIs on Day 29.

[b] The CNI dose of subjects randomly assigned to receive belatacept was tapered to 40% - 60% of the baseline dose by Day 15, 20% - 30% of the baseline dose by Day 22, and was then to be discontinued by Day 29 (± 3 days).

Abbreviations: AZA - azathioprine, CNI - calcineurin inhibitor, CsA - cyclosporine, EC-MPS - enteric-coated mycophenolate sodium LTE - long term extension, MMF - mycophenolate mofetil, MPA - mycophenolic acid, PK - pharmacokinetics, SRL - sirolimus

2.3.2. Bioanalytical methods

Quantitation of belatacept in human serum

Two enzyme linked immunosorbent assay (ELISA) methods were used that had previously been validated for belatacept by PPD., Richmond, VA (see table below). Both ELISA methods measure belatacept in human serum using capture antibody (coating onto a plate) and a biotin-labelled detection antibody. The 2 methods are identical with the exception that the ranges in undiluted human serum are from 3.00-72.4 ng/mL and 3.00-80.0 ng/mL, respectively (Table 2, Table 3).

Table 2 Characteristics of the ELISA assay used for the determination of belatacept serum concentrations

Validation/Method	(ELISA)	
Species and Matrix	Human Serum	
Analyte	belatacept	
Capture	(monoclonal anti-BMS-224818 antibody, clone 7F8)	
Detector	(biotinylated monoclonal anti-BMS-224818 antibody, clone 10A8)	
Regression Model, Weighting:	4-PL (Four-Parameter Logistic), unweighted	
Standard Curve		
LLOQ	3.00 ng/mL	3.00 ng/mL
ULOQ	72.4 ng/mL	80.0 ng/mL
QC Precision (% CV)		
Intra Assay	≤ 4.74 %	≤ 28.9%
Inter Assay	≤ 5.85 %	≤ 10.8%
QC Accuracy (% Bias)	Within ± 8.67 %	Within ± 3.91%
Stability		
RT	96 hours	
-25°C	4 months	
-80°C	1300 days	
Freeze-Thaw	13 cycles at -70°C	
Study in Which Method Was Used	IM103116	

Abbreviations: ELISA: enzyme linked immunosorbent assay. LLOQ: Lower limit of quantitation. QC: quality control. RT: room temperature. ULOQ: Upper limit of quantitation. LQC: low quality control HQC: high quality control. %CV: % Coefficient of variation

Source: Validation Reports

Table 3 Belatacept method performance summary

Clinical Study	Method	Number of Acceptable Runs	Accuracy (% Bias)[a] for Assay QCs	Precision (% CV)[b] for Assay QCs
IM103116	ICD 254 V2.03/V2.02	44	1.32 to 2.45	5.99 to 9.70
IM103116	ICD 254 V2.03/V2.02	42	0.688 to 3.91	7.07 to 10.8

[a] Accuracy acceptance criteria: ± 20% of nominal for the Low, Mid, and High Quality Controls

[b] Precision acceptance criteria: <% for the Low, Mid, and High Quality Controls

Source: Belatacept bioanalytical study report (BSR) for study IM103116[24, 25]

Detection of anti-belatacept antibodies (ADA) and neutralising antibodies (NAb) in human serum

A qualitative, bridging electrochemiluminescence (ECL) immunoassay using the Meso-Scale Discovery (MSD) platform (Method TLIAM-0018.29), was validated by Covance Laboratory (Previously called Tandem Labs), West Trenton, NJ. Due to the closure of Covance Laboratory, the ADA assay was

transferred to, and validated at Syngene International, Bangalore, India. An affinity-purified cynomolgus monkey anti-belatacept antibody (pAb) served as a positive control. The method is performed in three tiers (screening, confirmatory, and titer) using pre-established cut-points. Method parameters evaluated in the different laboratories are described in Table 4.

Table 4 Immunogenicity method parameters

Validation/Method	TNJR06-009/TLIAM-0018.29 (Bridging ECL Immunoassay)	U16342/ BAL-II/MOA/057 (version 3) (Bridging ECL Immunoassay)
Species and Matrix	Human Serum	Human Serum
Analyte	Anti-belatacept antibody	Anti-belatacept antibody
Testing	Screen, confirm, and titer	Screen, confirm, and titer
Positive Control	Monkey anti-BMS-224818 antibodies (pAb) in human serum (lot PC-1505-217)	Monkey anti-BMS-224818 antibodies (pAb) in human serum (lot PC-1505-217)
Sensitivity (Drug Interference)	6.25 ng/mL in normal serum and 12.5 ng/mL in patient serum (monkey polyclonal antibody)	6.25 ng/mL (monkey polyclonal antibody)
Drug Tolerance in PC (ng/mL anti-belatacept antibody) in Tier 1 and Tier 2	Up to 10.0 µg/mL belatacept at anti-BMS-224818 concentrations ≥ 250 ng/mL for both inhibitors	Up to 10.0 µg/mL belatacept at anti-BMS-224818 concentrations ≥ 400 ng/mL for both inhibitors
Screening assay cut point (ACP) and confirmatory Cut-Point (CCP)	ACP: 1.29 CCP: 30% for both belatacept and belatacept-tip	ACP: 1.44 CCP: 51.6% from BMS-224818 (Inhibitor A); 31.0% from BMS-224818-Tip (Inhibitor B)
NHV (Normal Healthy Volunteer)		
Liver Cirrhosis	ACP: 1.41	
Studies in Which Method Was Used	IM103116	IM103116

Abbreviations: ECL: electrochemiluminescence.
Source: Validation Report[26] for Method TLIAM-0018.29, Validation Report[27] for Method BAL-II/MOA/057 (version 3).

Serum samples from study IM103116 that were confirmed positive for ADA to the modified CTLA-4 portion of the molecule in the bridging ECL immunoassay, were further analysed for NAb using a validated, functional, in vitro cell-based bioassay at Wuxi AppTec, Shanghai, China (Method 16BASM180V3). Drug levels ≥ 1 µg/mL in undiluted pooled human serum were found to significantly interfere with belatacept response in the bioassay; therefore, only those clinical samples containing belatacept at a concentration less than 1 µg/mL were eligible for NAb testing.

The bioassay evaluates neutralising antibody activity by comparing the response of the post-dose seropositive serum sample to its corresponding Day 1 (baseline/pre-study) sample.

The assay can tolerate up to 300 ng/mL of drug, in the presence of 2.5 µg/mL of NAb. A murine anti-human CTLA4 mAb, 7F8, served as the positive control. A summary of the cell-based bioassay is provided in Table 5.

Table 5 Belatacept neutralising antibody method summary

Validation/Method	16BASM180V3 (Functional cell-based bioassay)
Species and Matrix	Human serum
Positive Control	Murine anti-human CTLA4 mAb 7F8
Drug Tolerance, can detect up to ng/mL amount of drug in the presence of 2.5 µg/mL belatacept Antibody 7F8	300

Source: Method Validation Report 16BAS0527 for Method 16BASM180V3[31]

2.3.3. Pharmacokinetics

Absorption

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

Study IM103010

Sparse pharmacokinetic (PK) samples (i.e. serum trough concentrations) were collected from all belatacept-treated subjects pre-dose at several time points (Table 6). In addition, samples were collected 30 minutes after the end of infusion (EOI, 1 hour after start of infusion) at Week 20, and at the time of a suspected acute rejection (AR) episode (Table 7).

Table 6 Summary statistics of belatacept trough concentrations (µg/mL) prior to infusion

		CONCENTRATION (ug/mL)						
TREATMENT	STATISTIC	DAY 29	DAY 169	DAY 365	DAY 393	DAY 533	DAY 729	DAY 925
BLA	N	81	77	79	56	74	76	71
	GEO.MEAN	10.47	3.36	4.16	3.80	4.28	4.65	4.44
	%CV	34	54	52	68	50	70	61

NOTE: VALUES BELOW LLQ(0.003 ug/mL) WERE SET TO 0.0015 ug/mL FOR COMPUTATION OF SUMMARY STATISTICS

Table 7 Summary statistics of belatacept concentration (µg/mL) at 30 minutes after the end of infusion on Day 141

		CONCENTRATION (ug/mL)
TREATMENT	STATISTIC	DAY 141
BLA	N	55
	MEAN	118.71
	S.D.	34.899
	GEO.MEAN	113.01
	%CV	29
	MEDIAN	119.00
	MIN	38.1
	MAX	189.0

The geometric mean trough serum concentrations of belatacept were 10.47 µg/mL on Study Day 29 and ranged from 3.36 to 4.65 µg/mL from Study Day 169 to Day 925. According to the Applicant, target belatacept trough concentrations were largely achieved (10-12 µg/mL in the first 8 weeks and 2 µg/mL thereafter). The higher trough concentration of belatacept on Study Day 29 in comparison to that on Study Days 169 through 925 was consistent with the greater frequency of belatacept dosing (every 2 weeks) in the first 8 weeks versus once every 4 weeks thereafter.

Study IM103116

In the study IM103116, mean serum trough belatacept concentrations were 14.5, 5.2, 5.0, 5.2, 5.4, and 5.7 µg/mL at Study Weeks 4, 20, 24, 52, 76, and 104 respectively. The higher trough concentration of belatacept observed at Study Week 4, in comparison to those at Study Weeks 20, 24, 52, 76, and 104 was consistent with the more frequent belatacept dosing (every 2 weeks) that occurred during the first 8 weeks, versus once every 4 weeks thereafter. Following the change from every 2- to every 4-week dosing, the mean, geometric mean, and median belatacept serum trough concentrations appeared to be at steady-state and remained consistent over the 24-month study period.

Table 8 Summary statistics of belatacept concentrations (µg/mL) in the study IM103116

Treatment	Study Week	Source	Nominal Time	N	MEAN	SD	GEO.MEAN	% CV	MEDIAN	MIN	MAX
BELATACEPT (UG/ML)	WEEK 4	CENTRAL	0 HOUR	201	15.822	9.780	14.524	61.810	14.500	4.71	125.00
	WEEK 20	CENTRAL	0 HOUR	191	8.455	22.335	5.222	264.169	5.230	0.62	247.00
		CENTRAL	0.5 HOUR	176	112.450	39.679	96.825	35.286	114.500	1.13	261.00
	WEEK 24	CENTRAL	0 HOUR	187	5.687	2.802	4.969	49.269	5.400	0.61	15.20
	WEEK 52	CENTRAL	0 HOUR	185	6.064	2.938	5.188	48.439	5.530	0.00	17.10
	WEEK 76	CENTRAL	0 HOUR	175	6.813	9.599	5.386	140.899	5.760	0.56	124.00
	WEEK 104	CENTRAL	0 HOUR	184	6.486	3.447	5.682	53.140	6.105	0.45	29.20

Distribution

No new distribution data have been submitted in this application, which is considered acceptable by the CHMP. Section 5.2 of the SmPC is considered up to date.

Elimination

No new elimination data have been submitted in this application, which is considered acceptable by the CHMP. Section 5.2 of the SmPC is considered up to date.

2.3.4. Pharmacodynamics

No new pharmacodynamics (PD) data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.5. Discussion on clinical pharmacology

Quantitation of belatacept in human serum was done via two ELISA methods that had previously been validated for belatacept. The detection of ADA in human serum was performed with a bridging ECL immunoassay. Serum samples from study IM103116 and IM103010 that were confirmed positive for ADA to the modified CTLA-4 portion of the molecule in the bridging ECL immunoassay, were further analysed for NAb using a validated, functional, in vitro cell-based bioassay. The bioanalytical methods used were considered acceptable by CHMP.

No formal PK studies were conducted in support of this application. PK data were collected from the two clinical efficacy and safety studies (IM103010 and IM103116). However, they only provided sparse PK data (i.e. trough belatacept concentrations) which were collected at specified time-points. Presented PK data can be regarded as the descriptive data which are implying desired systemic exposure of belatacept. The higher trough concentrations were observed at the study Week 4

compared to trough concentrations measured at later time-points. This was consistent with the greater frequency of belatacept dosing (i.e. 5 mg/kg every 2 weeks) in the first 8 weeks versus once every 4 weeks in the maintenance phase (i.e. 5 mg/kg every 4 weeks).

No PD data have been submitted and this was considered acceptable by the CHMP.

2.3.6. Conclusions on clinical pharmacology

Sparse PK data from two clinical studies where belatacept was administered every 2 weeks and once every 4 weeks thereafter were provided in order to evaluate the desired systemic exposure of belatacept. Overall, the observed belatacept trough concentrations in the presented two clinical studies are in line with the previously reported trough concentrations, and no updates in section 5.2 of the SmPC are needed. No additional PK data were deemed necessary by the CHMP since the proposed dosing in the maintenance phase is the same as the approved one in the maintenance phase in the current SmPC.

2.4. Clinical efficacy

Efficacy and safety of belatacept in the conversion setting was evaluated in two studies, the pivotal phase-3 study IM103116 and the supporting phase-2 study IM103010.

2.4.1. Dose response study

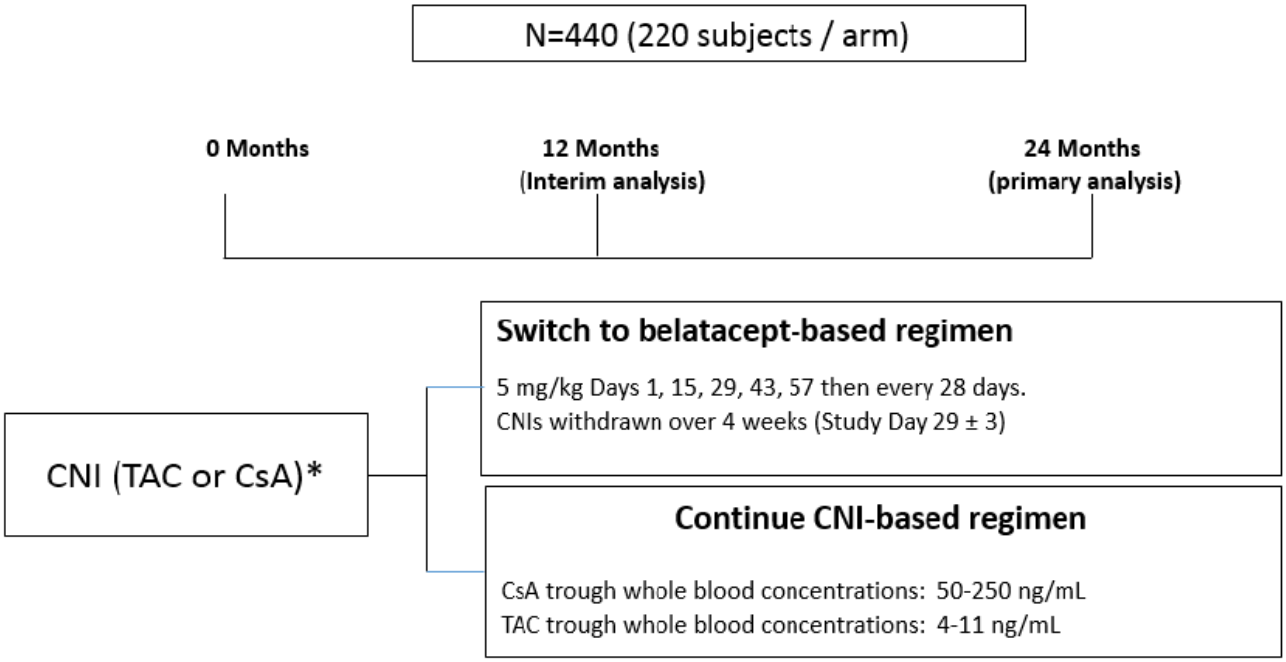
Conversion from a CNI-based regimen at least 6 months post-transplantation was evaluated in the pivotal study IM103116 and the supportive study IM103010 discussed in the next sections. No dose-response study was submitted which was considered acceptable to the CHMP.

2.4.2. Main study

Study IM103116 - Evaluation of the benefits and risks in maintenance renal transplant recipients following conversion to Nulojix (belatacept)-based immunosuppression

Methods

This was a randomised, open-label, active-controlled, parallel-group study. Approximately 440 subjects on CNI-based regimens were to be randomised in a 1:1 ratio to either convert to treatment with belatacept 5 mg/kg IV on days 1, 15, 29, 43, 57, and every 28 days, or to continue treatment with their established CNI Figure 1. Subjects randomised to belatacept were to discontinue CNIs on Day 29. The duration of study participation was 24 months with a subsequent 8-week follow-up period for safety post last dose.



* Background (concomitant) maintenance immunosuppressive regimen includes MMF or MPA and daily corticosteroids. Concomitant immunosuppressive medications to be kept at stable doses through Month 24 in both groups, unless otherwise indicated for clinical care of the individual subject.

Figure 1 Study design (IM103116)

Study participants

Key Inclusion criteria

- Men and women, ages 18 -75 inclusive;
- Adult recipients of a renal allograft from a living donor or a deceased donor between 6-60 months prior to enrolment [6-36 months up to Protocol amendment 05 dated 20-Aug-2014];
- Receiving a stable (≥ 1 month) regimen of CNI (CsA or TAC) on a background regimen of MMF or MPA, with concomitant corticosteroids;
- Calculated glomerular filtration rate (cGFR) ≥30 and ≤75 mL/min/1.73m^2 (Modification of Diet in Renal Disease study [MDRD] 7-point formula; criterion changed to 4-variable MDRD equation in protocol amendment 05 dated 20-Aug-2014). Subjects with cGFR >60 ml/min/1.73m^2 must have evidence of CNI toxicity (criterion removed in protocol amendment 03 dated 04 Sep 2013);
- Stable renal function within 3 months prior to enrolment (as defined by one local laboratory serum creatinine value ± 10% of the local laboratory screening value; in protocol amendment 05 dated 20-Aug-2014, criterion changed to calculated GFR ≥30 and ≤75 mL/min/1.73 m^2 by 4-variable MDRD equation on two occasions: once at the Screening evaluation and at one addition time point between 2 and 12 weeks prior to Screening).

Key Exclusion criteria

- Recipients with EBV serostatus negative or unknown;
- History of any of the following:

    - Treated for biopsy proven acute rejection (BPAR) within 3 calendar months prior to enrolment;
    - Antibody-mediated AR;
    - Recurrent AR in the current allograft;
    - Banff 97 Grade IIA or greater AR (or equivalent), steroid resistant AR or treatment with lymphocyte-depleting agents, plasmapheresis, or rituximab for AR since the time of transplantation of the current allograft;
    - Previous graft loss due to BPAR.
- Positive T-cell lymphocytotoxic cross match;
- Proteinuria >1 g/day or > 0.5 g/day if diabetic. (In protocol amendment 05 dated 20-Aug-2014, changed to: Absence of new onset proteinuria within 12 weeks prior to Screening, or pre-existing proteinuria >1 g/day or >0.5 g/day if diabetic.)

Treatments

Belatacept

The conversion regimen used in study IM103116 is based on that used in study IM103010.

Dosing was based upon historic experience in conversion studies. It has been shown that a replacement cornerstone immunosuppressive agent can be started at the customary maintenance dosage regimen, but that there may be an increased incidence of AR in the first few months following conversion. The target concentrations of belatacept in study IM103116 were identified based upon PK modelling conducted during the maintenance phase of the BENEFIT (IM103008) and BENEFIT-EXT trials (IM103027) (both studies supporting the initial marketing application), which studied the effects of belatacept when initiated at the time of transplant.

In order to manage the risk of AR around the time of conversion from CNI to belatacept, subjects randomised to belatacept underwent tapered discontinuation of their CNI over 2 weeks beginning at the time of the second belatacept dose, Study Week 2 and were to discontinue CNIs on Day 29. Subjects were to receive an infusion of belatacept, 5 mg/kg IV on Days 1, 15, 29, 43, 57, and every 28 days thereafter.

Home infusion services (from Protocol amendment 05) were to be available for belatacept subjects beginning at Week 16 (excluding visits for months 3, 6, 9, 12, 18 and 24) at selected sites where this was feasible. Any such home infusions were to occur within the protocol-defined window for the specified visit.

Active control

CsA doses were to be adjusted to maintain trough whole blood concentrations in the range of 50 - 250 ng/mL as determined by local laboratory assessment and methodology.

TAC doses were to be adjusted to maintain trough whole blood concentrations in the range of 4 - 11 ng/mL as determined by the local laboratory assessment and methodology.

Background Immunosuppressive Medications

Subjects were to be maintained on a stable daily dose of corticosteroids for the duration of the study unless a change in the medical condition of the subject warranted adjustment. Withdrawal of corticosteroids during the study was not permitted.

All subjects in this study were to be treated with Mycophenolate Mofetil (MMF), Enteric-coated Mycophenolate Sodium (EC-MPS) in addition to belatacept or CNI.

Anti-viral/Fungal Prophylaxis

It was recommended that subjects who received T-cell depleting agents at any time during the trial receive prophylaxis against Pneumocystis jiroveci pneumonia, cytomegalovirus and other herpes viruses, and Candida infections, for at least 6-12 weeks, as based upon KDIGO guidelines and/or in accordance with the local standard of care.

Objectives

The primary objective for this study was to evaluate patient and functional graft survival in maintenance renal transplant recipients (6 - 60 months post-transplantation) converted from CNI to belatacept-based immunosuppression as compared to subjects continuing CNI-based immunosuppression at 24 months post-randomisation.

Outcomes/endpoints

Primary efficacy endpoint:

- Proportion of subjects who survive with a functional graft at 24 months post-randomisation

For sensitivity analysis of the primary efficacy outcome, any subject with unknown subject and graft survival status at Month 24 (last follow-up date was Day 756), was considered as having an event of graft loss or death if at least one of the following criteria were met during the 24 months post-randomisation:

- The subject experienced BPAR prior to the last follow-up date;
- The subject developed post-transplant lymphoproliferative disorder (PTLD) prior to the last follow-up date;
- The subject was discontinued from study medication due to the reason "Lack of Efficacy";
- The subject had an AE of polyomavirus associated nephropathy with a start date that precedes the date of premature discontinuation;
- The subject's last cGFR was < 15 mL/min/1.73m^2.

Any remaining subjects with unknown patient or graft survival status were to be considered as having had no event of graft loss or death.

Pre-specified secondary endpoints:

- The incidence and severity of clinically suspected, biopsy proven acute rejection at 12- and 24-months post-randomisation;
- Mean cGFR and mean change in cGFR (per 4-variable MDRD equation) from baseline to 12- and 24-months post-randomisation (% and absolute);
- Slopes of cGFR and 1/serum creatinine, respectively from baseline as well as Month 3 to 12- and 24-months post-randomisation;
- Proportion of subjects with > 5% and > 10% improvement over baseline in cGFR at 12- and 24-months post-randomisation;

- UPCR at baseline, 3, 6, 12, and 24 months post-randomisation;
- Mean change in systolic and diastolic blood pressure and intensity of treatment regimen (defined as the total number of antihypertensive medications used to control hypertension) from baseline to 12- and 24-months post-randomisation;
- Proportion of subjects with DSA at Baseline/Day 1, 12- and 24-months post-randomisation
- The frequency of symptom occurrence and symptom distress as measured with the MTSOSD-59R at baseline, Week 6, and 3, 6, and 12 months post-randomisation.

Pre-specified exploratory endpoints:

- Impact of AR on renal function, infection and malignancy, and patient and functional graft survival;
- Proportion of patients who survive with a functioning graft to 12- and 24-months post-randomisation by acute rejection status up to 12 and 24 months, respectively;
- Calculated GFR at 12- and 24-months post-randomisation, by acute rejection status up to 12 and 24 months;
- Proportion of patients with infections or malignancies at 12- and 24-months post-randomisation, by acute rejection status up to 12 and 24 months, respectively;
- Change in lipid and metabolic status from baseline to 12- and 24-months post-randomisation;
- Mean change in lipid parameters (total serum cholesterol, high density lipoprotein, low density lipoprotein, non-high-density lipoprotein and triglycerides);
- Proportion of subjects who develop NODAT at 12- and 24-months post-randomisation;
- Treatment satisfaction measured with TSQM at baseline and 3, 6, and 12 months post-randomisation;
- PK of belatacept treated subjects at specified visits.

Sample size

Formal statistical testing of a research hypothesis was not performed in this study.

The primary objective of this study was to evaluate patient and graft survival in maintenance renal transplant recipients converted from CNI to belatacept as compared to continuation of CNI-based immunosuppression at 24 months post-randomisation. A sample size of approximately 220 subjects per treatment group was considered to provide sufficient power to rule out an unacceptable difference in patient and graft survival.

With a confidence level (one-sided) of 0.975 and assuming true rates of patient and graft survival by Month 24 in both treatment groups was 93%, the sample size of 220 subjects per arm afforded 90% probability to rule out a difference of 8.3% (sample size based on 1000 simulations per Newcombe methodology).

This sample size provided 93% power to detect a 10% absolute difference of mean percentage in cGFR at Month 24 between the belatacept regimen and the CNI regimen assuming a standard deviation of 30% (alpha 0.05, 2-sided).

