14 September 2017
EMA/648206/2017
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Nulojix

belatacept

Procedure no: EMEA/H/C/002098/P46/022

Note

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

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List of abbreviations

AE	Adverse event
AR	Acute rejection
cGFR	Calculated glomerular filtration rate
CNI	Calcineurin inhibitor
CSR	Clinical study report
DSA	Donor specific antibodies
EBV	Epstein-Barr virus
EC-MPS	Enteric coated mycophenolate sodium
MAH	Market authorisation holder
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
PDCO	Paediatric committee (EMA)
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PTLD	Post-transplant lymphoproliferative disorder
RfM	Request for modification
PML	Progressive multifocal leukoencephalopathy
RO	Receptor occupancy
SAE	Serious adverse event
SD	Singel dose
SOC	System organ class

1. Introduction

On 29-May-2017, the MAH submitted a completed paediatric study for Nulojix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study IM103144 (*A phase 2 multi-center, randomized conversion study to evaluate the pharmacokinetics, efficacy, and safety of belatacept administered to pediatric subjects with stable renal transplant)* is part of a clinical development program. A line listing of all the concerned studies is annexed.

A paediatric investigation plan (PIP, EMEA-000157-PIP01-07) for Nulojix powder for concentrate for solution for infusion for intravenous use was agreed upon by the PDCO (P/99/2008), and received an EMA decision on 3-Nov-2008. The PIP has been modified three times with EMA decisions received on 16-May-2012 (P/0083/2012), 10-Apr-2015 (P/0080/2015) and 12-Jan-2017 (P/0002/2017) and is comprised of 5 non-clinical studies and 2 clinical studies.

Initially, study IM103144 was the only clinical study in the PIP. However this study was the subject of the second modification (P/0080/2015).
At the outset, protocol IM103144 originally was designed as a 2-part study in stable paediatric renal allograft recipients 6 to <18 years old, with the following design:
Part I was planned to be a Phase 1 safety, tolerability and pharmacokinetic (PK) study of single-dose (SD) belatacept administration to each of 9 adolescents (13 to <18 years old) and 6 younger children (6 to 12 years old) receiving a stable regimen of maintenance immunosuppression per local standard of care. Part I was to be followed by an “observation period” of approximately 4-months for dose determination.
Part II was to begin as a prospective, 1:1 randomized, open-label safety and tolerability study of conversion of maintenance renal allograft recipients from a calcineurin inhibitor (CNI) - to a belatacept-based immunosuppressive regimen at least 6 months post-transplant. The 15 subjects who participated in Part I were to be randomized to Part II along with an additional, newly enrolled ~39 adolescent and 6-12 year-old subjects.

During the first year of study enrolment, a number of the participating paediatric nephrologist investigators indicated that the benefit-risk of treatment with belatacept to younger children is less favourable than that for adolescents. The rationale for this assessment was that children are increasingly likely to be seronegative for prior exposure to Epstein-Barr virus (EBV) the younger they are (EBV seropositivity is a requirement for treatment with belatacept), and that compliance with orally administered maintenance immunosuppressive drugs is measurably better in younger children than in adolescents, due to ongoing parental supervision in this regard. Therefore, adolescent renal transplant recipients were considered to represent the paediatric population with the more clearly defined unmet medical need.

A major request for modification (RfM) was submitted to the PDCO on 22-Dec-2014, with the following proposals:

- Secure a waiver for the existing requirement to study paediatric renal allograft recipients 6 to 11 years of age;
- Limit the SD PK portion of IM103144 to the evaluation of 9 stable, adolescent renal allograft recipients;
- Cancel Part II of the study and replace it with a separate Phase 2 adolescent conversion study.

The second RfM was approved on 10-Apr-2015 and the design of the study was limited to that of a SD PK, safety, and tolerability trial in 9 adolescent subjects (from 12 to less than 18 years of age) in stable renal transplant recipients receiving a calcineurin inhibitor (CNI) based maintenance immunosuppressant therapy.