Given a sample size of approximately 220 subjects per treatment group, if the true AR rates by Month 24 are 7% in the belatacept regimen and 1% in the CNI regimen, the half width of the 95% confidence

interval of the difference in AR rate was estimated to be 3.6% (alpha 0.05, 2-sided). With the assumed rates of AR, the confidence interval for the difference would be (2.4%, 9.6%).

Given a sample size of 220 subjects per treatment group, and assuming an event rate of PTLD of 0.74% the probability of observing at least 1 event was 80.5%.

Randomisation

Subjects were randomised in a 1:1 fashion to receive belatacept or continue to receive their previous CNI (CsA or TAC). Subjects were stratified by screening cGFR in a 1:2 ratio (≥ 30 to < 45 mL/min/1.73 m^2 or ≥ 45 to 75 mL/min/1.73 m^2).

Randomisation numbers were assigned in the order in which subjects qualified for treatment, not in the order of study enrolment. A randomisation schedule was generated and kept by the MAH.

At the time of enrolment, immediately after written informed consent was obtained and before performing any study-related procedures, each subject was assigned a unique sequential 5-digit subject number by the interactive voice response system (IVRS) for identification throughout the study. This subject number was not reused for any other participant throughout the study. The physician/coordinator contacted IVRS to enrol each subject into a centralised database at the time of signing consent. SAE reporting for all subjects began at the time of enrolment, immediately after written informed consent was obtained.

The subjects were to be randomised once all entry criteria (inclusion and exclusion) had been met. The physician/coordinator were to contact IVRS to randomise each subject into a centralised database.

Blinding (masking)

The study was open-label.

Statistical methods

General. No formal statistical testing of a research hypothesis was performed in this study. All analyses of efficacy and safety endpoints were summarised descriptively by treatment groups (belatacept vs CNI). All efficacy analyses were based on all randomised subjects (ITT analysis population), unless stated otherwise.

Primary endpoint. The effect of treatments on the primary endpoint "Proportion of subjects who survive with a functioning graft at 12 and 24 months post-randomisation" was analysed using a point estimate and 95% CI for the difference between belatacept and CNI (and point estimates of the proportion and 95% CI within each treatment group) using the "Newcombe" method (with normal approximation if >= 5 events in each arm with strata, else exact method without strata, see above). The analysis was performed in the ITT and PP analysis sets.

Secondary endpoints. The effect of treatments on key secondary endpoints "Proportion of subjects who experience clinically suspected, biopsy proven acute rejection by 12 and 24 months post-randomisation (overall vs classification of renal allograft pathology by the Banff criteria (2007)[1])" and "Mean change and mean percent change from baseline to Month 12 and 24 in cGFR" was analysed using point estimates and 95% confidence intervals for the between-group difference and for within-group change. cGFR was calculated using the 4-variable Modification of Diet in Renal Disease [MDRD]

[1] Solez K et al. Banff 07 classification of renal allograft pathology: updates and future directions. 2008 Apr;8(4):753-60

equation as published by Davidson et al. 2003[2]. For the continuous endpoint "cGFR" a linear mixed effects model was applied. In addition, other secondary and exploratory endpoints were studied, which are not reported here (see above).

Analysis Sets.

The "Intent-to-Treat" (ITT) population included all subjects who are randomised into the study. Subjects were grouped according to the treatment to which they were randomised.

The "Per-Protocol" population included all randomised subjects who did not violate terms of the protocol that might have affected the efficacy outcome. "Per-protocol" analyses were performed at Month 24 on the primary endpoint and "key" secondary endpoints only if the following occurred: More than 10% of the total number of subjects included into the "ITT" population at Month 24 have significant protocol violations/ deviations and consequently would be excluded from the "per-protocol" population.

The Safety population included all randomised and treated subjects (received at least one dose of study medication). Subjects were grouped according to the treatment received.

The PK population included subjects who received at least one dose of belatacept and have at least 1 PK sample post baseline.

Missing data.

Subject and graft survival status. Any subject (either randomised to belatacept or CNI) with unknown subject and graft survival status at Month 12 (Month 24) (last follow-up date was prior to Day 392 (Day 756), was considered as having an event of graft loss or death if at least one of the following criteria were met during 12 months (24 months) post-randomisation: 1) Subject has AR prior to last follow-up date; 2) Subject has PTLD prior to last follow-up date; 3) Subject's discontinuation reason for study medication is due to Lack of Efficacy; 4) Subject has polyomavirus associated nephropathy adverse event (AE) before discontinuation; 5) Subject's last cGFR < 15mL/min/1.73m^2. For the remaining subjects with unknown status, they were considered as having no event of graft loss or death.

cGFR. Imputation to zero for death and graft loss were performed for values for adjusted mean cGFR at Month 24 as sensitivity analysis.

Interim analysis. Selected analyses were performed at month 12. The purpose of the interim analysis was to obtain study data to assess the evolving benefit-risk profile of belatacept conversion at 12 months post-randomisation. Similar methods as those used for the 24-month analyses were performed for the 12-month interim analysis. The interim analysis was descriptive in nature, and no statistical tests were performed. The confidence level for the confidence interval of the estimate of the primary endpoint was adjusted for multiple testing using an O'Brien and Fleming alpha spending function.

Subgroups analyses. Descriptive summary statistics without testing were performed for primary and key secondary endpoints in the following subgroups: 1) Type of Transplant, 2) Recipient gender, 3) Recipient race, 4) Geographic region, 5) Recipient age, 6) Donor age, 7) End stage renal disease (ESRD) (Diabetes), 8) Initial CNI treatment, 9) Baseline GFR (ml/min/1.73m^2), 10) Time from Transplantation to Randomisation, 11) Baseline Treatment Regimen.

Sensitivity analyses. The primary analysis was performed in the ITT and PP analysis sets.

[2] Davidson J, Wilkinson A, Dantal J et al. New-onset diabetes after transplantation: 2003 international consensus guidelines. Transplantation. Vol. 75, SS3-SS24, No 10, May 27, 2008 Supplement.

A sensitivity analysis was performed, using the imputation methods for unknown subject and graft survival status (see above). An additional analysis was performed using no imputation, either for subjects lost to follow-up or for subjects with unknown subject and graft survival status. For subjects with unknown status, the number of subjects with AR, PTLD, AE of polyomavirus associated nephropathy, and last cGFR < 15mL/min/1.73m^2 was summarised.

Study conduct. The date of finalisation of the final statistical analysis plan (version 3.0) was not documented. The clinical database was locked on 2019-09-10.

Results

Participant flow

A total of 631 subjects were enrolled and 446 subjects were randomised (223 in each treatment group; 1 subject was randomised to the belatacept group but only received treatment with CNI).

The reasons for not being randomised are summarised in Table 9 and the study subject distribution is given in Table 10.

Table 9 Pre-randomised subject status summary 24-month analysis all enrolled subjects (IM103116)

Status (%)	Total N = 631
NOT RANDOMIZED	185 (29.3)
REASON FOR NOT BEING RANDOMIZED	
ADVERSE EVENT	4 (0.6)
SUBJECT WITHDREW CONSENT	7 (1.1)
PREGNANCY	0
LOST TO FOLLOW-UP	1 (0.2)
ADMINISTRATIVE REASON BY SPONSOR	0
DEATH	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	166 (26.3)
POOR/NON-COMPLIANCE	2 (0.3)
OTHER	5 (0.8)

Table 10 End of 24-month period status summary - all randomised subjects (IM103116)

Status (%)	Belatacept N = 223	CNI N = 223	Total N = 446
RANDOMIZED	223 (100.0)	223 (100.0)	446 (100.0)
RANDOMIZED BUT NOT TREATED	2 (0.9)	1 (0.4)	3 (0.7)
RANDOMIZED AND TREATED	221 (99.1)	222 (99.6)	443 (99.3)
COMPLETED THE TREATMENT PERIOD	195 (87.4)	186 (83.4)	381 (85.4)
NOT COMPLETED THE TREATMENT PERIOD	26 (11.7)	36 (16.1)	62 (13.9)
REASON FOR NOT COMPLETING THE TREATMENT PERIOD			
ADVERSE EVENT	12 (5.4)	7 (3.1)	19 (4.3)
DEATH	3 (1.3)	3 (1.3)	6 (1.3)
LACK OF EFFICACY	1 (0.4)	0	1 (0.2)
POOR/NON-COMPLIANCE	0	3 (1.3)	3 (0.7)
SUBJ REQUEST TO DISCONTINUE STUDY TRT	6 (2.7)	11 (4.9)	17 (3.8)
SUBJECT NO LONGER MEETS STUDY CRITERIA	3 (1.3)	10 (4.5)	13 (2.9)
SUBJECT WITHDREW CONSENT	1 (0.4)	2 (0.9)	3 (0.7)
CONTINUING THE STUDY	217 (97.3)	206 (92.4)	423 (94.8)
NOT CONTINUING THE STUDY	6 (2.7)	17 (7.6)	23 (5.2)

After the 24-month study duration, the subjects could enter an 8-week follow-up period. Subject disposition for the follow-up period is listed in Table 11.

Table 11 End of study subject status summary /24-month analysis/ all randomised subjects who entered follow up period (IM103116)

Status (%)	Belatacept N = 211	CNI N = 201	Total N = 412
BELATACEPT-TREATED SUBJECTS WHO TRANSITION TO COMMERCIALLY AVAILABLE BELATACEPT AND CNI-TREATED SUBJECTS (A)			
COMPLETING THE STUDY	109 (51.7)	201 (100.0)	310 (75.2)
NOT COMPLETING THE STUDY	0	0	0
FOR BELATACEPT SUBJECTS WHO RETURN TO STANDARD OF CARE POST STUDY (B)			
COMPLETING THE STUDY	90 (42.7)	0	90 (21.8)
NOT COMPLETING THE STUDY	10 (4.7)	0	10 (2.4)
REASON FOR NOT COMPLETING THE STUDY			
LACK OF EFFICACY	0	0	0
ADVERSE EVENT	7 (3.3)	0	7 (1.7)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	1 (0.5)	0	1 (0.2)
SUBJECTS WITHDREW CONSENT	0	0	0
DEATH	0	0	0
LOST TO FOLLOW-UP	0	0	0
POOR/NON-COMPLIANCE	0	0	0
PREGNANCY	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	2 (0.9)	0	2 (0.5)
ADMINISTRATIVE REASON BY SPONSOR	0	0	0
OTHER	0	0	0

Recruitment

Subjects were recruited at 85 sites in 10 countries (Argentina, Austria, Colombia, France, Germany, Netherlands, Norway, Sweden, Switzerland, United States of America).

Conduct of the study

Relevant protocol deviations were defined as related to inclusion or exclusion criteria, study conduct, study management, or subject assessment that were programmable and could potentially affect the interpretability of study results. Relevant protocol deviations are pre-specified in the SAP.

A review identified two subjects with relevant protocol deviations; one in each treatment arm (Table 12).

Table 12 Relevant protocol deviation summary /24-month study period/ all randomised subjects (IM103116)

	Belatacept N = 223	CNI N = 223
SUBJECTS WITH OUT ANY RELEVANT PROTOCOL DEVIATION (PER PROTOCOL SUBJECTS)	222 (99.6)	222 (99.6)
SUBJECTS WITH AT LEAST ONE RELEVANT PROTOCOL DEVIATION	1 (0.4)	1 (0.4)
RELEVANT PROTOCOL DEVATIONS		
RECIPIENTS WITH EBV SEROSTATUS NEGATIVE OR UNKNOWN	0	0
HISTORY OF ANY OF AR RELATED DEVIATIONS	0	1 (0.4)
SUBJECTS WITH A POSITIVE T-CELL LYMPHOCYTOTOXIC CROSS MATCH	1 (0.4)	0
DONOR'S AGE < 10 YEARS OLD	0	0
RECIPIENTS AGE < 18 YEARS OLD	0	0
SUBJECTS RECEIVED TREATMENT OTHER THAN ASSIGNED STUDY MEDICATION	0	0

Significant protocol deviations were defined as study conduct that differed significantly from the protocol, including GCP noncompliance. Approximately 200 significant protocol deviations were reported. Most significant protocol deviations concern failure to report AEs in a timely manner, failure to obtain written consent in a correct manner and deviation from inclusion/exclusion criteria. In the latter group, incorrect tapering of CNI, incorrect corticosteroid administration and failure to ensure stable renal function/immunosuppression were common issues.

The original protocol for this study was dated 22-May-2012. Study Initiation Date: 17-Apr-2013. The changes in the protocol as of 10-Sep-2019 (clinical cut-off date), are summarised in Table 13.

Table 13 Summary of Changes to Protocol (IM103116)

	Date	Summary of Change
Amendment 01 (Global)	07-Jan-2013	This amendment was developed to modify the inclusion/exclusion criteria (inclusion of clinical criteria for suspicion of PTLD). Changes were made to the time and events & pharmacokinetic assessment tables.
Amendment 02 (Germany)	01-Jul-2013	This revision removed the chest x-ray required at screening for patients who consent to participate in Germany.
Amendment 03 (Global)	04-Sep-2013	This revision updated the risk benefit assessment section to include potential risks and benefits for subjects converting from CNI to belatacept; clarified that there is no formal statistical hypothesis testing for primary endpoint; modified objectives; revised inclusion/exclusion criteria; classified that a renal biopsy may be conducted if there is new medical cause that occurs during the study; included data monitoring committee.
Amendment 04 (Argentina and Colombia)	04-Nov-2013	The purpose of this amendment was to incorporate post study access to therapy.
Amendment 05 (Global)	20-Aug-2014	This revision revised and clarified existing eligibility criteria to align them with current clinical practice and laboratory standards; allowed screen failure patients to be rescreened once; inserted wording to allow patients converted to belatacept to receive some of their monthly doses by home infusion.
Amendment 06 (France)	09-May-2016	The purpose of the amendment was to incorporate changes requested by French MOH.
Amendment 07 (Global)	07-Apr-2017	This revision decreased targeted enrollment from 600 to 440 randomized subjects per prior agreement with the US FDA; clarified requirement for daily dosing of maintenance corticosteroids throughout study period; allowed one time rescreening of patients who previously were screen failures; added wording to indicate that protocol-specified tacrolimus trough levels being locally determined would also be captured in the clinical database.
Amendment 08 (Global)	18-Apr-2018	This revision updated definition of serious breach per company guidelines; clarified belatacept dosing instructions for skipping of doses to include possibility of dosing out of defined visit windows; added PML for some biomarker labs; clarified "end of infusion" definition; allowed provision of central lab CNI trough values to sites.

Source: Protocols and protocol amendments in Appendix 1.1

Five global protocol amendments were executed during the study; four of them (Amendments 03, 05, 07 and 08) after the initiation of the study (17-Apr-2013) (see details in Table 13). In an open label, protocol amendments after study initiation date may raise concerns regarding study integrity and potentially data-driven decisions. Considering that no formal hypothesis testing was performed, no increase of the risk of false positive conclusions (type 1 error) is expected, however, bias of estimates of efficacy or safety of treatments may still be introduced. Here, considering only global amendments as relevant, only modification of study objectives and revision of eligibility criteria may raise concerns. In response to request for supplementary information, the MAH discussed in more details the amendments, underlying motivations and potential biases in the data.

- Amendment 01 was implemented prior to the opening of enrolment in April 2013 and so applied to all study participants.
- Amendment 02 was specific for the study sites in Germany and concerns the requirement for chest radiographies and the diagnosis of tuberculosis.
- Amendment 03 affected eligibility criteria but had minimal effect on enrolment. This is accepted.
- Amendment 04 was a country specific amendment implemented for Argentina and Colombia and concerned Post-Study Access to Therapy.
- Amendment 05 concerned enrolment and was motivated by the low recruitment and high screen failure rate. 89% of the enrolled patients were enrolled under Amendment 5.

In summary, no substantial impact of different clinical study protocols on patient characteristics and results was observed.

Baseline data

Baseline demographic and disease characteristics are summarised in Table 14 and Table 15, respectively.

Table 14 Demographic characteristics summary of transplant recipients 24-month analysis - all randomised subjects (IM103116)

	Belatacept N = 223	CNI N = 223
AGE (YEARS)		
N	223	223
MEAN	53.4	52.6
MEDIAN	55.0	54.0
MIN , MAX	22 , 75	20 , 75
Q1 , Q3	45.0 , 61.0	46.0 , 62.0
SD	11.3	11.7
AGE CATEGORIZATION (%)		
<65	184 (82.5)	186 (83.4)
>=65	39 (17.5)	37 (16.6)
GENDER (%)		
MALE	150 (67.3)	151 (67.7)
FEMALE	73 (32.7)	72 (32.3)
RACE (%)		
WHITE	191 (85.7)	187 (83.9)
BLACK/AFRICAN AMERICAN	24 (10.8)	24 (10.8)
AMERICAN INDIAN/ALASKA NATIVE	0	0
ASIAN	1 (0.4)	3 (1.3)
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	0	0
OTHER	7 (3.1)	9 (4.0)
ETHNICITY (%)		
HISPANIC/LATINO	9 (4.0)	15 (6.7)
NOT HISPANIC/LATINO	82 (36.8)	79 (35.4)
NOT REPORTED	132 (59.2)	129 (57.8)
COUNTRY BY GEOGRAPHIC REGION (%)		
NORTH AMERICA	91 (40.8)	94 (42.2)
UNITED STATES OF AMERICA	91 (40.8)	94 (42.2)
SOUTH AMERICA	35 (15.7)	37 (16.6)
ARGENTINA	31 (13.9)	33 (14.8)
COLOMBIA	4 (1.8)	4 (1.8)
EUROPE	97 (43.5)	92 (41.3)
AUSTRIA	7 (3.1)	7 (3.1)
FRANCE	24 (10.8)	19 (8.5)
GERMANY	47 (21.1)	49 (22.0)
NETHERLANDS	15 (6.7)	16 (7.2)
NORWAY	0	1 (0.4)
SWEDEN	1 (0.4)	0
SWITZERLAND	3 (1.3)	0

Table 15 Baseline disease characteristics summary of transplant recipients 24 month analysis - all randomised subjects (IM103116)

	Belatacept N = 223	CNI N = 223
WEIGHT (KG)		
N	222	221
MEAN	85.4	85.9
MEDIAN	84.4	84.0
MIN , MAX	42 , 157	50 , 161
Q1 , Q3	72.3 , 95.8	73.0 , 96.0
SD	20.4	19.2
PREVIOUS NUMBER OF TRANSPLANT (S)		
0	183 (82.1)	182 (81.6)
1	37 (16.6)	39 (17.5)
2	3 (1.3)	2 (0.9)
BASELINE GFR		
N	223	223
MEAN	49.6	50.7
MEDIAN	49.0	50.0
MIN , MAX	25 , 89	30 , 78
Q1 , Q3	40.0 , 59.0	42.0 , 59.0
SD	12.1	11.6
SCREENING GFR STRATA (BASED ON IVRS)		
cGFR e 30 to < 45 mL	78 (35.0)	77 (34.5)
cGFR e 45 to 75 mL/	145 (65.0)	146 (65.5)
SCREENING GFR STRATA (BASED ON LAB VALUES)		
CGFR < 30 mL/min/1.73m*2	1 (0.4)	0
CGFR e 30 to < 45 mL/min/1.73m*2	87 (39.0)	83 (37.2)
CGFR e 45 to < 75 mL/min/1.73m*2	131 (58.7)	136 (61.0)
CGFR >= 75 mL/min/1.73m*2	4 (1.8)	4 (1.8)
PANEL REACTIVE ANTIBODIES		
N	211	212
MEAN	8.3	9.9
MEDIAN	0.0	0.0
MIN , MAX	0 , 100	0 , 99
Q1 , Q3	0.0 , 4.0	0.0 , 5.0
SD	20.2	22.6
PRIMARY CAUSE OF END STAGE RENAL DISEASE		
CONGENITAL, RARE FAMILIAL, AND METABOLIC DISORDERS	5 (2.2)	3 (1.3)
DIABETES	38 (17.0)	30 (13.5)
GLOMERULAR DISEASE	45 (20.2)	54 (24.2)
HYPERTENSIVE NEPHROSCLEROSIS	24 (10.8)	27 (12.1)
NEOPLASMS	0	1 (0.4)
POLYCYSTIC KIDNEYS	43 (19.3)	45 (20.2)
RENOVASCULAR AND OTHER VASULAR DISEASES	8 (3.6)	6 (2.7)
RETRANSPLANT/GRAFT FAILURE	0	0
TUBULAR AND INTERSTITIAL DISEASES	9 (4.0)	9 (4.0)
OTHER	50 (22.4)	48 (21.5)
NOT REPORTED	1 (0.4)	0
SPECIFIC DISEASE HISTORY		
TYPE 1 DIABETES MELLITUS	14 (6.3)	4 (1.8)
TYPE 2 DIABETES MELLITUS	60 (26.9)	63 (28.3)
HYPERTENSION	208 (93.3)	210 (94.2)
HYPERCHOLESTEROLEMIA	100 (44.8)	104 (46.6)

The background information on donors are given below and in Table 16.

Table 16 Demographic characteristics summary of transplant donors 24 month analysis all randomised subjects (IM103116) (truncated by assessor)

	Belatacept N = 223	CNI N = 223
AGE (YEARS)		
N	222	222
MEAN	47.8	48.2
MEDIAN	50.0	50.0
MIN, MAX	10 , 83	17 , 83
Q1 , Q3	38.0 , 58.0	39.0 , 57.0
SD	15.1	13.8
AGE CATEGORIZATION (%)		
< 50	109 (48.9)	110 (49.3)
>= 50	113 (50.7)	112 (50.2)
NOT REPORTED	1 (0.4)	1 (0.4)
GENDER (%)		
MALE	107 (48.0)	105 (47.1)
FEMALE	115 (51.6)	117 (52.5)
NOT REPORTED	1 (0.4)	1 (0.4)
TYPE OF DONOR ORGAN TRANSPLANT (%)		
LIVING-RELATED	37 (16.6)	41 (18.4)
LIVING-UNRELATED	38 (17.0)	36 (16.1)
CADAVERIC	148 (66.4)	146 (65.5)

The distribution of donor-recipient HLA-A/B/DR mismatches was similar and balanced across the treatment groups, in particular, with regard to the percentages with 0-3 and 4-6 mismatches overall (52.5% and 47.6% in the belatacept group and 52.0% and 48.0% in the CNI group, respectively).

Donor and recipient serostatus for CMV and EBV are summarised in Table 17.

Table 17 Histocompatibility, viral serology and transplant characteristics between recipients and donors 24-month analysis all randomised subjects (IM103116)

Demographic Characteristic	Belatacept N = 223	CNI N = 223
CMV VIRAL SEROLOGY, X (%)		
D+ / R+	94 (42.2)	99 (44.4)
D+ / R-	39 (17.5)	42 (18.8)
D+ / U	1 (0.4)	0
D- / R+	39 (17.5)	43 (19.3)
D- / R-	47 (21.1)	39 (17.5)
D- / U	0	0
U / R+	2 (0.9)	0
U / R-	1 (0.4)	0
U / U	0	0
EBV VIRAL SEROLOGY, X (%)		
D+ / R+	139 (62.3)	150 (67.3)
D+ / R-	0	0
D+ / U	0	0
D- / R+	20 (9.0)	15 (6.7)
D- / R-	0	0
D- / U	0	0
U / R+	64 (28.7)	58 (26.0)
U / R-	0	0
U / U	0	0

Of the 223 subjects randomised to CNI continuation, 25 (11%) were receiving CsA, which was continued post-randomisation; an additional 198 subjects (89%) were receiving TAC, which was also continued post-randomisation.

Numbers analysed

The number of subjects analysed in each population is summarised in Table 18.

Table 18 Populations analysed in IM103116

Population	Characteristics	Number of Subjects	
		Belatacept	CNI
Intent-to-Treat (ITT)	Used for efficacy analyses. Includes all randomized subjects	223	223
As-treated	Used for safety analyses. Includes all randomized subjects who receive at least 1 dose of study medication	221	222

One subject in each treatment group withdrew consent after randomisation, but before receiving the first dose of belatacept or CNI as assigned study drug. One additional subject was randomised to the

belatacept group but was not treated. Since these subjects were not treated, they were excluded from the as-treated (safety) population.

Outcomes and estimation

Primary efficacy endpoint

The proportion of subjects alive with a functional graft at Month 24 was similar in the belatacept and CNI treatment groups (Table 19). A total of 8 subjects died (4 in the belatacept group and 4 in the CNI group), all with functioning grafts. Two graft losses (0.9%) were reported in the CNI arm versus none in the belatacept arm.

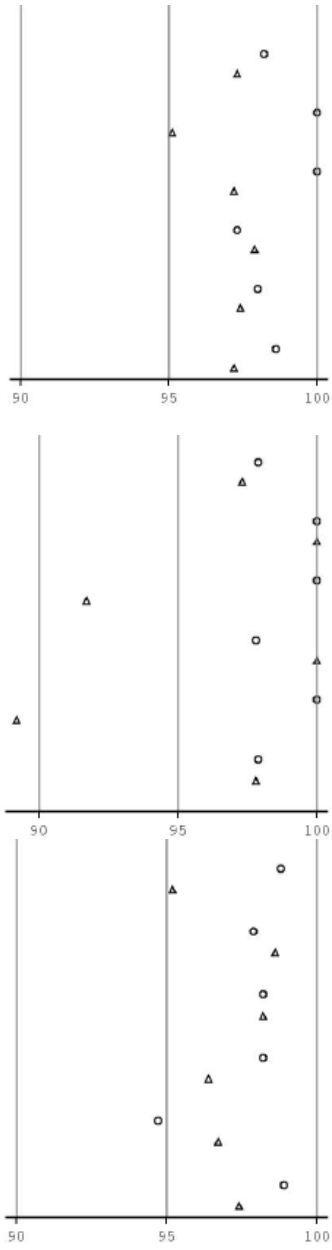
Table 19 Summary of graft loss and death (no imputation) 24-month study period - all randomised subjects (IM103116)

	Belatacept N = 223	CNI N = 223
Subject and Graft Survival at Month 24 (n, %)	219 (98.2)	217 (97.3)
Difference from CNI (95.1% CI OBF)[a]	0.9 (-8.6, 10.4)	
Graft Loss (n, %)	0	2 (0.9)
Death (n, %)	4 (1.8)	4 (1.8)
Imputed as Graft Loss or Death	0	0

Results for the imputation sensitivity analysis for subjects with unknown subject and graft survival status at Month 24 were consistent with the ITT analysis.

A subgroup analysis of the primary endpoint expressed as "Subjects surviving with a functioning graft at Month 24" is given in Figure 2.

SUBJECTS SURVIVING WITH A FUNCTIONING GRAFT AT MONTH 24		
ALL		
Belatacept	219	98.2
CNI	217	97.3
TYPE OF TRANSPLANT:LIVING RELATED		
Belatacept	37	100.0
CNI	39	95.1
TYPE OF TRANSPLANT:LIVING UNRELATED		
Belatacept	38	100.0
CNI	35	97.2
TYPE OF TRANSPLANT:CADAVERIC		
Belatacept	144	97.3
CNI	143	97.9
RECIPIENT GENDER:MALE		
Belatacept	147	98.0
CNI	147	97.4
RECIPIENT GENDER:FEMALE		
Belatacept	72	98.6
CNI	70	97.2
RECIPIENT RACE:WHITE		
Belatacept	187	97.9
CNI	182	97.3
RECIPIENT RACE:BLACK		
Belatacept	24	100.0
CNI	24	100.0
RECIPIENT RACE:OTHER		
Belatacept	8	100.0
CNI	11	91.7
GEOGRAPHIC REGION:NORTH AMERICA		
Belatacept	89	97.8
CNI	94	100.0
GEOGRAPHIC REGION:LATIN AMERICA		
Belatacept	35	100.0
CNI	33	89.2
GEOGRAPHIC REGION:EUROPE		
Belatacept	95	97.9
CNI	90	97.8
RECIPIENT AGE:<50YEARS OLD		
Belatacept	79	98.8
CNI	79	95.2
RECIPIENT AGE:>=50YEARS OLD		
Belatacept	140	97.9
CNI	138	98.6
DONOR AGE:<50YEARSOLD		
Belatacept	108	98.2
CNI	109	98.2
DONOR AGE:>=50YEARSOLD		
Belatacept	111	98.2
CNI	108	96.4
END STAGE RENAL DISEASE(DIABETES):YES		
Belatacept	36	94.7
CNI	29	96.7
END STAGE RENAL DISEASE(DIABETES):NO		
Belatacept	183	98.9
CNI	188	97.4



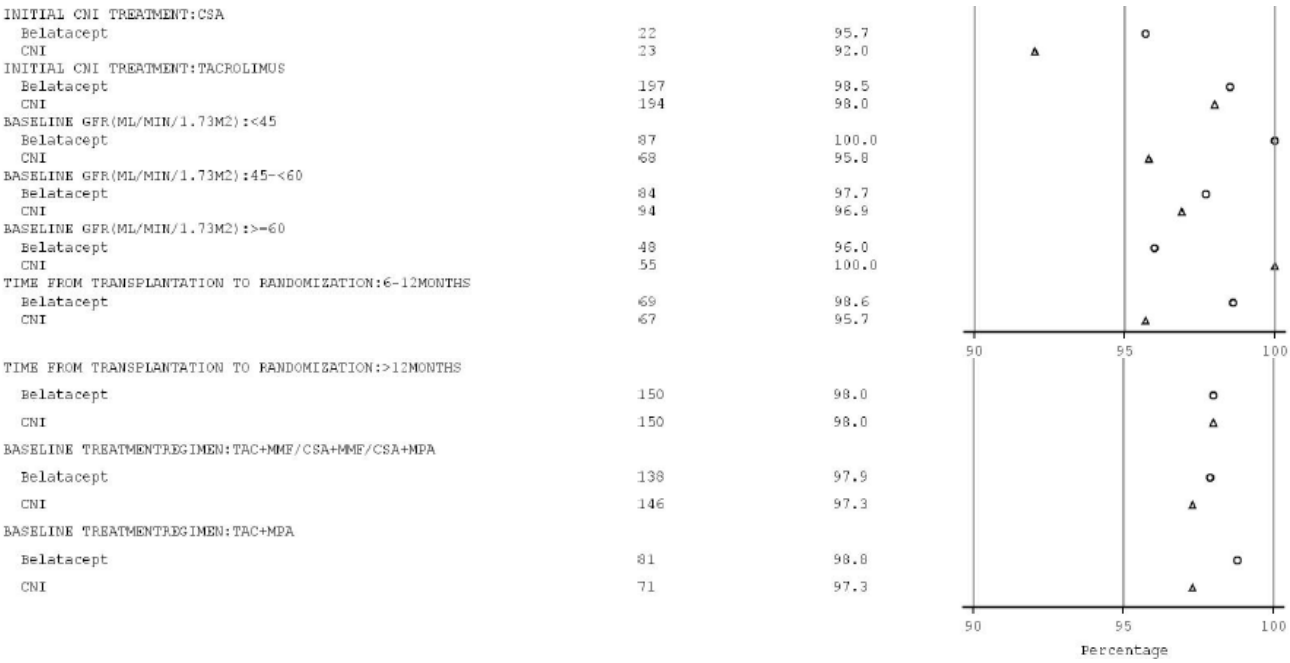


Figure 2 Forest plot of primary endpoint of death and graft loss by subgroup categories 24-month study period all randomised subjects (IM103116)

Secondary efficacy endpoint: Biopsy Proven Acute Rejection (BPAR)

Events of BPAR are summarised in Table 20.

Table 20 Summary of biopsy proven acute cellular rejection (Banff Grade 1A or higher), 24-month study period - all randomised subjects (IM103116)

	Belatacept N = 223	CNI N = 223
UP TO 12 MONTHS		
TOTAL NUMBER OF SUBJECTS	223	223
NUMBER OF SUBJECTS WITH BIOPSY PROVEN ACUTE REJECTION(BANFF GRADE IA OR HIGHER), X (%) (a)	18 (8.1)	3 (1.3)
PROPORTION (95% CI) (1)	8.1 (4.5, 11.6)	1.3 (0.3, 3.9)
DIFFERENCE FROM CNI (95% CI) (2)	6.7 (-2.8, 16.1)	
DIFFERENCE FROM CNI (99.69% CI OBF) (2)	6.7 (-7.5, 20.8)	
ADJUSTED (3)		
DIFFERENCE FROM CNI (95% CI) (3)	6.7 (2.7, 10.7)	
DIFFERENCE FROM CNI (99.69% CI OBF) (3)	6.7 (0.7, 12.7)	
TOTAL NUMBER OF BIOPSY PROVEN ACUTE REJECTION (BANFF GRADE IA OR HIGHER) (b)	20	3
SUBJECTS WITH 1, X (%)	16 (7.2)	3 (1.3)
SUBJECTS WITH 2, X (%)	2 (0.9)	0
SUBJECTS WITH 3 OR MORE, X (%)	0	0
BANFF GRADE, X (%) (b)	20 (9.0)	3 (1.3)
MILD ACUTE (IA), X (%)	2 (0.9)	2 (0.9)
MILD ACUTE (IB), X (%)	1 (0.4)	0
MODERATE ACUTE (IIA), X (%)	7 (3.1)	0
MODERATE ACUTE (IIB), X (%)	6 (2.7)	0
SEVERE ACUTE (III), X (%)	4 (1.8)	1 (0.4)
UP TO 24 MONTHS		
TOTAL NUMBER OF SUBJECTS	223	223
NUMBER OF SUBJECTS WITH BIOPSY PROVEN ACUTE REJECTION(BANFF GRADE IA OR HIGHER), X (%) (a)	18 (8.1)	6 (2.7)
PROPORTION (95% CI) (1)	8.1 (4.5, 11.6)	2.7 (0.6, 4.8)
DIFFERENCE FROM CNI (95% CI) (2)	5.4 (1.2, 9.5)	
DIFFERENCE FROM CNI (95.1% CI OBF) (2)	5.4 (1.2, 9.6)	
ADJUSTED (3)		
DIFFERENCE FROM CNI (95% CI) (3)	5.2 (1.0, 9.5)	
DIFFERENCE FROM CNI (95.1% CI OBF) (3)	5.2 (1.0, 9.5)	
TOTAL NUMBER OF BIOPSY PROVEN ACUTE REJECTION (BANFF GRADE IA OR HIGHER) (b)	20	6
SUBJECTS WITH 1, X (%)	16 (7.2)	6 (2.7)
SUBJECTS WITH 2, X(%)	2 (0.9)	0
SUBJECTS WITH 3 OR MORE, X (%)	0	0
BANFF GRADE, X (%) (b)	20 (9.0)	6 (2.7)
MILD ACUTE (IA), X (%)	2 (0.9)	4 (1.8)
MILD ACUTE (IB), X (%)	1 (0.4)	0
MODERATE ACUTE (IIA), X (%)	7 (3.1)	1 (0.4)
MODERATE ACUTE (IIB), X (%)	6 (2.7)	0
SEVERE ACUTE (III), X (%)	4 (1.8)	1 (0.4)

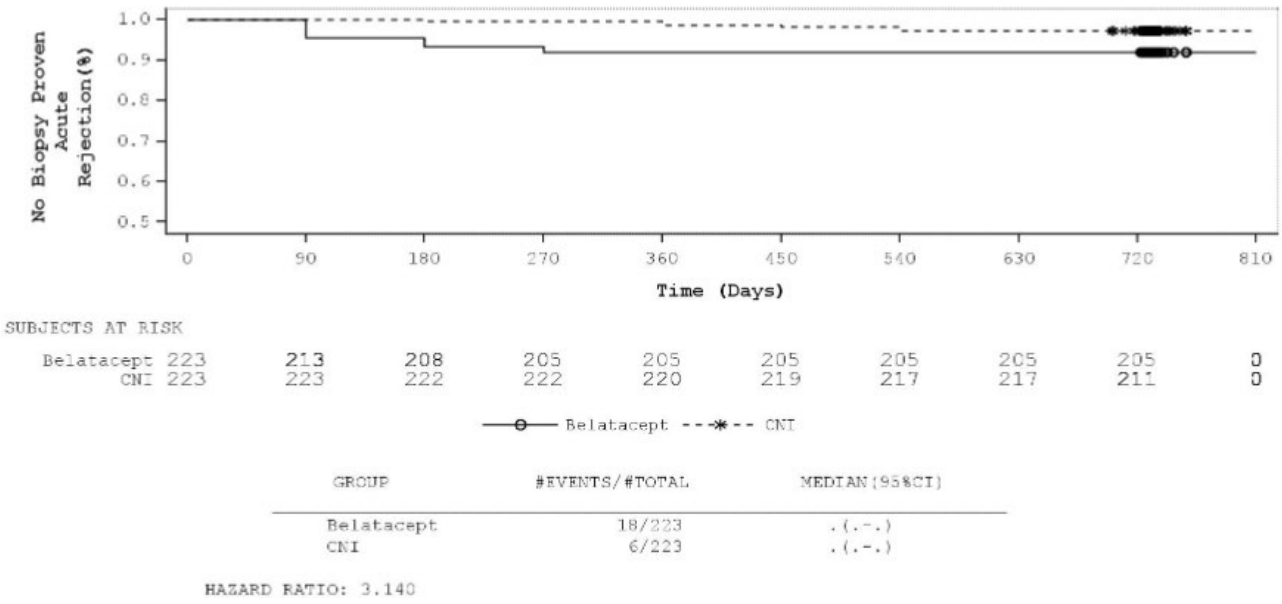
When analysed selectively for Banff Grade 1A or higher acute cellular rejection while excluding any borderline cellular or antibody mediated acute rejection events, the proportion of subjects with BPAR at Month 24 was higher in the belatacept group compared to the CNI group (18/223 [8.1%] vs 6/223 [2.7%] respectively, at Month 24). The Cox model hazard ratio estimate (95% CI) was 3.14 (1.25, 7.91). Of note, no additional events of BPAR occurred after Month 12 in the belatacept arm, whereas three of the six events in the CNI arm occurred between Month 12 and 24.

When BPAR was analysed to include antibody-mediated rejection beside Banff grade IA or higher cellular rejection, the proportion of subjects with BPAR or humoral (antibody-mediated) rejection was unchanged in the belatacept group (8.1%) but increased to 4.0% in the CNI continuation group. This was attributable to three additional subjects, each of whom developed isolated, antibody mediated acute rejection. The Cox model hazard ratio estimate (95% CI) was 2.09 (0.94, 4.65).

Between Months 12 and 24, two CNI continuation subjects were reported to have experienced functional graft loss, one of which events occurred following BPAR. Functional graft loss was reported for two additional CNI continuation subjects several days to several weeks beyond the Week 104 study visit; for one of them, the graft loss followed BPAR. To Month 24, no belatacept conversion subject experienced functional graft loss, with or without a preceding episode of BPAR.

In the sensitivity analyses, the proportion of subjects with BPAR, including borderline or higher cellular and antibody mediated acute rejection was higher in the belatacept group (9.9%) compared to the CNI group (5.8%). The proportion of subjects with clinically suspected acute rejection at Month 24,

independent of biopsy confirmation, was higher in the belatacept group (13.0%) compared to the CNI group (10.3%).



Symbols represent censored observations. Days are not the scheduled visits but the actual number of days from randomisation date. Number of subjects at risk is the number of subjects at risk at the beginning of the period. Includes the first event for every subject occurring during the 24 Month ITT analysis period (see definition in the SAP). Biopsy proven AR were either clinically suspected by protocol defined reasons or clinically suspected by other reasons and treated. Only the acute cellular rejection episode with the highest Banff severity grade for each subject is counted.

Figure 3 Kaplan-Meier estimates of biopsy proven acute rejection (Banff grade IA or higher) 24-month study period all randomised subjects (IM103116)

Secondary endpoints: Renal function parameters and Blood pressure

Key efficacy results from the secondary endpoints reflecting renal function and blood pressure are summarised in Table 21.

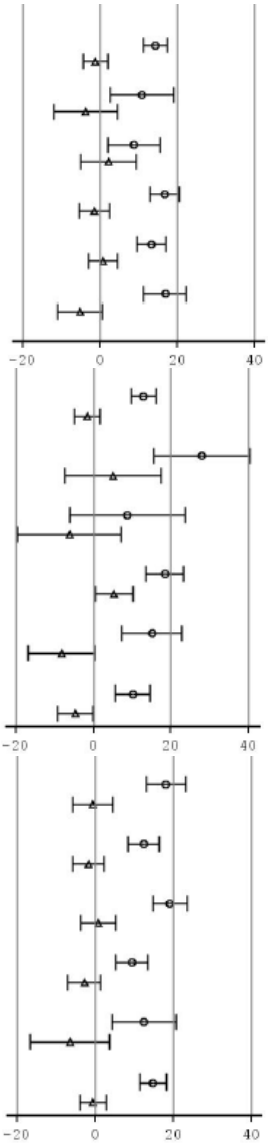
Table 21 Summary of key efficacy outcomes (IM103116)

	Belatacept N = 223	CNI N = 223
Adjusted Mean calculated GFR at Month 24 , mL/min/1.73 m^2		
N	189	171
Adjusted Mean	56.5	49.3
95% CI	55.0, 58.0	47.7, 50.8
Adjusted mean change from baseline (95% CI)	6.2 (4.7, 7.7)	-1.0 (-2.6, 0.5)
Adjusted mean percent change from baseline (95% CI)	14.3 (11.3, 17.4)	-1.2 (-4.3, 2.0)
Trend in cGFR from Baseline to Month 24		
Slope (mL/min/1.73m^2/month)		
Point Estimate (SE)	0.685 (0.1322)	-0.112 (0.1361)
95% CI	0.426, 0.945	-0.379, 0.155
Trend in cGFR from Month 3 to Month 24		
Slope (mL/min/1.73m^2/month)		
Point Estimate (SE)	0.658 (0.1661)	-0.277 (0.1717)
95% CI	0.332, 0.984	-0.614, 0.060
Trend of 1/Serum Creatinine from Baseline to Month 24		
Slope (mL/min/1.72m^2/month)		
Point Estimate (SE)	0.00868 (0.001687)	-0.00203 (0.001737)
95% CI	0.00537, 0.01199	-0.00544, 0.00138
Trend of 1/Serum Creatinine from Month 3 to Month 24		
Slope (mL/min/1.72m^2/month)		
Point Estimate (SE)	0.00814 (0.002053)	-0.00425 (0.002124)
95% CI	0.00412, 0.01217	-0.00842, -0.00009
Improvement from baseline in cGFR (mL/min/1.73 m2)		
> 5% improvement (n, %)	121 (54.3)	66 (29.6)
> 10% improvement (n, %)	108 (48.4)	49 (22.0)
Urine Creatinine to Protein Ratio (mg/mg)		
Baseline/Day 1:		
N	222	221
Mean:	0.158	0.165
95% CI	0.142, 0.173	0.133, 0.196
Month 24:		
N	188	169
Mean	0.255	0.217
95 % CI	0.210, 0.300	0.168, 0.266
Diastolic Blood Pressure at Month 24 (mmHg)		
N	193	174
Mean	75.9	80.2
Mean change from baseline	-1.7	0.5
95% CI	-3.3, 0	-1.3, 2.3
Systolic Blood Pressure at Month 24 (mmHg)		
N	193	174
Mean	131.2	136.5
Mean change from baseline	-1.3	1.2
95% CI	-4.1, 1.6	-1.7, 4.1

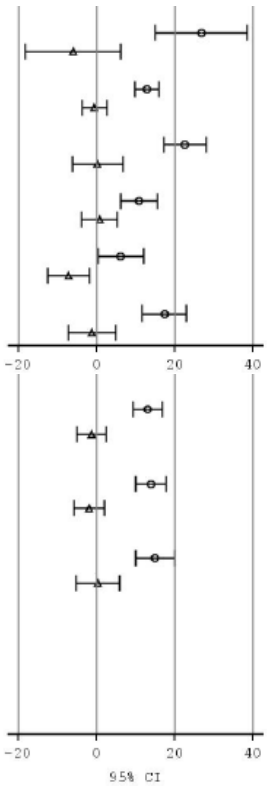
When analysed with imputation to zero for death and graft loss, values for adjusted mean cGFR at Month 24 were 55.5 and 48.5 mL/min/1.73 m^2, for the belatacept and CNI groups, respectively.

A subgroup analysis for percent change from baseline in cGFR is presented in Figure 4.

PERCENT CHANGE FROM BASELINE IN CALCULATED GFR (%) AT MONTH 24		
ALL		
Belatacept	189	14.3 (11.3,17.4)
CNI	171	-1.2 (-4.3,2.0)
TYPE OF TRANSPLANT:LIVING RELATED		
Belatacept	32	10.8 (2.7,19.0)
CNI	25	-3.7 (-11.9,4.4)
TYPE OF TRANSPLANT:LIVING UNRELATED		
Belatacept	32	8.7 (1.9,15.5)
CNI	29	2.1 (-5.0,9.3)
TYPE OF TRANSPLANT:CADAVERIC		
Belatacept	125	16.7 (12.9,20.5)
CNI	117	-1.5 (-5.4,2.4)
RECIPIENT GENDER:MALE		
Belatacept	127	13.2 (9.5,16.9)
CNI	117	0.8 (-3.0,4.5)
RECIPIENT GENDER:FEMALE		
Belatacept	62	16.9 (11.3,22.4)
CNI	54	-5.3 (-11.0,0.5)
RECIPIENT RACE:WHITE		
Belatacept	161	12.9 (9.7,16.1)
CNI	142	-1.6 (-4.9,1.7)
RECIPIENT RACE:BLACK		
Belatacept	20	28.0 (15.5,40.4)
CNI	20	5.1 (-7.3,17.4)
RECIPIENT RACE:OTHER		
Belatacept	8	8.8 (-6.1,23.7)
CNI	9	-6.2 (-19.5,7.0)
GEOGRAPHIC REGION:NORTH AMERICA		
Belatacept	73	18.5 (13.6,23.3)
CNI	72	5.3 (0.4,10.1)
GEOGRAPHIC REGION:LATIN AMERICA		
Belatacept	32	15.1 (7.3,22.8)
CNI	23	-8.3 (-16.9,0.3)
GEOGRAPHIC REGION:EUROPE		
Belatacept	84	10.1 (5.7,14.5)
CNI	76	-4.7 (-9.3,-0.1)
RECIPIENT AGE:<50YEARS OLD		
Belatacept	69	18.1 (13.1,23.1)
CNI	61	-0.7 (-5.8,4.4)
RECIPIENT AGE:>=50YEARS OLD		
Belatacept	120	12.4 (8.4,16.3)
CNI	110	-1.8 (-5.9,2.2)
DONOR AGE:<50YEARSOLD		
Belatacept	93	19.1 (14.7,23.5)
CNI	85	0.7 (-3.8,5.3)
DONOR AGE:>=50YEARSOLD		
Belatacept	96	9.3 (5.2,13.5)
CNI	86	-2.8 (-7.1,1.4)
END STAGE RENAL DISEASE(DIABETES):YES		
Belatacept	31	12.4 (4.2,20.6)
CNI	19	-6.5 (-16.6,3.6)
END STAGE RENAL DISEASE(DIABETES):NO		
Belatacept	158	14.8 (11.5,18.2)
CNI	152	-0.6 (-3.9,2.8)



INITIAL CNI TREATMENT:CSA		
Belatacept	20	26.8 (15.0,38.6)
CNI	17	-6.1 (-18.3,6.1)
INITIAL CNI TREATMENT:TACROLIMUS		
Belatacept	169	12.9 (9.8,16.0)
CNI	154	-0.6 (-3.8,2.7)
BASELINE GFR(ML/MIN/1.73M2):<45		
Belatacept	74	22.6 (17.1,28.1)
CNI	51	0.2 (-6.3,6.7)
BASELINE GFR(ML/MIN/1.73M2):45-<60		
Belatacept	77	10.8 (6.1,15.5)
CNI	74	0.7 (-3.9,5.3)
BASELINE GFR(ML/MIN/1.73M2):>=60		
Belatacept	38	6.2 (0.3,12.0)
CNI	46	-7.3 (-12.6,-1.9)
TIME FROM TRANSPLANTATION TO RANDOMIZATION:6-12MONTHS		
Belatacept	58	17.3 (11.6,23.0)
CNI	47	-1.2 (-7.3,4.9)
TIME FROM TRANSPLANTATION TO RANDOMIZATION:>12MONTHS		
Belatacept	131	13.0 (9.4,16.7)
CNI	124	-1.2 (-4.9,2.5)
BASELINE TREATMENTREGIMEN:TAC+MMF/CSA+MMF/CSA+MPA		
Belatacept	116	13.9 (10.0,17.8)
CNI	114	-1.9 (-5.8,2.0)
BASELINE TREATMENTREGIMEN:TAC+MPA		
Belatacept	73	15.0 (10.0,20.0)
CNI	57	0.3 (-5.2,5.8)



Number of subjects refers to the number of randomised subjects within each category for categorical parameters.
Percentages are based on this number of subjects. For continuous parameters, the number of subjects refers to the number of randomised subjects with non-missing values at both the Month and baseline.
Adjusted estimates based on repeated measures model with treatment, month (categorical), baseline cGFR (continuous) and interaction of treatment by month as covariates. The model includes data from all post-baseline Months during the 24 Month ITT analysis period. Calculated GFR (cGFR) (mL/min/1.73 m^2) based on the 4-variable MDRD formula. cGFR values after graft loss or resumption of maintenance dialysis are not included in the analysis.

Figure 4 Percent change from baseline in calculated GFR (ml/min/1.73 m^2) by subgroup categories 24-month study period all randomised subjects (IM103116)

Exploratory endpoint: Impact of AR on Renal Function, Infection and Malignancy, and Patient and Graft Survival

For the subjects who experienced at least one episode of BPAR and for whom a Month 24 result was available, the mean cGFR (change from baseline) were 49.7 (-0.1) mL/min/1.73m^2 in the belatacept group and 28.7 (-23.2) mL/min/1.73m^2 in the CNI group.