The Phase 2 study, which became the second clinical study in the current PIP, will evaluate the safety, efficacy, and PK of belatacept administered to adolescents aged 12 to less than 18 years with stable renal transplant. This trial is to be conducted upon demonstration of satisfactory safety and efficacy data from an ongoing study in adults (IM103116).

2.2. Information on the pharmaceutical formulation used in the study

Nulojix (belatacept) powder for concentrate for solution for infusion is distributed in 250 mg vials. Commercial belatacept has been used during the study.

2.3. Clinical aspects

2.3.1. Introduction

Belatacept is a fusion protein that binds to the B7 receptors on the surface of antigen-presenting cells, inhibiting requisite co-stimulation for T-cell activation. In combination with corticosteroids and mycophenolic acid (MPA), belatacept is approved for prophylaxis of graft rejection in adults receiving a renal transplant.

The MAH submitted a final report for IM103144 (*A phase 2 multi-center, randomized conversion study to evaluate the pharmacokinetics, efficacy, and safety of belatacept administered to pediatric subjects with stable renal transplant).*

2.3.2. Clinical study IM103144

2.3.2.1. Description

This was an open-label, multi-centre, SD PK study in stable EBV+ adolescent renal transplant recipients between 12 to 17 years of age who were continuing to receive CNI-based maintenance immunosuppression, and concomitant therapy with Mycophenolate mofetil (MMF) or enteric coated mycophenolate sodium (EC-MPS), for at least 6 months post-transplant. Initially, concomitant maintenance therapy with corticosteroids was required, but it was then made optional based upon the local standard of care, when the second part of the study was cancelled.

As indicated in section 2.1, the study was subject to a major modification 10-Apr-2015 (P/0080/2015), where children under the age of 12 were omitted from the study and the planned Part II was cancelled (for details, please refer to section 2.1). As a result of the prolonged period of subject recruitment for Part I, 7 of the 9 subjects had been participating in the study for more than 6 months after single dose

(SD) belatacept administration, while awaiting the start of Part II of the study per the original protocol design. With the cancellation of Part II, an end of study visit had been incorporated into Amendment 04, which the 7/9 subjects then completed. The duration of study participation for these 7 subjects was up to 22 months. The remaining 2 subjects were enrolled under Amendment 04 and participated for the specified 6 month period in the revised protocol.

2.3.2.2. Methods

Objective

The primary objective after protocol modification April 2015 was to evaluate the PK of single-dose belatacept in stable EBV+ paediatric renal transplant recipients, 12-17 years old.

The secondary objectives were to assess the safety and tolerability of a SD belatacept administration in stable EBV+ adolescent renal allograft recipients, 12 - 17 years old, on the following:

- Cumulative incidence of adverse events including death and graft loss
- Immunogenicity (IMG) of belatacept
- Development of donor specific antibodies (DSA)
- Proteinuria (albumin/creatinine ratio)
- PD (CD86 RO)
- Relationship between PK and PD (CD86 RO)

Study design

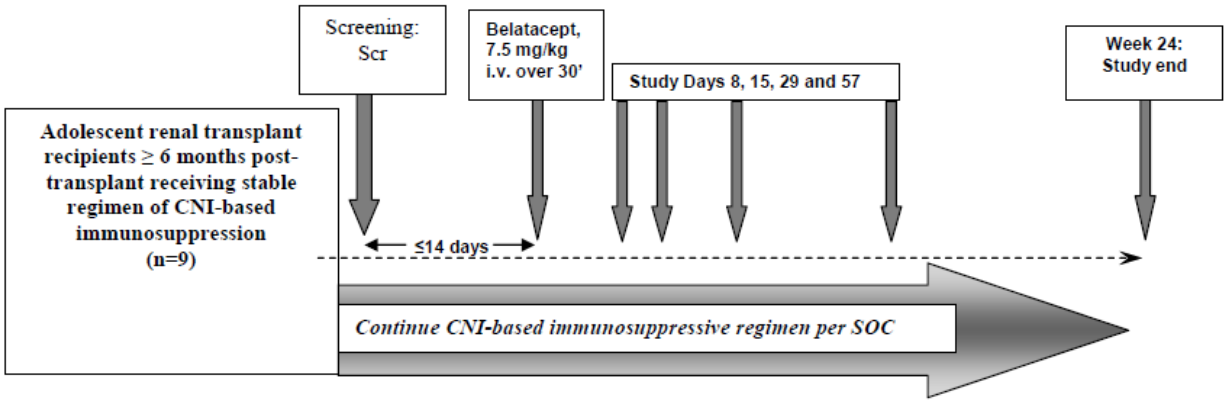
Nine adolescent subjects were enrolled to assess PK, safety and tolerability. A follow-up period occurred for subjects who completed the study or discontinued prior to the end of the study. All subjects received one infusion of belatacept 7.5 mg/kg IV over approximately 30 minutes.

The primary outcome of interest was PK, which was assessed following completion of the study.

The overall duration of study participation was approximately 6.5 months and included up to a 14 day screening period, a 30 minute SD infusion of belatacept, an 8 week (Day 57) post dose follow-up visit and a 24 week (safety follow-up/end of study) telephone or clinic visit. Adverse event (AE) monitoring continued from the time of obtaining written informed consent through the Week 24 telephone follow-up contact. The study design is summarised in Figure 1.

The date of first patient first visit was 28-Oct-2013. Last patient, last visit for this study was 06 Dec 2016.

Figure 1



Assessmentcomment:

The study protocol underwent a major modification with EMA decisions received on 10-Apr-2015 (P/0080/2015). As a result of the modification, the duration of study participation for 7/9 subjects was up to 22 months. The primary objective was to evaluate the PK of single-dose belatacept.

Study population /Sample size

The target population included male and female subjects, 12 to 17 years of age (up to but not including the date of their 18th birthday).

Subjects eligible for study inclusion were to meet the following criteria:

- EBV seropositive adolescent recipients of a renal allograft from a living donor or a deceased donor at least 6 months prior to enrolment,
- Receiving CNI-based maintenance immunosuppression since the time of renal transplantation in accordance with the local standard of care,
- Stable renal function, in the opinion of the investigator, with a cGFR ≥45 mL/Min/1.73m^2 at the time of enrolment (per updated Schwartz Formula),
- Receiving adjunctive maintenance immunosuppression with MMF or EC-MPS/MPA,
- Receiving maintenance corticosteroids in accordance with the local standard of care (optional requirement after implementation of Amendment 04), and
- Negative testing for latent infection with M. tuberculosis by an Interferon Gamma Release Assay (IGRA), such as the QuantiFERON®-TB Gold test or the T- Spot®- TB.

Subjects excluded from study participation were those who met one or more of the following criteria:

- EBV serostatus negative or unknown at the time of transplant and screening;
- Any history of biopsy proven, or clinically suspected and treated AR (acute rejection) (independent of biopsy findings) within 3 months prior to enrolment;
- Recipients of a renal allograft from a genetically identical donor;
- Biopsy-confirmed recurrence of primary focal segmental glomerulosclerosis or Type I or II membranoproliferative glomerulonephritis;

- A history of atypical hemolytic uremic syndrome/thrombotic thrombocytopenic purpura;
- Recipient of a concurrent solid organ (heart, liver) or cell (islet, bone marrow, stem cell) transplant;
- Recipient of paired kidneys (dual or en bloc kidney transplants)

Treatments

All subjects received a single dose of belatacept 7.5 mg/kg intravenously over 30 minutes.

Assessment comment:

The approved adult dose is 10 mg/kg at established time points during the first 12 weeks after transplantation and 5 mg/kg every fourth week after week 12.

Outcomes/endpoints

Primary endpoint:

- Pharmacokinetic Measures: Cmax, Tmax, AUC (0T), AUC (INF), T-