Of the 27 subjects who experienced at least one episode of BPAR, 2/18 (11.1%) in the belatacept group and 4/9 (44.4%) in the CNI group experienced serious infections. Out of the 416 subjects without BPAR, 35/203 (17.2%) in the belatacept group and 40/213 (18.8%) in the CNI group experienced serious infections. Of the subjects who experienced at least one episode of BPAR, no subjects in the belatacept group and 1/9 (11.1%) in the CNI group experienced a serious viral infection. No central nervous system (CNS) infections or tuberculosis infections were reported up to Month 24.

Of the 27 subjects who experienced at least one episode of BPAR, one malignancy was reported following an isolated episode of BPAR diagnosed 67 days after the initial belatacept infusion.

Of the 27 subjects with BPAR up to Month 24, 1/18 (5.6%) belatacept-treated subjects, and no CNI-treated subjects, died with a functioning graft by Month 24. Of the subjects with BPAR, 1/9 (11.1%) in the CNI group, and none in the belatacept group, experienced subsequent death censored graft loss.

Exploratory endpoints: Mean Change in Fasting Lipid Profiles and New-onset Diabetes after Transplantation

Mean changes from baseline fasting serum lipid concentrations are summarised in Table 22.

Table 22 Mean Changes in Lipids at Month 24 - All Randomised Subjects (IM103116)

Mean change from baseline (SE), mg/dL	Belatacept N = 223	CNI N = 223
Total cholesterol	-2.1	-12.0
HDL-cholesterol	0.5	-1.4
LDL-cholesterol	-1.5	-8.3
Triglycerides	-9.5	-12.8

Mean fasting HDL-cholesterol showed a slight numerical increase in the belatacept group, while total- and LDL cholesterol and triglycerides decreased. The improvements in total- and LDL-cholesterol and triglycerides were numerically larger in the CNI arm.

The proportion of subjects who developed new onset diabetes after transplantation was similar in the belatacept (5.4%) and CNI (4.0%) treatment groups. The adjusted difference from CNI (95% CI) was 0.6 (-2.6, 3.8). One additional subject in the CNI continuation group who met the prospectively defined protocol criteria for NODM was excluded from the analysis due to an error that was not identified until after the final database lock.

Exploratory endpoint: Patient-Reported Outcomes Research

The relative impact of belatacept conversion, as compared with CNI continuation on patient-reported symptom occurrence and symptom distress, as related to side effects of their immunosuppressive medication regimens, was evaluated using the updated Modified Transplant Symptom Occurrence and Distress Scale (MTSOSD-59R) up to Month 12 (Table 19). Higher scores in the MTSOSD-59R indicate a greater symptom and symptom distress burden than lower scores.

Table 23 Frequency Distribution of Symptom Occurrence and Symptom Distress Scale, All Randomised and Treated Subjects

	Belatacept N = 221	CNI N = 222
Baseline		
Total Symptom Occurrence		
M (Number of subjects reporting one or more symptoms or distress)	212	218
Mean (SD)	87.8 (20.06)	90.7 (21.04)
95% CI	85.1, 90.5	87.9, 93.5
Total of Symptom Distress		
M	211	216
Mean (SD)	28.7 (27.07)	34.8 (28.30)
95% CI	25.0, 32.4	31.0, 38.6
Month 12		
Total of Symptom Occurrence		
M	196	188
Mean (SD)	82.3 (20.08)	91.0 (22.33)
95% CI	79.5, 85.2	87.8, 94.2
Total of Symptom Distress		
M	185	186
Mean (SD)	25.8 (25.32)	34.4 (30.82)
95% CI	22.1, 29.4	29.9, 38.8

Treatment satisfaction was assessed by Treatment Satisfaction Questionnaire for Medication v2 (TSQM) (Table 24). The outcome is in ordinal scale 0-100. The higher the score, the better the outcome is.

Table 24 Treatment satisfaction summary - all randomised and treated subjects (IM103116) (summarised by Assessor)

		Belatacept N=221	CNI N=222
Baseline			
Effectiveness	Mean (SD) m	71 (24)	71 (22)
Side effects	Mean (SD) m	84 (24)	79 (25)
Convenience	Mean (SD) m	72 (21)	70 (18)
Global satisfaction	Mean (SD) m	72 (21)	70 (20)
12 Months			
Effectiveness	Mean (SD) m	78 (28)	71 (25)
Side effects	Mean (SD) m	91 (20)	81 (23)
Convenience	Mean (SD) m	80 (19)	76 (16)
Global satisfaction	Mean (SD) m	84 (17)	76 (17)

N is the number of all randomised and treated subjects.
M is the number of subjects with non-missing score value.

Both the patient reported outcome scales MTSOSD-59R and TSQM indicate an improvement in the belatacept arm. Self-reported symptom scales should however be interpreted with great caution in open-label studies with interim analysis.

Donor-Specific Antibodies (DSA)

A summary of *de novo* DSA at Month 24 is given in Table 25.

Table 25 Incidence of de novo DSA on treatment; 24 month study period, all randomised and treated subjects (IM103116)

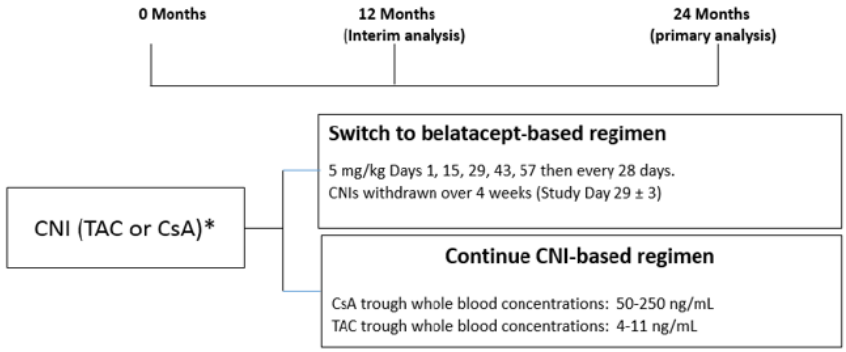
	Belatacept Conversion (N = 221)					CNI Continuation (N = 219)				
	N	Class I	Class II	Class I and Class II	Total	N	Class I	Class II	Class I and Class II	Total
Baseline (Pre-existing) DSA, n(%)	207	3 (1.5)	10 (4.8)	3 (1.5)	10 (4.8)	199	15 (7.5)	13 (6.5)	2 (1.0)	26 (13.1)
Month 12 (de novo) DSA, n(%)	207	2 (1.0)	0	0	2 (1.0)	199	4 (2.0)	8 (4.0)	3 (1.5)	9 (4.5)
Month 24 (de novo) DSA, n(%)	207	2 (1.0)	0	0	2 (1.0)	199	6 (3.0)	12 (6.0)	4 (2.0)	14 (7.0)

The incidence of *de novo* formation of anti-HLA DSAs was lower following belatacept conversion as compared to CNI continuation.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26 Summary of Efficacy for trial IM103116

Title: *Evaluation of the Benefits and Risks in Maintenance Renal Transplant Recipients Following Conversion to Nulojix (belatacept)-based Immunosuppression*		
Study identifier	IM103116	
Design	Randomised, open-label, active-controlled, parallel-group study.  	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 months Not applicable 8 weeks safety follow-up
Hypothesis	Formal statistical testing of a research hypothesis was not performed in this study.	
Treatments groups	Adults aged 18 -75years	
	Belatacept	Conversion from CNI-based therapy to belatacept 6-60 months after transplantation. (N=223)

	CNI		Randomised to continue CNI-based therapy. (N=223)
Endpoints and definitions	Primary endpoint	Graft loss/death	Number (%) of subjects with 24 Month survival with a functional graft
	Secondary end point	BPAR	Number (%) of subjects with biopsy proven acute rejection (BPAR) at 24-months
	Secondary end point	cGFR	Mean cGFR and Mean change in cGFR from baseline to 24-months post-randomisation
Database lock	10-Sep-2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: all randomised subjects (N=223 for both treatment arms)		
Descriptive statistics and estimate variability	Treatment group	Belatacept	CNI
	Primary endpoint: Graft loss/death at Month 24		
	Number of subjects	N=223	N=223
	Survival with functioning graft n (%)	219 (98) Death: 0 Graft loss: 4 (2)	217 (97) Death: 2 (1) Graft loss: 4 (2)
	Mean difference (95.1% CI OBF): 0.9 (-8.6, 10.4)		
	Secondary endpoint: BPAR at Month 24		
	Subjects with BPAR n (%)	18 (8.1)	6 (2.7)
	Mean difference (95.1% CI OBF): 5.4 (1.2, 9.6)		
	Secondary endpoint: cGFR at Month 24		
	Mean cGFR mL/min/1.73m^2 (95% CI)	56.5 (55.0, 58.0)	49.3 (47.7, 50.8)
	Mean change from baseline mL/min/1.73m^2 (95% CI	6.2 (4.7, 7.7)	-1.0 (-2.6, 0.5)
	Mean percent change from baseline (95% CI)	14.3 (11.3, 17.4)	-1.2 (-4.3, 2.0)
Notes	Only descriptive statistics apply		

2.4.3. Supportive study

Study IM103010: Belatacept Conversion Trial in Renal Transplantation

Methods

Study design

Study IM103010 was a phase 2, randomised, open-label, active-controlled, parallel-group study. The duration of the study was 12 months with a subsequent 8-week follow-up period for safety evaluations. All subjects who completed the 12-month phase of the initial study, and met inclusion criteria and provided consent to continue, were eligible to participate in a long-term extension (LTE)

Subjects on CNI-based regimens (approximately equal numbers of subjects on TAC-based and on CsA-based regimens) were randomised in a 1:1 ratio to either 1) discontinue CNI treatment and begin belatacept treatment (5 mg/kg intravenous [IV]), or 2) continue treatment with an established CNI regimen.

All subjects received background maintenance immunosuppressive regimen of MMF, MPA, sirolimus (SRL), or azathioprine (AZA), with or without adjunctive corticosteroids, according to their immunosuppressive regimen at the time of enrolment.

Key differences in study design between IM103010 and IM103116 are presented in Table 27.

Table 27 Key differences in the design of studies IM103010 and IM103116

IM103010	IM103116
Patient Population	
Recipients of LD or DD transplant 6-36 months pre-study entry	Recipients of LD or DD transplant 6-60 months pre-study entry
EBV serostatus not an eligibility criteria	Must be EBV seropositive
Lower limit of eligible baseline in GFR range 35 mL/min	Lower limit of eligible baseline in GFR range 30 mL/min
Primary Endpoint	
cGFR at Month 12	Survival with graft function at Month 24
CNI	
CsA: 44% and TAC: 56%	CsA: 11% and TAC: 89%
Concomitant Immunosuppression	
Corticosteroids: required only for subjects receiving them prior to, and at, study entry	Daily corticosteroids: required for all subjects at study entry, and post-randomization for the duration of the study
MMF, MPS, SRL, or AZA permitted	Only MMF or MPS permitted

Abbreviations: AZA=azathioprine; cGFR=calculated glomerular filtration rate; CNI=calcineurin inhibitor; CsA=cyclosporine; DD=deceased donor; EBV=Epstein-Barr virus; LD=living donor; MMF=mycophenolate mofetil; MPS=mycophenolate sodium; SRL=sirolimus; TAC=tacrolimus;

Study Participants

The study population included male and female (≥18 years of age) recipients of a renal allograft from a living donor or a deceased donor at least 6 months, but not longer than 36 months, prior to randomisation.

Subjects at low to moderate immunological risk were eligible. The study excluded subjects of greatest immunological risk as identified by prior graft loss due to AR, recent (< 3 months) AR, or Banff 97 Grade IIA or greater AR since transplantation of current allograft. For key differences between studies IM103010 and IM103116 concerning patient population and concomitant immunosuppression, please refer to Table 27 above.

Treatments

Apart from the possibility of home treatment added to study IM103116 in protocol amendment 05, belatacept dosing and CNI tapering in the belatacept arm were identical in both studies. Therefore, for details on belatacept dosing and CNI tapering, please see study IM103116 above.

Subjects treated with CNI who had completed 12 months of treatment and entered the LTE were allowed to switch from their CNI to belatacept after on or about 01-Jan-2010. Written confirmation from the Data Monitoring Committee (DMC) was required before a subject could convert from CNI to belatacept.

In October 2011, the CNI arm was discontinued after completing the Year-3 follow-up. If CNI subjects did not convert to belatacept, the subjects were removed from study participation.

Objectives

The primary objective in study IM103010 was to assess the effects of a belatacept-based immunosuppressive regimen relative to a CNI regimen on the change in cGFR from baseline to 12 months post-randomisation.

The primary objective of the LTE was long-term safety and tolerability of belatacept in subjects who completed 12 months of treatment in the main study and entered the LTE.

Outcomes/endpoints

Primary endpoint:

- Change in cGFR from Baseline to 12 months post randomisation

Secondary endpoints:

- Acute rejection
- Incidence of death and graft loss
- Change in S-creatinine
- Incidence of NODM
- Incidence of HLA antibodies
- QoL

Tertiary endpoints:

- Measures of hypertension
- Measures of dyslipidaemia
- Urinary albumin to creatinine ratio

The following efficacy measures were summarised for the Intent-to-treat long-term extension (ITT-LT) population:

- Calculated GFR and Serum Creatinine
- Acute Rejection
- Subject Survival and Graft Survival
- Dyslipidaemia-related Endpoints
- New-Onset Diabetes Mellitus (NODM)

Sample size

The primary objective was to estimate the effect of conversion from a CNI-based to a belatacept-based maintenance immunosuppression regimen on change in cGFR from baseline to 12 months post-randomisation. The sample size was determined in order to provide a reasonable precision of the effect to be estimated. The estimate of the treatment effect was given by the mean difference of change from baseline to 12 months post-randomisation between belatacept and CNI group. With 85 subjects per treatment group the half-width of a two-sided 95% confidence interval for the difference in mean changes in cGFR between the belatacept group and the CNI group was estimated to be 5.71 mL/min/1.73 m^2, assuming a standard deviation of 19 mL/min/1.73 m^2.

Randomisation

Subjects were randomised in a 1:1 fashion, stratified by site and initial CNI medication, to receive belatacept or to continue receiving their previous CNIs (CsA or TAC).

Each subject who qualified for treatment was assigned a unique randomisation number by IVRS. A randomisation schedule was generated and kept by the MAH. Randomisation numbers were assigned in the order in which subjects qualified for treatment, not in the order of study enrolment.

Blinding (masking)

This was an open-label study.

Statistical methods

Study IM103010 also included an LTE study to assess the ongoing safety and tolerability of belatacept in subjects who have completed 12 months of treatment in the main study IM103010. Since its objective is not related to the evaluation of efficacy, methods of the long-term extension study will not be discussed in this section.

General. The study evaluates the hypothesis that the belatacept-based regimen will result in preservation of renal function in the belatacept treatment group (relative to a CNI-based treatment group).

Primary endpoint analysis. The effect of belatacept vs CNI treatment on the primary endpoint "Change in calculated GFR from baseline to 12 months post randomisation" was evaluated by the estimation of the difference and 95% confidence intervals between treatment groups using an analysis of covariance model (ANCOVA). The analysis was supported by estimates and 95% confidence intervals of the primary endpoint within each treatment group. cGFR was calculated using the 4-variable Modification of Diet in Renal Disease [MDRD] equation as published by Davidson et al. (2003, PMID 12775942).

The "change in calculated GFR from baseline to Month 12" was analysed with an analysis of covariance (ANCOVA) model with factor for randomisation group (treatment), baseline calculated GFR and pre-randomisation CNI regimen (CsA or Tac) to assess the difference between the belatacept treatment group and the CNI group. If other factors are deemed to be clinically relevant, then they were used as covariates in additional ANCOVA analysis. The 95% CI for the estimated treatment difference from the ANCOVA model was reported. The primary analysis was performed using analysis set "All randomised with observation" (M1, see below). In all ANCOVA analyses, subjects with a missing baseline calculated GFR assessment were excluded.

Secondary endpoint analyses. The effect of belatacept vs CNI treatment on major secondary endpoints "Incidence of acute rejection at 6 months" and "Subject and graft survival at 6 months" was evaluated with similar methods, which are here only described for the former endpoint.

The effect of belatacept vs CNI treatment on the proportion of subjects who have at least 1 acute rejection up to Month 6 post-randomisation was evaluated by the estimation of the difference and 95% confidence intervals between treatment groups. The analysis was supported by estimates and 95% confidence intervals of the endpoint within each treatment group. Similar methods were used to analyse the incidence and severity of acute rejection by Month 12. The analysis was based on the analysis set "All randomised with observation" (M1, see below).

Confidence intervals (CIs) for analysis of proportions were computed using normal approximation, if the number of the events in that treatment arm was at least 5. Otherwise, confidence interval using an exact method were provided. Any between-treatment CI for the proportion analyses were computed using normal approximation, if the number of the events in each individual treatment arm was at least 5. Otherwise, confidence interval using an exact method were provided.

In addition, other secondary and exploratory endpoints were studied, which are not reported here (see above). Depending on the clinical relevance of any observed differences in baseline characteristics between treatment groups adjustments were made to the statistical models.

Analysis Sets.

Primary Efficacy Data Set (M1, ITT). All randomised subjects are included in this dataset following the intention-to-treat (ITT) principle based on observed values. In addition, an imputation of the primary endpoint is performed as described below ("M2" data set).

Secondary Efficacy Data Set (M3, PP). All randomised subjects, who did not violate terms of the protocol that might have affected the efficacy outcome following the per-protocol principle. "Per-protocol" analyses were performed on the primary endpoint of "change in calculated GFR from baseline to 12 months post-randomisation" and the secondary endpoints of "death/graft loss" and "acute rejection by 12 months", only if the following occurred: 1) More than 10% of the total number of subjects included into the "ITT" data set at Month 12 had relevant protocol deviations and consequently would be excluded from the "per-protocol" data set. 2) The "As-Treated" population included all randomised subjects who received at least one dose of CsA or belatacept.

Analyses for all other efficacy endpoints were performed using the primary efficacy analysis set ("ITT") only. All safety analyses were performed on the data set that included all randomised and treated

subjects. All available data from belatacept-treated subjects were included in analyses of PK and immunogenicity.

Missing Data.

Calculated GFR. For subjects who missed measurement due to death/graft loss, the calculated GFR value of 10 and 0 (sic) will be both imputed and carried forward up to month 12. Missing values of post-baseline calculated GFR due to reasons other than death/graft loss will be imputed using linear regression method as long as at least 2 post baseline time points with 4 months apart have calculated GFR values. The presence of missing data and its imputation using a combination of multiple approaches for the primary endpoint "cGFR" may have created bias in the estimation of treatment effect. In response to request for supplementary information, the MAH clarified the applied imputation method and performed the primary analysis based on 1) multiple imputation using relevant covariates (assuming missing-at-random data) and 2) a jump-to-reference imputation (using a conservative missing-not-random-data) for the primary endpoint.

Acute Rejection. An acute rejection-free subject who is not followed-up through the entire event-counting period due to any reason will be considered as having no acute rejection during that period.

Interim analyses. No interim analysis was performed.

Subgroup Analyses. Analyses of the primary endpoint "Calculated GFR" were performed for subgroups at various timepoints. Subgroup analyses of secondary endpoints of "subjects and graft survival" as well as "acute rejection by month 12" were performed only if 5% or more of the total number of subjects in each randomisation group had events that occurred during the event counting period. Summary statistics for efficacy measures by treatment arm were presented for only those subgroup categories that consisted of 10% or more of the total study population. No statistical tests were performed for subgroups.

Subgroups analysis were based on the following factors: 1) type of transplant, 2) recipient gender, 3) recipient race, 4) geographic region, 5) recipient age, 6) women recipient age, 7) ESRD, 8) initial CNI treatment, 9) baseline GFR, 10) time from transplantation to randomisation, 11) time to complete withdrawal of CNI in subjects randomised to belatacept, 12) pre-randomisation/baseline diabetes status.

Subgroup analyses of AEs were only done for subgroup factors of type of transplant, recipient gender, recipient race, geographic region, recipient age, women recipient age, initial CNI treatment.

Sensitivity Analyses.

ANCOVA analyses on the primary endpoint "Change in calculated GFR from baseline to month 12" using methods of M1, M2 and LOCF were performed. In the LOCF-based ANCOVA analysis, the last available post-baseline calculated GFR value prior to Month 12 was used as the imputed calculated GFR value at Month 12.

To assess the trend in renal function, piecewise regression was used to analyse the changes in calculated GFR from baseline to various time points post-randomisation for belatacept vs. CNI with terms for treatment, time points and baseline calculated GFR. The population mean slope and associated 95% CI was estimated for each treatment group. The analyses were performed in the analysis sets "All randomised with observation (M1)" and "All randomised with imputation (M2)" analysis sets.

Regarding the secondary endpoint "Acute Rejection", a sensitivity analysis was performed, in which an acute rejection-free subject who was not followed-up through the entire event-counting period was considered having an acute rejection if the histological evidence on any biopsy is graded as Banff grade IIA or higher by the local pathologist.

Results

Participant flow

The number of subjects randomised to the belatacept arm was 84 and to the CNI arm 89.

The number of subjects in each treatment group and their reasons for not completing 12 months of treatment are summarised in Table 28 and for not completing the LTE in Table 29.

Table 28 Subject Disposition by Month 12 (IM103010)

	Belatacept	CNI
Number randomized, N	84	89
Number randomized and not treated, N	1	1
Number discontinued treatment, N (%)	2 (2.4)	2 (2.3)
Death	0	1 (1.1)
Lack of efficacy	2 (2.4)	0
Other	0	1 (1.1)
Number continued treatment on or beyond Day 365	81 (97.6)	86 (97.7)

Table 29 Subject Disposition by Database Lock (IM103010 LTE)

	Belatacept	CNI	Total
Number of subjects who completed 12 months	81	86	167
Number of subjects entering LTE, N[a]	81	81	162
Number of subjects who discontinued treatment up to database lock, N (%)	11 (13.6)	17 (21.0)	28
Adverse event	1 (1.2)	5 (6.2)	6
Withdrawal of consent	4 (4.9)	7 (8.6)	11
Pregnancy	0 (0.0)	1 (1.2)	1
Lost to follow-up	1 (1.2)	0 (0.0)	1
Death	4 (4.9)	0 (0.0)	4
Lack of efficacy	0 (0.0)	2 (2.5)	2
Other	1 (1.2)	2 (2.5)	3
Number completed treatment up to database lock, N (%)	70 (86.4)	64 (79.0)	134

[a] 38 subjects randomized to CNI switched to belatacept during the LTE.

Datasets used:

ITT (Intent-to-Treat): All randomised subjects during the 12 months of study treatment

ITT-LT (Intent-to-Treat-Long Term Extension): All randomised and treated subjects who completed 12 months of study treatment, consented to continue in the LTE, and received at least one dose of belatacept or CNI after 12 months post-randomisation.

ITT-SW (Intent-to-Treat-Switch from CNI to Belatacept): ITT-LT subjects who converted from CNI to belatacept during the LTE. Subjects were grouped into one single treatment group, belatacept. Day of conversion is defined as the first belatacept infusion day.

Conduct of the study

The SAP (V1.0) was finalised in 2007-06 (day missing) and amended on 2009-06-03 after the 1-year and 1.8-year renal transplant data from the two ongoing pivotal studies (IM103008 and IM103027) became available. The date of the "month 36" (LTE) database lock was 2011-08-11.

Baseline data

The baseline demographics of transplant recipients is presented in *Table 30*.

Table 30 Baseline Demographics of Transplant Recipients - All Randomized Subjects (ITT) (IM103010)

Parameter	Belatacept N = 84	CNI N = 89
Age (Years)		
Mean (SD)	45.3 (13.5)	44.3 (13.0)
Range	19.0 - 72.0	18.0 - 71.0
Gender, N (%)		
Male	66 (78.6)	60 (67.4)
Female	18 (21.4)	29 (32.6)
Race, N (%)		
White	44 (52.4)	53 (59.6)
Black or African-American	6 (7.1)	4 (4.5)
Asian	16 (19.0)	12 (13.5)
Native Hawaiian or Other Pacific Islander	1 (1.2)	1 (1.1)
Other	17 (20.2)	19 (21.3)
Geographic Region		
North America	28 (33.3)	25 (28.1)
South America	28 (33.3)	31 (34.8)
Europe	15 (17.9)	22 (24.7)
ROW (Asia/Pacific)	13 (15.5)	11 (12.4)
Previous Number of Transplants, N		
0	74 (88.1)	77 (86.5)
1	10 (11.9)	10 (11.2)
2	0	2 (2.2)

The differences in baseline data between the treatment arms are not expected to affect the outcome of Study IM103010. Baseline cGFR, which is of utmost interest for the primary endpoint, was well balanced with cGFR 53.5 mL/min/1.73 m^2 in the belatacept arm and 54.5 mL/min/1.73 m^2 in the CNI arm.

Compared to study IM103116, the mean age in Study 103010 was approximately eight years lower (45 years versus 53 years). The number of white subjects and subjects from Europe was markedly lower in IM103010 than in Study IM103116 (56% versus 85% and 21% versus 42%, respectively). Baseline cGFR was similar in the two studies, whereas the prevalence of diabetes and hypertension at baseline was slightly lower in Study IM103010 which may reflect the lower mean age in the study.

The proportion of TAC subjects in the CNI arm was higher in study IM103116 compared to Study IM103010 (89% vs 56%). As discussed earlier, Study IM103010 was initiated six years before Study IM103116, and there may have been some alteration in standard immunosuppression during this time.

As opposed to Study IM103116, the eligibility criteria in Study IM103010 did not exclude EBV seronegative recipients. One EBV negative recipient in each treatment arm received an organ from an EBV positive donor. Six subjects (7%) EBV negative recipients in the CNI arm and 3 (4%) in the belatacept arm received a transplant from a donor with unknown EBV serostatus. Furthermore, in 36% of the subjects in the belatacept arm and 32% in the CNI arm, EBV serostatus was unknown for both recipient and donor.

Numbers analysed

Efficacy analyses for the primary analysis at 12 months were based on randomised subjects; safety analyses were based on randomised and treated subjects. For details, please see above.

Analysis Populations:

- Randomised (ITT) - belatacept 84, CNI 89
- Treated - belatacept 83, CNI 88
- ITT-LT – belatacept 81, CNI 81

ITT-SW: randomised and treated subjects who converted from CNI to belatacept during the LTE (n = 38).

Outcomes and estimation

- **Results from Month 12 primary analysis**

Key efficacy endpoints up to 12 months are summarised in Table 31.

Table 31 Summary of key efficacy results at month 12 (IM103010)

	Belatacept N = 84	CNI N = 89
Mean (SD) cGFR* with Imputed Values	60.5 (16.2)	56.5 (14.4)
n subjects	82	87
Mean (SD) Change from Baseline in Imputed cGFR*	7.0 (12.0)	2.1 (10.3)
Mean (SD) cGFR* with Observed Values	60.5 (16.2)	57.1 (13.6)
n subjects	82	86
Mean (SD) Change from Baseline in Observed cGFR*	7.0 (11.99)	2.6 (9.49)
Acute Rejection	6 (7.1)	0
Banff Grade, n (%)		
Mild Acute (IA)	1 (1.2)	0
Mild Acute (IB)	1 (1.2)	0
Moderate Acute (IIA)	3 (3.6)	0
Moderate Acute (IIB)	1 (1.2)	0
Severe Acute (III)	0	0
Subject and Graft Survival	84 (100)	88 (98.9)

*mL/min/1.73 m^2

- **Results from long-term extension**

Change from baseline in cGFR

In the ITT-LT population analysis of cGFR (81 belatacept conversion subjects and 81 CNI continuation subjects) at Month 12, the mean (SD) as observed cGFRs were 60.3 (16.2) and 57.8 (13.6) mL/min/1.73 m^2, respectively. The corresponding mean (SD) changes from baseline were +7.1 (12.0) and +2.8 (9.7) mL/in/1.73 m^2, in the belatacept conversion group and CNI continuation group, respectively.

Changes in cGFR with error bars representing the 10^{th} and 90^{th} percentiles over time up to 36 months are shown in Figure 5. No formal comparisons were planned between the belatacept and CNI treatment groups.

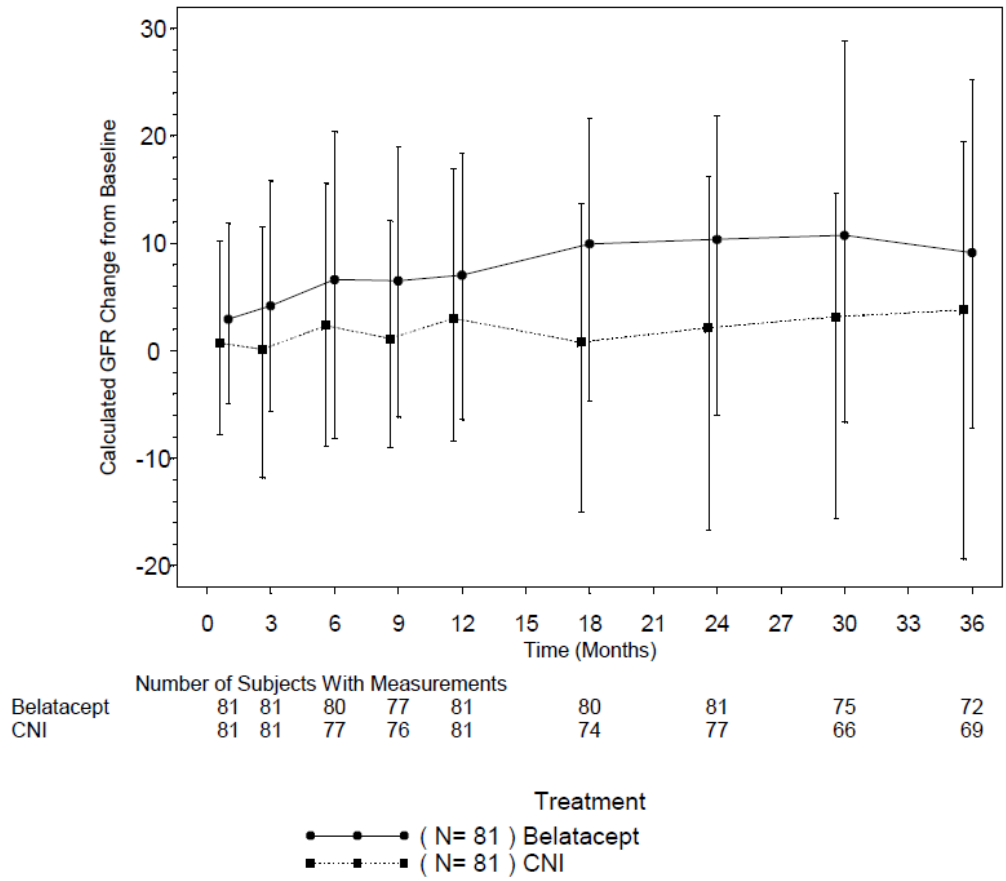


Figure 5 Plot of calculated GFR change from baseline over time up to month 36 - imputed values (all ITT-LT subjects) (IM103010 LTE)

Acute rejections

AR was defined as a biopsy-proven rejection that was either clinically suspected for protocol-defined reasons or clinically suspected for other reasons and treated. All biopsies were confirmed by a blinded central pathologist.

In the first 12 months of the study for the ITT population, by Month 6 post-randomisation, 6 of 84 subjects (7%) in the belatacept group had AR compared with none of 89 subjects in the CNI group. There were no additional AR episodes after Month 6 through Month 12.

In the ITT-LT population, AR occurred in 4 subjects during the first 12 months of the study, and in 1 subject from Month 12 to Month 36 for belatacept. For CNI, ARs occurred in 4 subjects from Month 12 to Month 36. No recurrences of the 7 post-conversion events of BPAR (1 after Month 12) were reported in the belatacept conversion group. Of the subjects with BPAR, two (one in each treatment arm) had graft loss by Month 36.

Death and Graft Loss

In the ITT population during the first 12 months of the study, no graft loss was reported in either treatment arm. In addition, no deaths were reported in the belatacept group during the first 12 months. One subject in the CNI conversion group died with a functioning graft within 12 months post-randomisation; the death was attributed to myocardial infarction. Therefore, this subject's death is not included in the ITT-LT population analysis.

In the ITT-LT population up to 36 months, two subjects experienced functional graft loss (one in the belatacept conversion group following an episode of BPAR [Day 126] and one in the CNI continuation group), and 1 subject died with a functioning graft in the belatacept conversion group. No subjects in the CNI treatment group died after Month 12.

Metabolic endpoints

Mean systolic and diastolic blood pressure up to Month 12 are summarised in Table 32. Analysis of changes in blood pressure were not performed beyond 12 months, during the LTE.

Table 32 Mean changes in blood pressure values at month 12 based on ANCOVA - all randomised subjects (IM103010)

Mean change from baseline (SE), mmHg	Belatacept N = 78	CNI N = 78
Diastolic	-3.5 (1.01)	-1.7 (1.02)
Systolic	-4.0 (1.68)	-1.6 (1.69)

Table 33 presents a summary of mean changes in lipid parameters at Month 12 for all randomised subjects.

Table 33 Mean changes in lipids at month 12 - all randomised subjects (IM103010)

Mean change from baseline (SE), mg/dL	Belatacept n	CNI n
Total cholesterol	2.7 (36.73) 82	0.1 (40.14) 86
Non HDL-cholesterol	2.0 (35.87) 82	0.3 (36.57) 86
HDL-cholesterol	0.7 (11.83) 82	-0.2 (11.19) 86
LDL-cholesterol	2.5 (30.73) 78	1.6 (31.28) 81
Triglycerides	-4.4 (77.74) 79	-1.9 (128.83) 83

By Month 12, one subject in the belatacept arm versus two in the CNI arm were reported with new onset of diabetes (NODM).

At Month 36 in the ITT-LT population, the incidence of NODM for subjects without a prior history of diabetes was 7% (4 subjects) in the belatacept group and 5% (3 subjects) in the CNI group. HbA1c values at Month 36 were similar between groups for those subjects with a history of diabetes mellitus at baseline.

There were no major differences between the treatment arms regarding blood pressure, dyslipidaemia and NODM at Month 12.

Donor-Specific Antibodies (DSA)

At baseline, three subjects in each treatment reported positive DSA. At Month 12, one additional subject in the CNI arm had developed DSA.

Testing for DSA was not performed after Month 12.

Patient reported outcome

The SF-36 was used to evaluate the changes in patient quality of life (QoL).

At Month 12, there were no statistical differences in the SF-36 subscale scores, physical component summary score, or mental component summary score between treatment arms. Similarly, when examining the change in scores from baseline to Month 12, there were no differences in the change in SF-36 subscale scores or the physical and mental component summary scores between treatment arms (p-value ranging from 0.26 to 0.83 for the eight subscales.

At Month 36, no statistical differences were observed between the belatacept conversion and CNI continuation groups in terms of the SF-36 subscale scores

The Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD-59R) was used to assess the occurrence and distress of symptoms associated with immunosuppressive therapies. Ridit scores were calculated at 12 months for overall symptom occurrence score and overall symptom distress. The Ridit score reflects the probability that a score observed for an individual randomly selected from a group would be higher (worse symptom) than a score observed for a randomly selected individual from the reference group. No difference in Ridit scores between the 2 groups were observed in IM103010.

No clinically relevant differences were reported in QoL-related measurements. As discussed for Study IM103116, self-reported scoring of QoL in open-labelled studies need to be interpreted with great caution.

- **Safety and efficacy in subjects who were allowed to switch from CNI to belatacept**

As of 01-Jan-2010, subjects were allowed to switch from CNI to belatacept, if clinically indicated (SW population). A total of 16 subjects switched. The most common reason for switching was "Patient preference" (10/16 switches). Of these 16 subjects, one discontinued treatment because of an AE after 140 days of exposure. Up to the Month-36 database lock, 7 subjects had been on belatacept for 253 to 364 days and 7 had been on belatacept for 365 days or more. The remaining 2 subjects were on belatacept less than 168 days.

Of the 16 subjects who switched to belatacept, one subject had AR 182 days after switching to belatacept without graft loss.

On the day of switch, mean cGFR was 62.6 ± 18.43 ml/min/1.73m^2 in subjects who switched from CsA and 64.7± 10.48 ml/min/1.73m^2 in those who switched from TAC.

At Week 4 post-switch, mean percentage change from switch to Week 4 post switch was 2.5 ± 9.93 ml/min/1.73m^2 in subjects who switched from CsA and 2.1 ± 9.50 ml/min/1.73m^2. At Week 24 post switch, the mean percentage change from switch in subjects who switched from CsA was -7.1 ± 21.68 ml/min/1.73m^2 and +10.5± 21.04 ml/min/1.73m^2 for subjects who switched from TAC. cGFR values for the 16 subjects at Week 24 post-switch are summarised in Table 34.

Table 34 Summary of calculated GFR based on imputed values at specified time points before and after the conversion all ITT-SW subjects (IM103010 LTE)

	Belatacept N=16	SUBJECTS INITIALLY TREATED WITH CsA N=5	SUBJECTS INITIALLY TREATED WITH TAC N=11
CHANGE FROM SWITCH TO WEEK 24 POST SWITCH			
N	14	5	9
MEAN (SD)	1.6(14.02)	-6.4(12.29)	6.1(13.48)
MEDIAN	-0.1	-4.7	7.3
Q25 - Q75	-6.9 - 9.7	-11.0 - -2.1	-1.3 - 11.5
MIN - MAX	-23.8 - 29.2	-23.8 - 9.7	-15.3 - 29.2
PERCENTAGE CHANGE FROM SWITCH TO WEEK 24 POST SWITCH			
N	14	5	9
MEAN (SD)	4.2(22.22)	-7.1(21.68)	10.5(21.04)
MEDIAN	0.2	-6.8	8.9
Q25 - Q75	-12.2 - 21.7	-22.1 - -2.7	-1.8 - 21.7
MIN - MAX	-30.3 - 45.7	-30.3 - 26.1	-19.3 - 45.7

Imputation: for subjects who died or had graft loss, the value of 0 will be imputed and carried forward after death or graft loss up to the end of the analysis period.
GFR Measurement Unit: mL/min/1.73 m2

2.4.4. Analysis performed across trials (pooled analyses and meta-analysis)

This section summarises key efficacy findings from the conversion studies IM103010 and IM103116 as compared to the pivotal *de novo* studies IM103008 and IM103027. The maintenance dosing regimen of 5 mg/kg every 4 weeks used in both conversion studies was the same as that administered during the maintenance phase of both pivotal phase 3 *de novo* transplant studies.

BPAR

As observed in the belatacept treatment groups in pivotal phase 3 studies IM103008 and IM103027, in study IM103116, the distribution of BPAR severity, as based on the Banff classification of renal allograft pathology was skewed toward a greater number of moderate and severe events following belatacept conversion. However, the allograft histopathologic findings consistent with pure humoral (antibody-mediated) rejection (n = 3), and the only death-censored (pure) graft loss reported post-BPAR (n = 1), occurred only in the CNI continuation treatment group.

In both studies IM103010 and IM103116, the observed frequency of acute rejection in the belatacept arm through 36 and 24 months (8.4 % and 8.1%, respectively), was lower to a clinically meaningful extent than that observed in the approved (less intense) treatment regimen in *de novo* renal transplant recipients in pivotal studies IM103008 and IM103027 through 36 months (17.3% in IM103008 and 18.9% in IM103027).

Based upon the above observations, in particular, those from the larger phase 3b study IM103116, the approach to surveillance for clinical and laboratory evidence of acute allograft rejection following conversion of existing renal allograft recipients to belatacept is expected to be not different from that employed in standard of care monitoring following use of belatacept in *de novo* renal transplantation.

Renal Function

In studies IM03010 and IM103116, despite the higher observed rate and severity of BPAR following belatacept conversion, renal filtration function, as determined from baseline adjusted, cGFR, was higher at the end of each study period than those of the groups randomised to continue CNI-based immunosuppression. This treatment difference was apparent in both studies, but even more so in the larger, more robust IM103116, in which higher mean levels of cGFR were observed beginning at 3 months post-conversion and subsequently persisted through the end of the 24-month study period. In

both studies, the pattern of change was subjectively similar to the trends observed in the phase 3 pivotal studies IM103008 and IM103027.

In study IM103116, renal function, as determined from baseline-adjusted cGFR, was lower among subjects who experienced BPAR in both treatment groups; however, adjusted mean cGFR was lower at Month 24 in CNI continuation subjects than in belatacept conversion subjects. This finding is similar to that observed in the pivotal phase 3 clinical trials in *de novo* renal allograft recipients.

2.4.5. Discussion on clinical efficacy

The current standard of care immunosuppressive therapies with renal transplantation, the CNIs, CsA and TAC, are associated with renal and cardiovascular toxicities. Belatacept represents a class of selective co-stimulatory immunomodulators approved in the EU in 2011 for prophylaxis of graft rejection in adults **receiving** a renal transplant, i.e., treatment with belatacept should be initiated in immediate association to renal transplantation, as a substitution for a CNI in a triple immunosuppressive therapy. However, according to the MAH, it is currently estimated that approximately 80% belatacept in clinical practice is used in conversion from a CNI-based therapy to belatacept, months to years after the transplantation. The MAH proposes a modification to the current indication statement to include the conversion use. The intended new population, adult renal transplant recipients, is considered similar to the approved population in all other aspects except that they have been given CNI since the transplantation. Therefore, the present indication is to a large extent supported by existing data. In this light, the lack of formal statistical testing in the conversion studies was found acceptable to the CHMP.

The concept "*de novo*"-transplant recipients is used in the dossier for subjects receiving belatacept according to the approved indication, i.e. in immediate association to the transplantation and not as "first time renal recipients". This term is defined as "the newly transplanted patients" in the SmPC.

Design and conduct of clinical studies

Study IM103116

The main study IM103116 was a randomised, open-label, active-controlled, parallel-group study. Approximately 440 subjects on CNI-based regimens were to be randomised in a 1:1 ratio to either convert to treatment with belatacept or to continue treatment with their established CNI. The duration of study participation was 24 months with a subsequent 8-week follow-up period for safety post last dose.

The open-label design, though associated with inherent weaknesses, is considered acceptable to the CHMP. Belatacept is administered IV every fourth week in maintenance phase as opposed to CNI-based therapy, which is normally administered orally twice daily. Furthermore, the dosing of CNI is determined by trough serum concentrations, which would preclude a double-blind design.

The inclusion and exclusion criteria were considered acceptable by CHMP.

Five global protocol amendments were executed during the study; four of them (Amendments 03, 05, 07 and 08) after the initiation of the study (17-Apr-2013). In an open label study, protocol amendments after the study initiation date may raise concerns regarding study integrity and potentially data-driven decisions. Considering that no formal hypothesis testing was performed, no increase of the risk of false positive conclusions (type 1 error) is expected; however, bias of estimates of efficacy or safety of treatments may still be introduced. Here, considering only global amendments as relevant, only modification of study objectives and revision of eligibility criteria may raise concerns.

The MAH was asked to discuss the amendments and their justification in more detail. As requested, the MAH described and motivated the protocol amendments, which were clinically and methodologically justified. No substantial impact of different clinical study protocols on patient characteristics and results was observed. Therefore, it was agreed by the CHMP that the protocol amendments did not impact the data integrity.

Several issues potentially leading an inflation of the risk of false positive conclusions based on statistical testing were identified, including unclear description and possible use of an inadequate statistical model for testing a non-inferiority hypothesis and inconsistencies between the descriptive objectives and the used inferential statistical methods (eg CIs). However, given the level of efficacy demonstrated, as well as the support from data on the use of belatacept post *de novo* transplantation, data are considered sufficiently interpretable for regulatory decision-making. The MAH was asked to comment on the identified problems. The MAH described the objectives and statistical methods in the study. Although the use of inferential statistical methods in a descriptive study is not completely consistent, considering the context of the application for an extension of an existing indication with extensive off-label use the presented descriptive results are regarded as sufficiently robust to allow an assessment of the benefit-risk ratio.

No substantial missing data was found in the primary endpoint and key secondary endpoint (BPAR). However, the presence of substantial missing data and a limited imputation model for the endpoint "cGFR" may have created bias in the estimation of endpoints. As discussed in the safety section, 9/18 subjects in the belatacept arm of IM103116 experiencing a BPAR discontinued study treatment. For the majority of subjects remaining on treatment after a BPAR, mean cGFR values at all timepoints in both treatment arms was above 40 mL/min/1.73m^2 in IM103116. However, as both events of BPAR and treatment discontinuation related to BPAR was higher in the belatacept arm, the approach not to impute missing values may have resulted in an overestimation of renal function in the belatacept arm in IM103116. Therefore, additional sensitivity analyses based on 1) multiple imputation with relevant covariates (assuming missing-at-random data) and 2) a jump-to-reference imputation (conservatively assuming a missing-not-at-random data) were performed upon CHMP request and provided by the MAH. The results supported the conclusions from the results previously presented in the clinical study report. This was found acceptable to the CHMP.

The date of finalisation of the final SAP (version 3.0) was initially not documented. As requested by the CHMP, the MAH provided the relevant dates. The SAP was finished after initiation of the study, which may create concerns regarding study integrity. However, considering the context of the application for an extension of an existing indication with extensive off-label and overall robust descriptive results, these potential concerns were considered of minor relevance by the CHMP.

According to the CHMP guideline on Clinical investigation of immunosuppressants for solid organ transplantation (CHMP/EWP/263148/06, 2008), the primary efficacy endpoint for induction, initial and/or maintenance prophylaxis (primary prophylaxis) should be efficacy failure rate using a composite endpoint consisting of patient death, graft failure, BCAR and graft function. The primary endpoint of study IM103116 was the proportion of subjects who survive with a functional graft at 24 months post-randomisation, i.e. the components BCAR and graft functions were not included in the composite primary endpoint. BCAR and graft function are included among the pre-specified secondary endpoints. The primary endpoint is clinically relevant and considered acceptable to the CHMP, as belatacept is already approved for a similar indication.

Study IM103010

Study IM103010 was a phase 2, randomised, open-label, active-controlled, parallel-group study. The duration of the study was 12 months with a subsequent 8-week follow-up period for safety

evaluations. All subjects who completed the 12-month phase of the initial study, and met inclusion criteria and provided consent to continue, were eligible to participate in a LTE.

The study population included male and female (≥18 years of age) recipients of a renal allograft 6- 36 months prior to randomisation, e.g., there was a shorter time frame after transplantation for inclusion in IM103010 compared to IM103116. The lower limit of eligible baseline in GFR was slightly higher in IM103010 versus IM103116 (35 vs 30 mL/min/1.73m^2). Furthermore, the eligibility criteria concerning concomitant immunosuppressive treatment were narrower in IM103116. As opposed to Study IM103116, EBV serostatus was not an eligibility criterium in Study IM103010. The amendment requiring EBV seropositivity reflects the wording of section 4.4 of the approved SmPC. Despite these differences, the two study populations are considered comparable and both representative of the renal transplant recipient population.

The primary endpoint in Study IM103010 was change in cGFR from baseline to 12 months post-randomisation. This is considered acceptable for a supportive phase 2 study.

Month 12 data from study IM103010 were in part assessed in the original MAA for belatacept (EMEA/H/C/2098). The 36 Month ITT-population (ITT-LT) contains all subjects randomised in the beginning of IM103010 entering the LTE, i.e., data from subjects discontinuing the study up to Month 12 and subjects not choosing to enter the LTE are not included in the analyses.

The statistical methods in this supportive study are endorsed by the CHMP to provide descriptive results without claims based on statistical hypothesis testing. Multiple minor inconsistencies were noted regarding the definition of objectives and related statistical analyses (e.g. descriptive vs. inferential). CHMP considered therefore that the interpretation of study results should be only descriptive. The MAH was asked to describe the primary analysis and key secondary analysis more clearly with respect to selected analysis sets, visits, imputation methods, within- and between-treatment comparisons, covariate selection procedure, etc which were pre-specified as relevant for decision-making. The MAH described the objectives and statistical methods of this supportive study. Although the use of inferential statistical methods in a descriptive study is not completely consistent, the study design and statistical methods in this supportive study are acceptable to the CHMP. Considering the context of the application with an intended new population similar to the approved population in all aspects except that these patients have received CNI since the transplantation, the presented descriptive results are regarded as sufficiently robust to allow an assessment of the benefit-risk ratio.

The presence of missing data and its imputation using a combination of multiple approaches for the primary endpoint "cGFR" may have created bias in the estimation of treatment effect. The statement on cGFR imputation included in the SAP "*the calculated GFR value of 10 and 0 will be both imputed and carried forward up to month 12*" did not describe clearly the imputed value. The MAH was thus asked to clarify the applied imputation method and to perform the primary analysis based on 1) multiple imputation using relevant covariates (assuming missing-at-random data) and 2) a jump-to-reference imputation (using a conservative missing-not-random-data) for the primary endpoint. As requested by the CHMP, the MAH clarified the raised ambiguities and provided relevant sensitivity analyses and corresponding results, which supported the previously reported results in the clinical study report. This was found acceptable to the CHMP.

Literature search

The MAH has provided a literature review identifying clinical abstracts and published papers up to October 2019 related to conversion of existing renal transplant recipients from CNI- to belatacept-based immunosuppression. Excluding publications summarising data from study IM103010, 26 abstracts and manuscripts reporting conversion from CNI- or mammalian target of rapamycin

inhibitors (mTORi)- based immunosuppression to belatacept were identified, summarising approximately 967 patients. A supplemental literature search was conducted in February 2020, identifying four additional manuscripts.

The duration of follow-up, time from transplantation to switch and demographic baseline data varied largely between the studies, which represented single- and multiple-case reports, randomised clinical trials, retrospective reviews, and retrospective case control single-centre and multi-centre studies of any size. In 21 single-and multicentre reports of 6 or more patients converted to belatacept, patient survival varied between 84% and 100%, all studies but two with a patient survival of >90%. Median follow-up time in these studies were 6-26.5 months with all studies except one having a follow-up time of ≥12 months. Graft survival in the same studies varied from 80% to 100%. In general, renal function improved, or remained stable in most patients following conversion. There was substantial variability in the extent to which mean estimated glomerular filtration rate (eGFR) improved following conversion from approximately 6 to 38 mL/min/1.72 m2 in different studies by about 12 months later.

The MAH has also summarised data from a prospective, observational cohort study from France, in which 228 recipients of a renal allograft from a living or deceased donor who had, in all but 2 cases, were started on CNI-based immunosuppression at the time of transplantation, and subsequently converted to belatacept based therapy. In brief summary, the mean (SD) follow-up time post-conversion was 28 (16) months. Graft survival was 93% and mean (SD) eGFR increased from 31 (14) mL/min pre-conversion to 40 (16) mL/min 12 months post-conversion.

In summary, although, detailed assessment of literature data is precluded, the literature review presented by the MAH could be considered to support efficacy of belatacept in the conversion setting.

Efficacy data and additional analyses

Participant flow

In study IM103116, 446 subjects were randomised to belatacept or CNI; 223 in each treatment group. Slightly more subjects in the belatacept arm versus the CNI arm completed the treatment period (87% versus 84%, respectively). The most common reason for treatment discontinuation in the belatacept arm was AEs (5.4 % vs 3.1% in the CNI arm). It was however noted that subjects in the CNI arm continued their usual treatment. The most common reason for treatment discontinuation in the CNI treatment arm was at the patient's request.
At the end of the study, 109 subjects in the belatacept arm transitioned to commercially available belatacept whereas 90 subjects returned to standard of care.

In study IM103010, 173 subjects were randomised, 84 to belatacept and 89 to CNI. The slight imbalance was explained by stratification.
In both treatment arms, 98% of the subjects completed the 12-months treatment period. More subjects in the belatacept compared to the CNI arm completed the LTE (86% vs 70%). CNI subjects were considered completing treatment, not discontinued, when the CNI treatment arm was discontinued, if they did not switch to belatacept. Thirty-eight (38) subjects randomised to CNI switched to belatacept during the LTE, of whom 16 did so before closure of the CNI arm.

Baseline data

In both studies, baseline cGFR was balanced between the treatment arms, which is of relevance for the outcome of the study. There were some imbalances between the treatment arms in both studies, e.g. the baseline prevalence of diabetes type I was higher in the belatacept arm versus the CNI arm (6.3 vs 1.8 %) in IM103116 and the number of white subjects and European subjects was lower in the belatacept compared to the CNI arm (52% versus 60% and 18% versus 25%, respectively) in

IM103010. However, the CHMP did not consider that these discrepancies in baseline characteristics would have a major impact on study outcome.

Study IM103010 was initiated six years before study IM103116. Changes to the clinical practice have been introduced in the meantime and therefore standard of care immunosuppression, organ preservation, and donor and recipient criteria may not be entirely identical between the studies.

Compared to study IM103116, the mean age in study IM103010 was approximately eight years lower (45 years versus 53 years). The number of white subjects and subjects from Europe was markedly lower in IM103010 than in study IM103116 (56% versus 85% and 21% versus 42%, respectively). Baseline cGFR was similar in the two studies, whereas the prevalence of diabetes and hypertension at baseline was slightly lower in study IM103010 which may reflect the lower mean age in the study. The proportion of TAC subjects in the CNI arm was higher in study IM103116 compared to study IM103010 (89% vs 56%).
Both study populations are considered representative of the renal transplant population.

Survival with functional graft

24-month survival with functional graft was the primary endpoint in study IM103116 and secondary endpoint in study IM103010. There were no remarkable differences in cause of death between the treatment arms in either study.

In study IM103116, the 24-month survival with functional graft was similar in the belatacept conversion and CNI continuation treatment groups (98.2% and 97.3%, respectively). Four deaths (1.8%) were reported in each treatment arm, whereas two graft losses (0.9%) were reported in the CNI arm versus none in the belatacept arm.
Extensive subgroup analyses showed that for all subgroups except "End stage renal disease (diabetes): yes", the proportion of subjects surviving with a functional graft in the belatacept treatment arm was ≥ 95%. For "End stage renal disease (diabetes): yes", the proportion of subjects surviving with a functional graft in the belatacept treatment arm was 94.7% versus 96.7% in the CNI arm.

In study IM103010, 12-month survival with functional graft was 100% in the belatacept arm versus 98.9% in the CNI arm. No graft loss was reported in either treatment arm up to Month 12. In addition, no deaths were reported in the belatacept group during the first 12 months. One subject in the CNI conversion group died with a functioning graft within 12 months post-randomisation.
In the ITT-LT population up to 36 months, two subjects experienced functional graft loss (one in the belatacept conversion group following an episode of BPAR and one in the CNI continuation group), and one subject died with a functioning graft in the belatacept conversion group. No subjects in the CNI treatment group died after Month 12. The survival with functional graft was 97.5% in the belatacept arm and 98.8% in the CNI arm.

In summary, up to Month 24 in study IM103116 and to Month 36 in study IM103010, there were five fatal events for each treatment. Three events of graft loss were reported in the CNI arms and one in the belatacept arms. Survival with a functioning graft was >97% in both treatment arms in both studies. Thus, conversion from CNI to belatacept did not impair graft or subject survival up to 24 and 36 months, respectively, in studies IM103010 and IM103116. In the pivotal "*de novo*-studies", patient survival with a functioning graft was higher in the belatacept arms than the CNI arms, but overall, lower compared to the conversion studies. This was anticipated, as the early post-transplant period is considered the highest risk for rejections and/or graft loss.
Patient and graft survival are considered robust outcome measures, not affected by the open-label design of the studies. The CHMP considers that the high survival rate with a functioning graft of 98% of the subjects in the belatacept arms is a strong support for efficacy of belatacept treatment also in the conversion setting.

Change in cGFR from baseline

Mean change in cGFR from baseline to 12 months post randomisation was the primary endpoint in IM103010 and Mean change in cGFR from baseline to 24 months post randomisation was a secondary endpoint in IM103116.

In both studies, mean baseline cGFR was well balanced between the treatment arms; 50 mL/min/1.73m^2 in the belatacept arm and 51 mL/min/1.73m^2 in the CNI arm for IM103116 and 53 mL/min/1.73 m^2 in the belatacept arm and 54 mL/min/1.73 m^2 in the CNI arm for IM103010.

At Month 24 in IM103116, adjusted mean cGFR in the belatacept arm had increased to 56 mL/min/1.73m^2 (+14.3%) (n=189 [85%]) in the belatacept arm compared to a decrease to 49 mL/min/1.73m^2 (-1.2%) (n=171 [77%]) in the CNI arm. Similar results were seen in all subgroups.

At Month 12 in IM103010, mean cGFR had increased in both treatment arms; however, the increase was numerically larger in the belatacept arm: 60 mL/min/1.73m^2 (+7.0%) (n=82 [98%]) in the belatacept arm versus 56 mL/min/1.73m^2 (+2.1%) (n=87 [98%]) in the CNI arm.

The baseline values for the ITT-LT population are not entirely identical to the baseline values for the IM103010 ITT population, as data from subjects in IM103010 not entering the LTE were not included. At the end of the 12-month treatment period, mean change from baseline in cGFR in the ITT-LT population was +7.1 and +2.8 mL/in/1.73 m^2, in the belatacept conversion group and CNI continuation group, respectively (n=81 in both arms).

In the initial variation submission, the MAH presented the Month 36 data in different ways (either as "Week 148" or "Month 36") in different documents. Upon request, the MAH clarified that the "Month 36 analysis in the IM103010 LTE closeout report" was based on "28-day-months", whereas Month 36 in the IM103010 clinical study report (CSR) is based on the actual number of days from entering the study. In the CSR, Month 36 equals Week 148. This explains the apparent differences between the IM103010 CSR and the IM103010 LTE closeout report.
Both ways, there was a "target day" with an analysis window, in which the measurements should be done. The day range for analysis in the Month 36 CSR Addendum (i.e. Week 148) corresponds to the protocol planned study visit schedule and therefore most subjects had available cGFR measurements in that analysis window. This supports the inclusion of Week 148 results, with a larger difference between the treatment arms data in section 5.1 of the SmPC. This is accepted by the CHMP.

In summary, in both studies, there was an increase in cGFR compared to baseline in the belatacept arm. In the CNI arms, mean cGFR decreased (IM103116) or showed a small increase (IM103010). This is consistent with the pivotal *de novo*-studies, in which there was a small increase in cGFR in the belatacept arm versus a decrease in the CNI arm between Month 1 and Year 3 after the transplantation. After the first couple of months post-transplantation, the renal function of the graft is usually stable or slowly deteriorates. Even a small increase in cGFR is therefore considered to be of clinical relevance. The small increase in the CNI-arm in IM103010 is not fully understood. However, as discussed under methodology, the imputation method may have created bias in the estimation of treatment effect.

Biopsy-proven acute rejection (BPAR)

BPAR was a secondary endpoint in both studies.

In IM103116, BPAR (Banff Grade 1A or higher acute cellular rejection while excluding any borderline cellular or antibody mediated acute rejection events) was more commonly reported in the belatacept versus the CNI treatment arm (18/223 [8.1%] vs 6/223 [2.7%], respectively, at Month 24). In addition, three events of humoral rejection were reported in the CNI arm versus none in the belatacept

arm up to Month 24, giving a total number of rejections in the CNI treatment arm of 9/223 (4.0%). Of note, no additional events of BPAR occurred after Month 12 in the belatacept arm, whereas three of the six events in the CNI arm occurred between Month 12 and 24. It should be noted that whereas none of the subjects experiencing a BPAR in the belatacept arm lost the graft, 9/18 subjects discontinued study treatment in the association with the event.

In IM103010, during the first 12 months, six subjects in the belatacept arm (7%) experienced AR versus none in the CNI arm. All AR were reported during the first six months and none of the events led to graft loss by Month 12. Two of the subjects discontinued study treatment reporting "lack of efficacy", whereas the remaining four completed the 12-month treatment period and entered the LTE. Between Month 12 and Month 24 there were three events of AR in the CNI arm versus none in the belatacept arm, and between Month 24 and Month 48, one additional AR was reported in each treatment arm. It should however be noted that the subject reported with AR after Month 24 in the CNI arm had switched to belatacept on study day 988 whereas the event of rejection occurred on Study day 1170. It is thus questionable whether this event should be regarded as a late rejection in the CNI arm or rather as a rejection approximately 6 months after switch to belatacept. Notwithstanding, the 6/7 events of AR reported in the belatacept arm (the event discussed above not included) occurred during the first six months after the transition. In summary, during the first 12 months of both studies, 24 events of BPAR were reported in the belatacept arms versus three in the CNI arm, resulting in a 12-month rate of BPAR of 7-8% in the belatacept arm versus 0-3% in the CNI arm. In the initial marketing authorisation of the "*de novo*"-indication, a higher number of BPAR was seen in the belatacept arm compared to the CNI arm in both pivotal studies. The number of BPAR was numerically lower in both treatment arms in the conversion studies compared to the "*de novo*"-studies, as was expected as most episodes of acute rejections are normally reported in the early post-transplant period. Both in the "*de novo*"- and conversion setting, the vast majority of BPAR in the belatacept arm were reported up to Month (6-)12. In the conversion setting, the number of BPAR reported after Month 12 were comparable between the treatment arms indicating that the increased risk of BPAR with belatacept compared to CNI is not maintained. This is consistent with the finding that the development of de novo donor specific antibodies, considered a risk factor for rejection and graft loss, was smaller in the belatacept arm of the conversion studies (Table 25). It should also be noted that there was no increase of graft loss in the belatacept versus CNI arms, neither in the "*de novo*"- nor conversion studies.

Additional secondary and exploratory endpoints

Additional secondary and exploratory endpoints in both studies included effect on lipid profiles, new onset of diabetes, blood pressure and self-reported quality of life-assessments. The MAH did not propose to include these outcomes in the SmPC, which is agreed by the CHMP. The differences between the treatment arms were generally modest and no safety concern was raised by the results.

Safety and efficacy in subjects who were allowed to switch from CNI to belatacept

Sixteen subjects were allowed to switch from CNI treatment to belatacept during the LTE in IM103010 after 01 Jan 2010. The switches were made between post-transplantation Day 760 and Day 1130. The most common reason for switching was "Patient preference" (10/16 switches). One subject discontinued belatacept treatment due to an AE; the other fifteen subjects remained on belatacept treatment. One subject experienced an acute rejection without graft loss after the switch.
cGFR data at Week 24 was divergent, with mean percentage change from switch of -7.1 ± 21.68 ml/min/1.73m^2 in subjects who switched from CsA and +10.5± 21.04 ml/min/1.73m^2 for subjects who switched from TAC.
It is agreed with the MAH, that the results of the analysis in the switch population should be interpreted with caution in view of the low number of subjects who switched to belatacept. The MAH

was nevertheless asked to present the outcome of the major primary and secondary endpoints (survival with functioning graft, BPAR and change in cGFR) in both IM103010 and IM103116 for subjects randomised to belatacept from a TAC based and from a CsA based therapy separately. Even though improvement in baseline-adjusted mean cGFR was numerically greater following conversion to belatacept from CsA versus TAC in both studies, the outcome in both arms was consistent with the outcome of the study population, i.e., a larger improvement in the belatacept vs CSI arm. The likelihood of survival with a functioning allograft was similar regardless of initial therapy.

The most striking finding was that all belatacept conversion subjects who experienced at least one event of acute cellular BPAR in study IM103116 (with or without a humoral component; n=18) were receiving TAC at baseline, whereas the rates of cellular or antibody-mediated acute rejection were the same in the CNI continuation subgroups. The same difference was not seen in IM103010.
As pointed out by the MAH, a possible explanation to the imbalance in background treatment in subjects with BPAR in IM103116 may be that 89% of the subjects in in study IM103116 were treated with TAC before conversion. This is accepted.

Wording of the indication and posology

The proposed final wording of the indication is "*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)".

In the conversion studies, the studied population was narrower than the broader indication of adult recipients of a renal transplant. Indeed, the eligibility criteria restrict the studied population by excluding subjects with cGFR <30 (<35 in IM103010) and >75 mL/min/1.73m^2 and limiting inclusion of subjects with a history of acute rejections and high immunological risk. It is assumed that the upper limit of cGFR for inclusion was set to identify subjects with beginning CNI toxicity, which is considered a subpopulation with a need for non-CNI based immunosuppression. Likewise, it is supposed that the lower cGFR limitation was set to exclude subjects with extensive chronic allograft nephropathy, less likely to benefit from conversion to another immunosuppressive therapy. However, there are other clinical situations in which the use of belatacept may be advantageous, for example in subjects with AEs on CNI. Furthermore, in subjects with poor compliance, the use of belatacept given in a health care setting every four weeks may be a better option. The CHMP agrees that there is no reason to assume that the efficacy of belatacept in the conversion setting in subjects with better renal function than 75 mL/min/1.73m^2 would be different from that reported in the studies. This is supported by the data provided in the original MAA, where no clinically relevant effects on belatacept clearance was seen with decreased renal function. This is reflected in the approved SmPC, including a wording in section 4.2 that no dose adjustment is recommended in patients with renal impairment or undergoing dialysis. The CHMP agrees therefore that the results from the studies can be extrapolated to subjects with all levels of renal function. The broad population in the proposed wording of section 4.1 of the SmPC is accepted. The eligibility criteria further restrict the study population by excluding subjects with high immunological risk. This is not considered to affect the wording of the indication but has been reflected in section 4.4 of the SmPC which states that "*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.*"

Furthermore, the initial additional proposed wording in section 4.1 of the SmPC "*For induction therapy in de novo renal transplant recipients, the addition of an interleukin-2 (IL-2) receptor antagonist to this Nulojix based regimen is recommended*" is moved to section 4.2 of the SmPC as this is not an absolute

condition for use and to make it clearer in which population the IL-2 receptor antagonist should be given.

In the approved indication, belatacept is started at the day of transplantation. The risk of graft loss and/or acute rejections is highest in the early post-transplantation period, slowly decreasing over 6-12 months after transplantation. To adjust immunosuppression to this increased risk, a more intense belatacept treatment is administered in the initial phase in the *de novo* setting. After 12 weeks, the subjects are transferred to a maintenance dose of 5 mg/kg every 4 weeks. According to the literature, there is a tendency to an increased risk of graft loss and/or acute rejections after conversion of immunosuppressive therapy. To meet this risk in the proposed conversion setting, the MAH proposed that belatacept should not be started at the maintenance dose in the conversion setting; instead, belatacept is administered more often (5mg/kg every 2 weeks) during the first eight weeks, in parallel with a slow tapering of CNI. After two months, the same maintenance therapy as in the "*de novo*"-setting was given. This posology was used in the conversion studies (studies IM103116 and IM103010) and was found effective in prophylaxis of graft rejection. The MAH proposed to amend section 4.2 of the SmPC with this information as a recommended posology for the conversion setting. This is agreed by the CHMP. Furthermore, 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. This is reflected in section 4.4 of the SmPC.

2.4.6. Conclusions on the clinical efficacy

The efficacy data indicate that conversion from CNI to belatacept did not impair graft or subject survival up to 24 and 36 months, respectively, in studies IM103010 and IM103116. In both studies, there was a larger improvement in mean cGFR change compared to baseline in the belatacept arm. Furthermore, although a higher incidence of BPAR was shown comparing belatacept and CNI in the conversion studies, the data do not indicate a higher rate of BPAR in the conversion studies than in the pivotal *de novo* studies. The majority of BPAR in the belatacept arm occurred during the first year of treatment.

Therefore, from an efficacy point of view, the proposed revised indication is agreed by CHMP: *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).* The posology for conversion use is also acceptable: 5 mg/kg every 2 weeks for the first 8 weeks, followed by the same dose every 4 weeks thereafter.

Consequently, the sections 4.1, 4.2, 4.4 and 5.1 of the SmPC have been updated to reflect the new indication, the posology at time of conversion, a warning about conversion from CNI-based maintenance regimen and the results of the two conversion studies.

2.5. Clinical safety

Introduction

Clinical investigation of belatacept has been ongoing since 19-Nov-1998. As of 14-Jun-2019, approximately 2,037 subjects have been exposed to belatacept through the MAH-sponsored clinical trials, and an estimated 6,011 subjects have been exposed to commercially available belatacept.

In the latest approved RMP (version 17.2, dated March 05, 2020), no important identified or potential risks are included in the Summary of safety concerns. The known safety profile of belatacept is consistent with that of immunosuppressive therapies. Typical AEs for this class of drugs are PTLD, infections and malignancies. Furthermore, injection-related reaction including anaphylaxis and graft thrombosis have been reported for belatacept.

Due to differences in study design, data across studies were not pooled. All safety presentations were based on the population of randomised and treated subjects and were presented by treatment group.

Patient exposure

IM103010

In the as-treated population through Month 12, 98% of belatacept subjects and 98% of CNI subjects remained on assigned treatment. The mean (median) days of exposure through Month 12 was 357 (364) days for the belatacept group and 358 (364) days for the CNI group.

By the 36-month database lock, 93% of belatacept subjects and 74% of CNI subjects had received study medication for 1093 days or more. The mean (median) exposure through the end of the study was 1270 (1264) for the belatacept group and 1195 (1242) days for the CNI group.

IM103116

The mean (median) duration of exposure to study medication up to Month 24 was comparable in both treatment groups: 690 (756) days for belatacept conversion and 658 (737) days for CNI continuation

Adverse events

IM103010

The majority of subjects had an AE up to Month 12 (primary endpoint). A higher percentage of belatacept-treated subjects (94%) compared to CNI-treated subjects (83%) was reported to have experienced one or more AEs (Table 35).

Table 35 Adverse events reported after first dose date up to Month 12 (ITT-population) and Month 36 (ITT-LT-population) post-randomisation (IM103010)

	Month 12		Month 36	
	Belatacept N=83 n (%)	CNI N=88 n (%)	Belatacept N=81 n (%)	CNI N=81
TOTAL SUBJECTS WITH AN EVENT	78 (94.0)	73 (83.0)	79 (97.5)	76 (93.8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	10 (12.0)	8 (9.1)	21 (25.9)	17 (21.0)
CARDIAC DISORDERS	2 (2.4)	7 (8.0)	5 (6.2)	10 (12.3)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	-	-	2 (2.5)	2 (2.5)

EAR AND LABYRINTH DISORDERS	1 (1.2)	0	2 (2.5)	0
ENDOCRINE DISORDERS	1 (1.2)	3 (3.4)	5 (6.2)	5 (6.2)
EYE DISORDERS	8 (9.6)	2 (2.3)	20 (24.7)	8 (9.9)
GASTROINTESTINAL DISORDERS	32 (38.6)	30 (34.1)	46 (56.8)	41 (50.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	25 (30.1)	19 (21.6)	43 (53.1)	28 (34.6)
HEPATOBILIARY DISORDERS	1 (1.2)	2 (2.3)	5 (6.2)	3 (3.7)
IMMUNE SYSTEM DISORDERS	2 (2.4)	2 (2.3)	2 (2.5)	3 (3.7)
INFECTIONS AND INFESTATIONS	56 (67.5)	40 (45.5)	67 (82.7)	55 (67.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	16 (19.3)	10 (11.4)	27 (33.3)	20 (24.7)
INVESTIGATIONS	19 (22.9)	12 (13.6)	29 (35.8)	21 (25.9)
METABOLISM AND NUTRITION DISORDERS	25 (30.1)	26 (29.5)	42 (51.9)	38 (46.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	26 (31.3)	13 (14.8)	39 (48.1)	21 (25.9)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	4 (4.8)	7 (8.0)	13 (16.0)	12 (14.8)
NERVOUS SYSTEM DISORDERS	18 (21.7)	13 (14.8)	28 (34.6)	23 (28.4)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	1 (1.1)	0	1 (1.2)
PSYCHIATRIC DISORDERS	10 (12.0)	6 (6.8)	16 (19.8)	14 (17.3)
RENAL AND URINARY DISORDERS	11 (13.3)	11 (12.5)	24 (29.6)	19 (23.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	5 (6.0)	2 (2.3)	15 (18.5)	5 (6.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	19 (22.9)	12 (13.6)	31 (38.3)	24 (29.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	15 (18.1)	11 (12.5)	27 (33.3)	18 (22.2)
SOCIAL CIRCUMSTANCES	-	-	0	1 (1.2)
VASCULAR DISORDERS	13 (15.7)	10 (11.4)	19 (23.5)	10 (12.3)

The percentage of subjects with drug-related AEs, assessed by the investigator, was 29% in belatacept and 31% in CNI Month 12 and 43% for belatacept and 51% for CNI Month 36.

IM103116

In Study IM103116 up to Month 24, 96% of belatacept conversion and 92% of CNI continuation subjects were reported to have experienced one or more AEs (Table 36).

Table 36: Exposure Adjusted Most Common Adverse Event (Reported in at Least 5% of Subjects in any Treatment Group) Summary 24 Month Study Period All Randomized and Treated Subjects

	BELA N = 221			CNI N = 222		
SYSTEM ORGAN CLASS PREFERRED TERM	N (%)	P-Y	IR/ 100 P-Y	N (%)	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	211 (95.5)	60.7	347.6	204 (91.9)	75.1	271.8
INFECTIONS AND INFESTATIONS	141 (63.8)	221.1	63.8	151 (68.0)	196.8	76.7
NASOPHARYNGITIS	44 (19.9)	358.5	12.3	50 (22.5)	335.4	14.9
URINARY TRACT INFECTION	42 (19.0)	349.1	12.0	34 (15.3)	363.4	9.4
BRONCHITIS	23 (10.4)	376.6	6.1	18 (8.1)	390.1	4.6
UPPER RESPIRATORY TRACT INFECTION	17 (7.7)	386.5	4.4	18 (8.1)	382.4	4.7
INFLUENZA	11 (5.0)	396.0	2.8	11 (5.0)	389.0	2.8
SINUSITIS	11 (5.0)	390.0	2.8	8 (3.6)	391.5	2.0
GASTROINTESTINAL DISORDERS	108 (48.9)	263.7	41.0	97 (43.7)	278.5	34.8
DIARRHOEA	48 (21.7)	346.8	13.8	63 (28.4)	328.9	19.2
ABDOMINAL PAIN	13 (5.9)	396.3	3.3	14 (6.3)	387.7	3.6
NAUSEA	15 (6.8)	389.5	3.9	12 (5.4)	389.7	3.1
VOMITING	10 (4.5)	395.6	2.5	13 (5.9)	387.2	3.4
ABDOMINAL PAIN UPPER	10 (4.5)	396.5	2.5	11 (5.0)	389.3	2.8
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	85 (38.5)	309.8	27.4	92 (41.4)	287.5	32.0
ARTHRALGIA	21 (9.5)	384.9	5.5	23 (10.4)	377.5	6.1
BACK PAIN	18 (8.1)	384.6	4.7	22 (9.9)	377.2	5.8
PAIN IN EXTREMITY	11 (5.0)	394.1	2.8	20 (9.0)	380.8	5.3
MUSCLE SPASMS	11 (5.0)	389.7	2.8	6 (2.7)	392.3	1.5
MUSCULOSKELETAL PAIN	5 (2.3)	399.4	1.3	12 (5.4)	386.2	3.1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	86 (38.9)	289.6	29.7	72 (32.4)	309.1	23.3
OEDEMA PERIPHERAL	22 (10.0)	380.3	5.8	35 (15.8)	360.0	9.7
PYREXIA	22 (10.0)	378.6	5.8	17 (7.7)	382.4	4.4
FATIGUE	22 (10.0)	373.2	5.9	15 (6.8)	382.1	3.9
ASTHENIA	11 (5.0)	393.1	2.8	6 (2.7)	395.0	1.5
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	69 (31.2)	330.5	20.9	70 (31.5)	324.5	21.6
CONTUSION	11 (5.0)	395.3	2.8	6 (2.7)	395.6	1.5
NERVOUS SYSTEM DISORDERS	69 (31.2)	314.5	21.9	62 (27.9)	322.1	19.2
HEADACHE	27 (12.2)	369.5	7.3	23 (10.4)	371.0	6.2
DIZZINESS	15 (6.8)	384.7	3.9	8 (3.6)	390.5	2.0
TREMOR	6 (2.7)	399.9	1.5	12 (5.4)	383.9	3.1

The proportion of subjects with AEs reported to Month 24 and considered by the investigator to be related to study medication was 36% in the belatacept conversion group and 33% in the CNI continuation group. The majority of AEs reported to Month 24 were mild to moderate in intensity.

In study IM103010, the incidence rate (IR) of infections (events/100 patient years) was higher in the belatacept versus CNI arm at Month 36 (72 vs 43), whereas the opposite was reported at Month 24 in IM103116 (64 vs 77). In both studies, the IR for malignancies were comparable between the treatment arms (5.3 vs 5.0 for belatacept and CNI, respectively, in IM103010 and 6.6 vs 6.3 in IM103116).

Serious adverse event/deaths/other significant events

Serious adverse event (SAE)

In IM103116, 48% of the subjects in the belatacept arm and 43% in the CNI arm reported a SAE. The corresponding numbers for IM103010 Month 12 was 24% and 19%, respectively and for Month 36 46% and 44%.

Listings of AEs reported in ≥1% of the subjects (i.e. >2 subjects) in IM103116 are presented in Table 37.

Table 37 Exposure Adjusted Serious Adverse Events (Preferred Terms Reported in ≥1% of Subjects) Summary 24 Month Study Period All Randomized and Treated Subjects (IM103116)

	Belatacept N = 221			CNI N = 222		
SYSTEM ORGAN CLASS PREFERRED TERM	N (%)	P-Y	IR/ 100 P-Y	N (%)	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	107 (48.4)	291.7	36.7	95 (42.8)	306.1	31.0
INFECTIONS AND INFESTATIONS	37 (16.7)	362.2	10.2	44 (19.8)	361.2	12.2
URINARY TRACT INFECTION	7 (3.2)	396.5	1.8	7 (3.2)	395.0	1.8
UROSEPSIS	6 (2.7)	400.8	1.5	3 (1.4)	398.3	0.8
PNEUMONIA	5 (2.3)	397.2	1.3	7 (3.2)	396.9	1.8
SEPSIS	4 (1.8)	401.0	1.0	2 (0.9)	400.6	0.5
GASTROENTERITIS	1 (0.5)	404.5	0.2	6 (2.7)	398.4	1.5
CELLULITIS	1 (0.5)	404.0	0.2	3 (1.4)	398.4	0.8
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	18 (8.1)	387.6	4.6	13 (5.9)	390.7	3.3
BASAL CELL CARCINOMA	11 (5.0)	394.5	2.8	5 (2.3)	396.4	1.3
SQUAMOUS CELL CARCINOMA	3 (1.4)	400.9	0.7	5 (2.3)	398.3	1.3
SQUAMOUS CELL CARCINOMA OF SKIN	4 (1.8)	400.6	1.0	1 (0.5)	400.0	0.2
IMMUNE SYSTEM DISORDERS	19 (8.6)	387.9	4.9	9 (4.1)	393.6	2.3
KIDNEY TRANSPLANT REJECTION	19 (8.6)	387.9	4.9	7 (3.2)	394.5	1.8
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11 (5.0)	395.7	2.8	16 (7.2)	384.5	4.2
CARDIAC DISORDERS	13 (5.9)	393.6	3.3	11 (5.0)	393.9	2.8
CARDIAC FAILURE CONGESTIVE	1 (0.5)	403.5	0.2	3 (1.4)	399.6	0.8
GASTROINTESTINAL DISORDERS	9 (4.1)	397.7	2.3	14 (6.3)	387.0	3.6
DIARRHOEA	1 (0.5)	404.8	0.2	6 (2.7)	394.1	1.5
RENAL AND URINARY DISORDERS	9 (4.1)	396.0	2.3	9 (4.1)	393.4	2.3
ACUTE KIDNEY INJURY	4 (1.8)	401.0	1.0	5 (2.3)	398.1	1.3
VASCULAR DISORDERS	9 (4.1)	394.2	2.3	5 (2.3)	396.9	1.3
METABOLISM AND NUTRITION DISORDERS	5 (2.3)	402.7	1.2	8 (3.6)	395.0	2.0
DIABETIC KETOACIDOSIS	1 (0.5)	404.8	0.2	3 (1.4)	397.9	0.8

The spectrum of SAEs reported in the belatacept arm of both studies is consistent with the known safety profile of belatacept. No new and unexpected SAEs are reported.

Deaths

In Study IM103010, three fatal events, one in the CNI arm (a 58-year-old male) and two in the belatacept arm (a male aged 27 years, and a female aged 58 years with multiple cardiovascular risk factors, were reported up to the Month 36 data lock point (DLP). One of the subjects was <30 years of age. None of the events was assessed as related to study drug by the Investigator. All three subjects experienced sudden death at home. The recorded cause of death was myocardial infarction in the two older subjects, both with risk factors for cardiovascular events. It is agreed with the Investigators that a causal association to the study drug is less probable in these two cases. It is however considered that an assessment of causality to belatacept cannot be made for the 27-year-old man due to limited information.

Two additional deaths (males, aged 51 and 32 years) occurred subsequent to the DLP in IM103010, after approximately 4.5 years of belatacept treatment. The cause of death were sepsis and brain abscess, respectively. The event of brain abscess was assessed probably related to the study treatment, whereas the event of cellulitis was assessed as unrelated.
As severe infections and sepsis are common AEs with immunosuppressive therapy, both events are considered possibly/probably related to the study drug.

In IM103116, three belatacept conversion subjects (males, aged 64 years, 65 years and 69 years) experienced unwitnessed death at home that was attributed to probable acute coronary events. Of them, two had a past history of coronary artery disease and the third had a history of hypertension. It is agreed with the Investigators that a causal association to the study drug is less probable in these cases.

The four deaths in the CNI continuation group of IM103116 were attributed to gram negative sepsis (65-year old male), disseminated histoplasmosis (56-year old male), acute myocardial infarction with complications (49-year old male), and complications of a strangulated small bowel obstruction after surgery (47-year old female). None of the deaths were considered related to study drug by the investigator.
It is agreed with the Investigators that the events of myocardial infarction and strangulated bowel could be considered unrelated to study drug. However, as severe infections and sepsis are common AEs with immunosuppressive therapy, the events of histoplasmosis and gram-negative sepsis a reconsidered possibly related to treatment. In this context, it should be noted that the subject reporting gram-negative sepsis had discontinued study treatment with CNI approximately 150 days before the event and was now on belatacept treatment.

Two additional deaths occurred after study completion. A 57-year old male in the CNI arm presented at the Week 104 study visit with symptoms indicative of malignancy. Work-up showed pulmonary adenocarcinoma and the subject died on Day 833, 3 months beyond the Week 104 data analysis window.
As neoplasms are known AEs of immunosuppressive therapy, this event is considered possibly related to the study drug.

Furthermore, a 75-year old male died due to complications of injuries suffered in an unrelated accident, approximately 15 months after completion of study participation. This event is considered unrelated to study treatment.

In summary, of the 14 fatal events reported during and after the DLP of IM103010 and IM103116, three in IM103010 and seven in IM103116 up to Month 36 and Month 24 respectively. Two additional deaths in each study were reported after these time points. Four events, two in each treatment arm, are considered possibly related to the study drug by the Assessor. One additional subject reporting a fatal event possibly related to treatment had been treated with both CNI and belatacept. A causal assessment is not considered possible in one case.

No cause of death indicative of a new and unexpected AE of belatacept was reported in any of the subjects. As part of the responses to the request for supplementary information, the MAH provided a comparison of the IR of deaths, serious AEs and AEs leading to discontinuation in IM103010, IM103116, IM103008 and IM103027 to allow for comparisons of these parameters at different time points after conversion to or *de novo* treatment with belatacept. The outcome was comparable or better in the belatacept arms of the conversion studies compared to the belatacept LI arms of both *de novo* studies.

Adverse Events of Special Interest (AESI)

AESI discussed in the MAH's Summary of clinical safety were PTLD, malignancies other than PTLD, serious infections, Progressive Multifocal Leukoencephalopathy (PML), tuberculosis (TB) infections, viral infections, CNS infections, fungal infections, infusion-related reactions within 24 hours, thrombotic and embolic events, autoimmune diseases, and congestive heart failure and pulmonary oedema.

PTLD

In total, one event of PTLD was reported with belatacept treatment versus none in the CNI arm. The subject was EBV positive, but there is no data provided on the donor's EBV serostatus. Despite that EBV negative recipients were allowed to enter study IM103010, no event of PTLD was reported from this study.

Malignancies (other than PTLD)

The overall IR of malignancies other than PTLD was higher in IM103116 compared to IM103010 and higher in the belatacept arms (4.4 vs 3.1 events/100 PY for belatacept and CNI, respectively, in IM103116, and 2.9 vs 2.6 events/100 PY in IM103010).

In total, 55 events of malignancies other than PTLD were reported, 31 in the belatacept arms and 24 in the CNI arms. Of those, 46 events (84%) were non-melanoma skin cancers (27 and 19 events in the belatacept and CNI arms, respectively).

Serious infections

In study IM103010, up to Month 12, the frequency of serious infections was higher in the belatacept group (13%) than in the CNI group (8%). No serious infection was reported by more than 1 subject in a group, except for pyelonephritis and urinary tract infection (UTI) in 2 subjects each in the belatacept group and CMV infection in 2 subjects in the CNI group.

Up to Month 36 in the ITT-LT population, the frequency of serious infections was similar for the two treatment groups: 27% for belatacept and 28% for CNI. The IR of serious infections was 9.02/100 p-y for belatacept and 9.58 /100 p-y for CNI. More subjects treated with belatacept experienced serious urinary tract infections (9%) than subjects treated with CNI (1%).

In study IM103116, by the end of the Month 24 safety analysis period, serious infections occurred in a similar proportion of subjects in the belatacept conversion (17%) and CNI continuation groups (20%). Furthermore, the adjusted exposure rate of serious infections was similar between the 2 treatment groups: 10.2 p-y and 12.2/100 p-y for the belatacept and CNI groups, respectively.

The most commonly reported infections in the belatacept group were Urinary Tract Infection (3.2%) and Urosepsis (2.7%). The most commonly reported infections in the CNI group were Urinary Tract Infection and Pneumonia (3.2% each).

The IR of serious infections were largely comparable between the treatment arms in both studies. Serious infections are labelled in section 4.8 of the SmPC.

PML

No event of PML was reported in either study. PML is labelled in section 4.8 of the SmPC.

TB infections

A single event of tuberculosis was reported. The subject was randomised to the belatacept arm in study IM103010. Tuberculosis is labelled in section 4.8 of the SmPC.

Viral Infections

In IM103010, one serious viral infection was reported in the belatacept arm and 5 in the CNI-arm up to Month 36. In IM103116, up to Month 24, 14 serious viral infections were reported, 5 in the belatacept conversion group and 9 in the CNI continuation group.

The MAH has provided IR for viral infections in the two conversion studies and the two pivotal de novo studies. There is a marked difference in IR of viral infections between IM103010 (12.60/100 PY and 10.03/100 PY, for belatacept and CNI respectively.) and IM103116 (1.2/100 PY and 2.3/100 PY, respectively). The IR reported in IM103010 is more comparable to IRs for viral infections reported for the pivotal *de novo*-studies.

As part of the responses to request for supplementary information, the MAH provided the IR on "viral infections" for IM103116. The IR for "viral infections" was lower in IM103116 than both IM103010 and the two pivotal *de novo* studies. There was no consistent difference between the treatment arms, as the IR was higher for belatacept (14.7 vs 11.4 events/ 100 patient years) in IM103010 and lower (8.6 vs 11.9 events/ 100 patient years) in IM103116.

The risk of viral infections is reflected in the SmPC.

CNS infections

No event of CNS infection was reported in either study. The risk of CNS infections is reflected in the SmPC.

Fungal Infections

One serious fungal infection was reported throughout the studies. This was a fatal event of disseminated histoplasmosis in the CNI-arm of IM103116. This event is discussed in the above section 'Deaths'. The risk of fungal infections is reflected in the SmPC.

Infusion-related Reactions Within 24 Hours of the Start of an Infusion

All infusion-related reactions in either study were reported as non-serious. The risk of infusion-related reactions is reflected in the SmPC.

Thrombotic and Embolic Events

In IM103010 up to Month 36, two thromboembolic events were reported in the belatacept arm versus none in the CNI arm. The corresponding number fort IM103116 at Month 24 were seven events in each arm. It is however considered that the event of "thrombotic microangiopathy" reported in the CNI arm of IM103116 should not be counted here as this condition has a different aetiology than other thromboembolic events. Venous and arterial thrombosis and thrombophlebitis are labelled in section 4.8 of the SmPC for Nulojix.

Autoimmune Disease

One event of psoriasis was reported in the belatacept arm of IM103010. This does not affect the safety profile of belatacept.

Congestive Heart Failure and Pulmonary Edema

A small number of reports on congestive heart failure and pulmonary oedema was reported. There was no significant difference between the treatment arms.

Safety of Belatacept in Conversion Use Compared to Use in *De Novo* Renal Transplantation

In both conversion studies, all reported safety events, including those related to infection and malignancy, were consistent with the safety profile of belatacept as described in the approved labelling for use in *de novo* renal allograft recipients in the phase 3 pivotal studies and the corresponding long-term extensions for up to 7 years post-transplant. The maintenance dosing regimen—that of 5 mg/kg every 4 weeks, as used in both conversion studies, was the same as that administered during the maintenance phase of both pivotal phase 3 *de novo* transplant studies.

Incidence rates of key AEs of special interest in the conversion studies and *de novo* studies were similar (Table 38).

Table 38: Incidence Rate of Adverse Events of Special Interest from Studies IM103010, IM103116, IM103008, and IM103027

	Incidence Rate per 100 Patient - years									
	Conversion Studies				De Novo Studies					
	IM103010		IM103116		IM103008			IM103027		
	Belatacept (N=81)	CNI (N=81)	Belatacept (N=221)	CNI (N=222)	Belatacept MI (N=155)	Belatacept LI (N=166)	CsA (N=136)	Belatacept MI (N=104)	Belatacept LI (N=113)	CsA (N=87)
PTLD	0	0	0.2	0	0.23	0.15	0.18	0.21	0.73	0.12
Malignancies	2.89	2.62	4.4	3.1	2.09	1.51	2.78	3.38	3.25	2.94
Serious Infections	9.02	9.58	10.2	12.2	9.08	8.75	13.64	21.71	15.15	15.88
PML	0	0	0	0	0	0	0	1 subject*	0	0
TB Infections	0.42	0	0	0	0.49	0.09	0.23	0.46	0.41	0
CNS Infections	NA	NA	0	0	0.10	0	0	0.45	0.27	0
Viral Infections	12.60	10.03	1.2	2.3	14.69	13.01	12.47	17.21	14.18	13.97

Abbreviations: CNI - calcineurin inhibitors, CNS - central nervous system, LI - less intensive, MI - more intensive, PML - progressive multifocal leukoencephalopathy, PTLD - post-transplant lymphoproliferative disorders, TB - tuberculosis
*Incidence rate not available in CSR

Laboratory findings

In total, 93 events of markedly abnormal laboratory values were reported in the belatacept arm compared to 95 in the CNI arm up to 24 Months in IM103116. The corresponding values for IM103010 up to Month 36 was 30 for belatacept and 28 for CNI. Thus, there was no different in the reporting of markedly abnormal laboratory values between the treatment arms in either study.

According to the prespecified definition for "markedly abnormal" laboratory values, "absolute lymphopenia" represents $<0.5 \times 10^9$/L. Absolute lymphopenia was more common in the belatacept arms in both studies. The MAH speculates that this may be explained by adjustments of e.g. mycophenolate in association with the conversion. Notwithstanding, lymphopenia is labelled in section 4.8 of the SmPC with the frequency common.

Hypophosphataemia was more common in the belatacept arm in both studies. Hypophosphataemia is labelled in section 4.8 of the SmPC.

In IM103010 as opposed to IM103116, hypermagnesemia of "markedly abnormal" degree was more commonly reported in the belatacept arm (n=5 [6%] for belatacept versus n=1 [1%] for CNI at Month 12, and n=6 [7%] versus n=1 [1%] at Month 36). No such events were reported in IM103116. In response to request for supplementary information, the MAH discussed the imbalance in hypermagnesemia between the treatment arms in IM103010.

No AEs of elevated serum Mg levels or "hypermagnesemia" were reported in IM103010; however, six belatacept conversion patients and one CNI continuation patients met the prospectively defined criteria for "marked abnormality" at Month 18. Of these subjects, only one elevated value was observed in all subjects except in one subject, who reported two elevated values.

Mean serum magnesium in the belatacept conversion arm increased from 1.46 mEq/L at baseline to 1.66 mEq/L at Month 3 and remained stable at these levels thereafter. No such increase was seen in the CNI continuation arm. The MAH argued that persistent increase in serum Mg levels that was observed post-conversion to belatacept may be due to the presence, prior to randomisation, of a reversible component of tubular Mg wasting that previously has been described as a manifestation of CNI nephrotoxicity. This is not considered plausible. Notwithstanding, no similar increase in serum magnesium was seen in IM103116, nor in the two pivotal *de novo* studies.

Discontinuation due to adverse events

In IM103010, three subjects, two in the belatacept arm and one in the CNI arm discontinued study treatment due to AEs.

In study IM103116, the IR of study treatment discontinuation was higher in the belatacept arm, both looking at SAAs (2.5 vs 1.5) and total AEs (3.0 vs 2.0). The difference was driven by the PT Kidney transplant rejection. In total, 12 subjects discontinued study treatment due to AEs in the belatacept arm. Of those, 9 subjects in the belatacept arm (7 SAE and 2 AE) versus none in the CNI-arm reported Kidney transplant rejection as the reason for discontinuation.

Table 39: Exposure Adjusted Serious Adverse Events Leading to Discontinuation of Study Therapy Summary 24 Month Study Period All Randomized and Treated Subjects (IM103116)

	Belatacept N = 221			CNI N = 222		
SYSTEM ORGAN CLASS PREFERRED TERM	N (%)	P-Y	IR/ 100 P-Y	N (%)	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	10 (4.5)	403.9	2.5	6 (2.7)	400.2	1.5
IMMUNE SYSTEM DISORDERS	7 (3.2)	404.2	1.7	0	401.4	0
KIDNEY TRANSPLANT REJECTION	7 (3.2)	404.2	1.7	0	401.4	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (0.9)	404.9	0.5	1 (0.5)	401.2	0.2
BASAL CELL CARCINOMA	0	405.2	0	1 (0.5)	401.2	0.2
PAPILLARY THYROID CANCER	1 (0.5)	405.1	0.2	0	401.4	0
POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER	1 (0.5)	405.0	0.2	0	401.4	0
GASTROINTESTINAL DISORDERS	0	405.2	0	1 (0.5)	401.1	0.2
DIARRHOEA	0	405.2	0	1 (0.5)	401.1	0.2
INFECTIONS AND INFESTATIONS	0	405.2	0	1 (0.5)	401.2	0.2
HISTOPLASMOSIS DISSEMINATED	0	405.2	0	1 (0.5)	401.2	0.2
INVESTIGATIONS	0	405.2	0	1 (0.5)	401.2	0.2
BLOOD CREATININE INCREASED	0	405.2	0	1 (0.5)	401.2	0.2
METABOLISM AND NUTRITION DISORDERS	0	405.2	0	1 (0.5)	401.2	0.2
DIABETES MELLITUS	0	405.2	0	1 (0.5)	401.2	0.2
NERVOUS SYSTEM DISORDERS	0	405.2	0	1 (0.5)	401.2	0.2
NEUROPATHY PERIPHERAL	0	405.2	0	1 (0.5)	401.2	0.2
RENAL AND URINARY DISORDERS	1 (0.5)	405.1	0.2	0	401.4	0
ACUTE KIDNEY INJURY	1 (0.5)	405.1	0.2	0	401.4	0

P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): event count * 100/person-years of exposure.

Post marketing experience

The first approval for belatacept was granted on 15-Jun-2011 by the FDA in the US. Belatacept was approved by the European Commission in the EU initially on 17-Jun-2011.

Post-marketing reports identifying use in conversion are considered to be off-label use reports. These reports are evaluated as part of routine pharmacovigilance on an ongoing basis, and the data are summarized in the belatacept periodic safety update reports (PSURs).
In the most recent PSUR (EMEA/H/C/PSUSA/00000311/201906 - reporting period 15-Jun-2016 through 14-Jun-2019), 59 of the 84 cases of off label use during the reporting period were due to conversion from another immunosuppressant agent to belatacept. Examination of AEs from post-marketing reports involving conversion has not identified risks different from those already described for belatacept.

Overall, review of available post-marketing data presented in the most recent PSUR did not reveal any new significant safety findings for belatacept. The post-marketing data were consistent with the safety profile of belatacept as previously reported and described in the product label.

Immunogenicity

16/18 subjects with BPAR in IM103116 were negative for anti-belatacept-antibodies at all time points. Out of 2 remaining BPAR subjects, one subject was positive at baseline and at Day 15. No record of ADA testing is available for the other subject.

3/4 subjects experiencing a fatal event in IM103116 were negative at all time points whereas the remaining subject was positive only at baseline.

The single belatacept-treated subject who developed PTLD tested positive for anti-belatacept antibody, but only at baseline.

One event of infusion-related reaction assessed as related to study drug by the investigator in a subject for whom anti-belatacept antibody testing was positive at one or more time points was reported. This subject tested positive for anti-belatacept antibodies only at baseline, prior to any belatacept exposure.

In IM103010, one subject met the prospectively defined criteria required to test for NAb and tested positive at all points assessed. In IM103116, none of the subjects meeting the criteria for NAb-testing tested positive.

There was no relevant association with positive anti-belatacept antibodies and death, BPAR or infusion-related reactions.

2.5.1. Discussion on clinical safety

Adverse events

In both Study IM103010 and IM103116, most subjects in both treatment arms experienced at least one AE. In both studies, the number of subjects reporting an AE was slightly higher in the belatacept arm (98% vs 94% at Month 36 in IM103010 and 96% vs 92% at Month 24 in IM103116). All AEs reported for at least 5% of the subjects in the belatacept arm in either study are already labelled in the SmPC for belatacept.

Deaths

In total, 14 fatal events were reported up to and after the DLP of IM103010 and IM103116. Three deaths in IM103010 and seven in IM103116 were reported up to Month 36 and Month 24, respectively, and two additional deaths in each study were reported after these time points. Eight fatal events were reported in the belatacept arms and six in the CNI arms (see further details in "Death" section).
Only one fatal event was assessed as "probably associated" by the investigator; the remaining 13 events were assessed as not related.

The number of fatal events was comparable between the treatment arms. Four events, two in each treatment arm, are considered possibly related to the study drug by the assessors after secondary assessment of narratives. One additional subject reporting a fatal event possibly related to treatment had been treated with both CNI and belatacept. No cause of death indicative of a new and unexpected AE of belatacept was reported in any of the subjects.

Upon request, the MAH has provided a comprehensive a table of the IR of deaths, SAEs and AEs leading to discontinuation in IM103010, IM103116, IM103008 and IM103027 to allow for comparisons of these parameters at different time points after conversion to or *de novo* treatment with belatacept. The outcome was comparable or better in the belatacept arms of the conversion studies compared to the belatacept LI arms of both *de novo* studies.

Serious adverse events (SAE)

In IM103116, 48% of the subejcts in the belatacept arm and 43% in the CNI arm reported a SAE. The corresponding numbers for IM103010 Month 12 was 24% and 19%, respectively and for Month 36 46% and 44%.
The spectrum of SAEs reported in the belatacept arm of both studies is consistent with the known safety profile of belatacept. No new and unexpected SAEs are reported.

Adverse event of special interest (AESI)

AESI were PTLD, malignancies other than PTLD, serious infections, PML, TB infections, viral infections, CNS infections, fungal infections, infusion-related reactions within 24 hours, thrombotic and embolic events, autoimmune diseases, and congestive heart failure and pulmonary oedema.

In total, one event of *PTLD* was reported with belatacept treatment versus none in the CNI arm. The subject was EBV positive, but there is no data provided on the donor's EBV serostatus. PTLD is already labelled in sections 4.4 and 4.8 of the SmPC. No further updates are considered necessary.

The overall IR of *Malignancies other than PTLD* was higher in IM103116 compared to IM103010 and higher in the belatacept arms (4.4 vs 3.1 events/100 PY for belatacept and CNI, respectively, in IM103116, and 2.9 vs 2.6 events/100 PY in IM103010).
In total, 55 events of malignancies other than PTLD were reported, 31 in the belatacept arms and 24 in the CNI arms. Of those, 46 events (84%) were non-melanoma skin cancers (27 and 19 events in the belatacept and CNI arms, respectively). Such malignancies are labelled with the frequency common in the Nulojix SmPC. The differences between the treatment arms was entirely attributable to a higher rate of cutaneous basal cell cancer in the belatacept conversion versus CNI continuation groups (11 events [5.0%] versus 5 events [2.3%], respectively). The MAH has clarified that there were more subjects in the belatacept arm with either a prior history of skin cancer or a family of skin cancer which may indicate a higher risk for such events in the belatacept arm. Furthermore, two of the events were diagnosed within 5 days after the first dose of belatacept, precluding a causal association. All events have been presented in detail to the independent Data Monitoring Committee for study IM103116; their conclusion was that this imbalance did not represent a new safety signal. Such malignancies are labelled with the frequency common in the Nulojix SmPC.

Of the remaining malignancies reported in the belatacept arms, only Papillary thyroid carcinoma is not specifically labelled in section 4.8 of the SmPC. However, the general increased risk of malignancies is reflected in section 4.4 of the SmPC.

The IRs of *Serious infections* were largely comparable between the treatment arms in both studies. A single event of *Tuberculosis* was reported. The subject was randomised to the belatacept arm in study IM103010. One serious *Fungal infection* was reported throughout the studies. This was a fatal event of disseminated histoplasmosis in the CNI-arm of IM103116.

In IM103010, one serious viral infection was reported in the belatacept arm and 5 in the CNI-arm up to Month 36. In IM103116, up to Month 24, 14 serious viral infections were reported, 5 in the belatacept conversion group and 9 in the CNI continuation group. The MAH has provided IRs for viral infections in the two conversion studies and the two pivotal *de novo* studies. There is a difference in IR of *Viral infections* between IM103010 (14.7/100 PY and 11.4/100 PY, for belatacept and CNI respectively.) and IM103116 (8.6/100 PY and 11.9/100 PY, respectively). There was no consistent difference between the treatment arms, as the IR was higher for belatacept in IM103010 and lower in IM103116.

No events of *PML* or *CNS infections* were reported. A small number of reports on *Congestive heart failure, Pulmonary oedema* and *Thromboembolic events* with no clinically significant difference between the treatment arms was reported throughout the studies. All *Infusion-related reactions* in either study were reported as non-serious.

The MAH has provided a summary over IR of PTLD, other malignancies and serious infections in the two conversion studies compared to the two pivotal *de novo* studies. The results from the conversion studies should be compared to the "less intensive" (LI)-arm of the *de novo* studies as it is the LI posology that is approved and used in the conversion studies. Due to some differences in the eligibility criteria between IM103008 (standard criteria donors) and IM103027 (extended criteria donors), the IR for all events except Viral infections are higher in IM103027. The conversion studies could be considered more similar to IM103008. The IR of PTLD was slightly higher in IM103008, whereas the IR was lower for malignancies and slightly lower for serious infections in IM103008 compared to both conversion studies. Taken together, the results from the conversion studies are considered comparable to the results from the *de novo* studies concerning the key AESI.

In summary, there were no unexpected finding in the review of AESI in the two conversion studies. The AESI are included in section 4.4 and/or 4.8 of the SmPC of Nulojix. No further action is required.

Clinical Laboratory Evaluations

In summary, 93 events of markedly abnormal laboratory values were reported in the belatacept arm compared to 95 in the CNI arm up to 24 Months in IM103116. The corresponding values for IM103010 up to Month 36 was 30 for belatacept and 28 for CNI. Thus, there was no different in the reporting of markedly abnormal laboratory values between the treatment arms in either study.

Hypophosphataemia and Lymphopenia were more commonly reported in the belatacept arm in both studies. Both AEs are labelled in section 4.8 of the Nulojix SmPC.

In IM103010 as opposed to IM103116, hypermagnesemia of "markedly abnormal" degree was more commonly reported in the belatacept arm (n=5 [6%] for belatacept versus n=1 [1%] for CNI at Month 12, and n=6 [7%] versus n=1 [1%] at Month 36. No such events were reported in IM103116. Hypermagnesemia is not labelled for belatacept. No similar increase in serum magnesium was seen in IM103116, nor in the two pivotal *de novo* studies. The MAH has not proposed any further actions with respect to the elevated magnesium values in IM103010. This is agreed by the CHMP.

Discontinuation due to adverse events

In IM103010, three subjects, two in the belatacept arm and one in the CNI arm discontinued study treatment due to AEs.

In study IM103116, the IR of study treatment discontinuation was higher in the belatacept arm, both looking at SAEs (2.5 vs 1.5) and total AEs (3.0 vs 2.0). The difference was mainly driven by the preferred term (PT) Kidney transplant rejection. In total, 12 subjects discontinued study treatment due to AEs in the belatacept arm. Of those, 9 subjects in the belatacept arm (7 SAE and 2 AE) versus none in the CNI-arm reported Kidney transplant rejection as the reason for discontinuation.

Immunogenicity

One subject in study IM103010 tested positive for NAb to belatacept and no NAb positive subjects were identified in study IM103116. There was no relevant association with positive anti-belatacept antibodies and death, BPAR or infusion-related reactions.

2.5.2. Conclusions on clinical safety

No new and unexpected safety findings were identified for belatacept in the conversion studies. The safety profile of belatacept in the conversion setting was consistent with the known safety profile of the product. No risks different from those already described for belatacept were identified from reports of off label conversions from other immunosuppressive therapies, according to the most recent PSUR for belatacept (EMEA/H/C/PSUSA/00000311/201906). It is also not expected that the safety profile of belatacept used in a conversion setting would differ in a relevant way from the safety profile of belatacept used in a *de novo* setting. The sections 4.4 and 4.8 of the SmPC have been updated accordingly.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 18.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 18.0 with the following content:

Safety concerns

Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Missing information: Pregnancy and lactation	Routine risk minimisation measures: SmPC Section 4.6 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: To identify reports of pregnancy and characterize the event and outcomes through the use of a supplemental form. Additional pharmacovigilance activities: None.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes are also made to the product information to bring it in line with the QRD template version 10.1 and requirement on sodium excipients is added. Editorial changes have been made in the labelling.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- The readability of the PL of Nulojix (belatacept), in English, was assessed during the assessment of the initial MAA and accepted by CHMP;
- The new indication that is hereby applied for concerns the same route of administration and has a similar safety profile as the previously approved indication (i.e., key safety messages for the existing and new applied for indication are essentially the same);
- Administration of Nulojix is done by a health care professional. The instructions for dose calculation, preparation, administration, storage and disposal that are currently reflected in the approved PL were also successfully tested as part of the user consultation performed for the initial MAA and remain unchanged;
- The general design and layout of the proposed PL have not changed compared to the tested one.

Overall, the proposed leaflet shares large text sections with the reference one. The modifications now proposed in the package leaflet (i.e., those relevant to the new indication) do not represent major changes. This is agreed by the CHMP.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Renal transplantation is the preferred treatment for ESRD because it confers improved survival and quality of life over dialysis.

In 2017, more than 88,000 subjects across Europe started renal replacement therapy, i.e. starting dialysis or receiving a pre-emptive renal transplantation (a renal transplantation without preceding dialysis) for ESRD, according to the 2017 European renal association/ European Dialysis and Transplant Association (ERA-EDTA) Annual report[3]. Common causes of ESRD include hypertension, diabetes and primary renal diseases, e.g. glomerulonephritis. Renal transplantation is the most effective treatment for ESRD; however, requires lifelong immunosuppressive therapy to prevent immune-mediated allograft injury. On 31 December 2017, over 200,000 subjects in the ERA-EDTA registry were living with a functioning graft after renal transplantation.

3.1.2. Available therapies and unmet medical need

With renal transplantation, maintenance rejection prophylaxis typically consists of a triple immunosuppression therapy including a CNI, most commonly TAC or CsA, an antimetabolite (most often mycophenolate) and steroids. However, the CNIs have been shown to directly contribute to long-term allograft loss and death, because they are inherently nephrotoxic, and may also contribute to the development or exacerbation of cardiovascular comorbidities, including hypertension, hypercholesterolemia, and diabetes mellitus. Therefore, there is an unmet medical need for immunosuppressive agents that can provide control of the alloimmune response comparable to CNIs without the renal and cardiovascular toxicities that may contribute to long-term graft loss and death.

Belatacept represents a class of selective co-stimulatory immunomodulators approved in the EU in 2011 for prophylaxis of graft rejection in adults receiving a renal transplant, i.e., treatment with belatacept should be initiated in immediate association to renal transplantation, as a substitution for a CNI in a triple immunosuppressive therapy. However, according to the MAH, it is currently estimated that approximately 80% of belatacept in clinical practice is used in conversion from a CNI-based therapy to belatacept, months to years after the transplantation. The MAH therefore proposed a modification to the current indication statement to include the conversion use. Of note, the risk of graft loss and/or acute rejections is highest in the early post-transplantation period, slowly decreasing over 6-12 months. This period is already covered by the approved indication.

3.1.3. Main clinical studies

The efficacy and safety of belatacept in the conversion setting was evaluated in two studies, the pivotal phase-3 study IM103116 and the supporting phase-2 study IM103010.

IM103116 was a randomised, open-label, active-controlled, parallel-group study. 446 subjects on CNI-based regimens were randomised in a 1:1 ratio to either convert to treatment with belatacept 5 mg/kg IV on days 1, 15, 29, 43, 57, and every 28 days, or to continue treatment with their established CNI. Subjects randomised to belatacept were to discontinue CNIs on Day 29. The duration of study

[3] https://www.era-edta.org/en/registry/publications/annual-reports/

participation was 24 months with a subsequent 8-week follow-up period for safety post last dose. The primary (descriptive) composite endpoint was the proportion of subjects who survived with a functioning graft at Month 24. Mean change in cGFR from baseline to 24 months post randomisation and BPAR were secondary endpoints.

IM103010 was a randomised, open-label, active-controlled, parallel-group study. 84 subjects were randomised to conversion to belatacept as described for IM103116 and 89 to continue treatment with CNI. The duration of the study was 12 months with a subsequent 8-week follow-up period for safety evaluation. The primary (descriptive) endpoint was renal function (change in eGFR from baseline) at 12 months. 12 Month survival with functional graft and BPAR were secondary endpoints.
All subjects who completed the 12-month phase of the initial study were eligible to participate in a LTE. In the LTE-population (ITT-LT), baseline values for the subset of subjects entering the LTE were used as baseline; therefore e.g. "baseline cGFR" in the IM103010 ITT population differs slightly from "baseline cGFR" in the IM103010 ITT-LT population.

3.2. Favourable effects

None of the studies used formal statistical hypothesis testing; therefore, all data presented below are descriptive.

The efficacy data indicate that conversion from CNI to belatacept did not impair graft or subject survival up to 24 and 36 months, respectively, in IM103116 and IM103010 studies. In IM103116, 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. Four patients (1.8%) in each group had died and two (0.9%) in the CNI continuation group had lost a graft. In IM103010, 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. 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.

In both studies, there was a larger improvement in mean cGFR change compared to baseline in the belatacept arm. In IM103116, 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. 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).

With regard to BPAR, although a higher incidence of BPAR was shown comparing belatacept and CNI in the conversion studies, the data does not indicate a higher rate of BPAR in the conversion studies than in the pivotal *de novo* studies.
In IM103116, 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.
In IM103010, at Month 12 BPAR was reported in 7.1% (6/84) patients in the belatacept conversion group and none in the CNI continuation group. 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.

Overall, in the conversion setting, the number of BPAR reported after Month 12 were comparable between the treatment arms indicating that the increased risk of BPAR with belatacept compared to CNI is not maintained. This is consistent with the finding that the development of *de novo* donor specific antibodies, considered a risk factor for rejection and graft loss, was smaller in the belatacept arm of the conversion studies (Table 25).

The section 4.4 of the SmPC has been updated to reflect that 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. The section 5.1 of the SmPC has also been updated to reflect the above conversion studies results.

Additional secondary and exploratory endpoints in both studies included effect on lipid profiles, new onset of diabetes, blood pressure and self-reported quality of life-assessments. The MAH does not make any claim in the SmPC concerning these outcomes, which is agreed by the CHMP and in line with the SmPC guideline. The differences between the treatment arms were generally modest and no safety concern was raised by the results.

3.3. Uncertainties and limitations about favourable effects

The conversion studies (IM103116, IM103010) showed weaknesses regarding the study design (open label) and statistical methodology such as inadequate statistical model for testing a non-inferiority hypothesis between the descriptive objectives and the used inferential statistical methods. However, CHMP considered that these did not have an impact on the data integrity and that the presented descriptive results could allow for a sufficiently robust assessment of the benefit-risk balance of Nulojix in the proposed indication (see "Discussion on clinical efficacy").

The proposed wording of section 4.1 of the SmPC is "*Nulojix, in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for prophylaxis of graft rejection in adult recipients of a renal transplant*". However, the patient population included in the conversion studies was narrowed. Indeed, the eligibility criteria restrict the study population by excluding subjects with cGFR <30 (<35 in IM103010) and >75 mL/min/1.73m^2 and limiting inclusion of subjects with a history of acute rejections and high immunological risk. It is assumed that the upper limit of cGFR for inclusion was set to identify subjects with beginning CNI toxicity, which is considered a subpopulation with a need for non-CNI based immunosuppression. Likewise, it is supposed that the lower cGFR limitation was set to exclude subjects with extensive chronic allograft nephropathy, less likely to benefit from conversion to another immunosuppressive therapy. However, there are other clinical situations in which the use of belatacept may be advantageous, for example in subjects with AEs on CNI. Furthermore, in subjects with poor compliance, it is agreed with the MAH that the use of belatacept given in a health care setting every four weeks would be a better option. There is no reason to assume that the efficacy of belatacept in the conversion setting in subjects with better renal function than 75 mL/min/1.73m^2 would be different from that reported in the studies. In the original MAA, no clinically relevant effects on belatacept clearance was seen with decreased renal function. This is reflected in the approved SmPC including a wording in section 4.2 that no dose adjustment is recommended in patients with renal impairment or undergoing dialysis. The CHMP agrees therefore that the results from the studies can be extrapolated to subjects with all levels of renal function and therefore, the broad population in the proposed wording

of section 4.1 of the SmPC is accepted. The eligibility criteria further restrict the study population by excluding subjects with high immunological risk. This has been addressed in section 4.4 of the SmPC which states that "*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*."

In summary, there are no remaining uncertainties about favourable effects of Nulojix in the proposed indication.

3.4. Unfavourable effects

In both conversion studies, the number of subjects reporting an AE was slightly higher in the belatacept arm compared to placebo (98% vs 94% at Month 36 in IM103010 and 96% vs 92% at Month 24 in IM103116). All AEs reported for at least 5% of the subjects in the belatacept arm in either study are already labelled in the SmPC for belatacept.

In total, 14 fatal events were reported up to and after the DLP of IM103010 and IM103116. Three deaths in IM103010 and seven in IM103116 were reported up to Month 36 and Month 24, respectively, and two additional deaths in each study were reported after these time points. Eight fatal events were reported in the belatacept arms and six in the CNI arms

Only one fatal event was assessed as "probably associated" by the investigator; the remaining 13 events were assessed as not related.

In IM103116, 48% (n=107) of the subjects in the belatacept arm and 43% (n=95) in the CNI arm reported a SAE. The corresponding numbers for IM103010 Month 12 was 24% and 19%, respectively, and 46% and 44% for Month 36.

The system organ class (SOC) with the most reported SAEs in both studies and both treatment arms was Infections and infestations, reported by approximately 60% of the subjects with a SAE in IM103010 at Month 36. In IM103116, the three SOCs with most commonly reported SAEs in the belatacept arms were Infections and infestations (37 subjects), Immunosystem disorders (19 subjects) and Neoplasms (18 subjects). In the CNI arm, 44 subjects reported SAEs in the SOC Infections and infestations, 9 subjects in the SOC Immunosystem disorders and 13 subjects in the SOC. Of note, all SAE in the SOC Immunosystem disorders for belatacept represented Kidney rejection.

In IM103010, three subjects, two in the belatacept arm and one in the CNI arm discontinued study treatment due to AEs.

In study IM103116, the IR of study treatment discontinuation was higher in the belatacept arm. The difference was mainly driven by the PT Kidney transplant rejection. In total, 12 subjects discontinued study treatment due to adverse events in the belatacept arm. Of those, 9 subjects in the belatacept arm (7 SAE and 2 AE) versus none in the CNI-arm reported Kidney transplant rejection as the reason for discontinuation.

Among the AESI were PTLD, malignancies other than PTLD, serious infections, PML, TB infections, viral infections, CNS infections, fungal infections and infusion-related reactions within 24 hours.

In total, one event of PTLD in an EBV seropositive subject was reported with belatacept treatment versus none in the CNI arm.

55 events of malignancies other than PTLD were reported, 31 in the belatacept arms and 24 in the CNI arms of the studies. Of those, 46 events (84%) were non-melanoma skin cancers including basal cell cancer (27 and 19 events in the belatacept and CNI arms, respectively).

The IRs of serious infections were largely comparable between the treatment arms in both studies (27% for belatacept and 28% for CNI up to Month 36 in IM103010, and 17% for belatacept and 20% for CNI up to Month 24 in IM103116). A single event of tuberculosis was reported. The subject was randomised to the belatacept arm in study IM103010. One serious fungal infection was reported throughout the studies. This was a fatal event of disseminated histoplasmosis in the CNI-arm of IM103116.

In IM103010, one serious viral infection was reported in the belatacept arm and 5 in the CNI-arm up to Month 36. In IM103116, up to Month 24, 14 serious viral infections were reported, 5 in the belatacept conversion group and 9 in the CNI continuation group.

No events of PML or CNS infections were reported.

In summary, 93 events of markedly abnormal laboratory values were reported in the belatacept arm compared to 95 in the CNI arm up to 24 Months in IM103116. The corresponding values for IM103010 up to Month 36 was 30 for belatacept and 28 for CNI. Hypophosphataemia and Lymphopenia were more commonly reported in the belatacept arm in both studies.

No subject in either study was reported with neutralising antibodies to belatacept. There was no relevant association with positive anti-belatacept antibodies and death, BPAR or infusion-related reactions.

The overall safety profile of belatacept in the two conversion studies was consistent with the known safety profile in the existing clinical population from studies in newly transplanted patients. No new adverse drug reaction is therefore proposed to be included in the section 4.8 of the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

The causal attribution of deaths was questioned during the assessment. Four events, two in each treatment arm, are considered possibly related to the study drug. One additional subject reporting a fatal event possibly related to treatment had been treated with both CNI and belatacept. However, this does not affect the overall conclusion, as no cause of death indicative of a new and unexpected AE of belatacept was reported in any of the subjects.

The MAH addressed during the procedure a small number of issues regarding safety, for example the IR of deaths, SAEs and AEs leading to discontinuation in the conversion studies compared to the pivotal *de novo* studies, an increased rate of non-melanoma skin cancers in the belatacept arm of IM103010 and the IR of viral infections in different studies. No further actions are considered warranted.

3.6. Effects Table

Table 40 Effects Table for Nulojix (conversion setting)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Death /graft loss	24-Month survival with functioning graft	n/N (%)	219/223 (98%)	217/223 (97%)		**IM103116**
Death /graft loss	36-Month survival with functioning graft	n/N (%)	82/84 (98%)	87/89 (98%)		**IM103010**
cGFR	Change from baseline cGFR Month 24	mL/min/1.73 m^2 (95% CI)	6.2 (4.7, 7.7)	-1.0 (-2.6, 0.5)	Treatment difference: 7.2 mL/min/1.73 m^2 Uncertainty: method of imputation	**IM103116**
cGFR	Change from baseline cGFR Month 12	mL/min/1.73 m^2 (SD)	7.0 (12.0)	2.6 (9.5)	Treatment difference: 4.9 mL/min/1.73 m^2 Uncertainty: method of imputation	**IM103010**
cGFR	Change from baseline cGFR Month 36	mL/min/1.73 m^2 (SD)	9.9 (12.6)	2.8 (14.1)	Treatment difference: 7.1 mL/min/1.73 m^2 Uncertainty: method of imputation	**IM103010**
DSA	Subjects developing DSA through Month 24	n/N (%)	2/223 (1%)	14/223 (7%)		**IM103116**
DSA	Subjects developing DSA through Month 12 #	n/N (%)	0/84 (0%)	1/89 (1.1%)		**IM103010**
Unfavourable Effects						
BPAR	Subjects with BPAR through Month 24 *	n/N (%)	18/223 (8.1%)	6/223 (2.7%)		**IM103116**
BPAR	Subjects with BPAR through Month 36 **	n/N (%)	7/84 (8.3%)	3/89 *** (3.4%)		**IM103010**
Death	Number of fatal events	n	8	6		**Both studies**
PTLD	Number of subjects with PTLD	n	1	0		**Both studies**
Malignancies	Malignancies other than PTLD (of which non-melanoma skin cancer including BCC)	n	31 (27)	24 (19)		**Both studies**
Serio	Proportion of	%	17	20		**IM103116**

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
us infecti ons	subjects with serious infections through Month 24					
Serio us infecti ons	Proportion of subjects with serious infections through Month 36	%	27	28		**IM103010**

Abbreviations: BCC basal cell cancer BPAR Biopsy proven acute rejection; cGFR calculated glomerular filtration rate; DSA donor specific antibodies; PTLD post-transplant lymphoproliferative disease;

Notes: # No measurements of DSA were performed after Month 12 in IM103010 * 0/18 events in the belatacept arm and 3/6 events in the CNI arm occurred after Month 12 ** 1/7 events in the belatacept arm and 3/3 events in the CNI arm occurred after Month 6. *** One additional subject in the CNI arm reported a BPAR after Month 36.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Belatacept is approved since 2011 in adult subjects receiving a renal transplant. In this context, belatacept is used as a substitution for a CNI in a triple immunosuppressive therapy "*de novo*'" setting. The intended new population in the conversion setting of adult renal transplant recipients, is similar to the approved population in all aspects except that these patients have received CNI since the transplantation. Therefore, the present indication is supported to a large extent by existing data. Therefore, the lack of formal statistical testing in the conversion studies was found acceptable to the CHMP.

Data from the conversion studies indicate that the efficacy of belatacept in the conversion setting is comparable to the efficacy in the approved "*de novo*" setting concerning the key efficacy endpoints survival with functioning graft. In both studies, 98% of the subjects in the belatacept arms survived with a functioning graft up to Month 24 and Month 36 for IM103116 and IM103010, respectively. These results strongly support efficacy of belatacept treatment in the conversion setting. The number of BPAR was numerically lower in both treatment arms in the conversion studies compared to the "*de novo*"-studies. This finding was expected as most episodes of acute rejections are normally reported in the early post-transplant period. Altogether, the available data support the efficacy claim in the proposed extended indication. No new and unexpected safety findings were identified in the conversion setting studies compared to the known safety profile of belatacept.

It is notable that the proposed target population is broader than the study population, as eligibility criteria included restriction both to renal function and immunological risk. It is however considered acceptable to extrapolate the study results to all levels of renal function. There is no reason to assume that the efficacy of belatacept in the conversion setting in subjects with better renal function than 75 mL/min/1.73m^2 would be different from that reported in the studies. Furthermore, data provided in the original MAA showed no clinically relevant effects on belatacept clearance was seen with decreased renal function. The restrictions to immunological risk have been reflected in the SmPC.

3.7.2. Balance of benefits and risks

The efficacy data from the 2 clinical studies in the conversion setting indicated that conversion from CNI to belatacept did not impair graft or subject survival up to 24 and 36 months, respectively, in the conversion setting. In both studies, there was a larger improvement in mean cGFR change compared to baseline in the belatacept arm. Furthermore, although a higher incidence of BPAR was shown comparing belatacept and CNI in the conversion studies, the data does not indicate a higher rate of BPAR in the conversion studies than in the pivotal *de novo* studies. The majority of BPAR in the belatacept arm occurred during the first year of treatment.

The overall safety profile of belatacept in the two conversion studies was consistent with the known safety profile in the existing clinical population in *de novo* renal transplant populations

In conclusion, efficacy and safety in the conversion setting is comparable to the approved "*de novo*" indication.

3.8. Conclusions

The overall benefit/risk balance of belatacept used in conversion from a CNI-based regimen to a belatacept-based regimen post transplantation in combination with corticosteroids and a mycophenolic acid, for prophylaxis of graft rejection in adult recipients of a renal transplant is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include the use of belatacept in conversion from a calcineurin inhibitor - based regimen to a belatacept-based regimen post transplantation; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 18.0 of the RMP has also been updated. Furthermore, the product information is brought in line with the latest QRD template version 10.1 and requirement on sodium excipients is added. Editorial changes have been made in the labelling.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion "Nulojix EMEA/H/C/002098/II/0070".

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted)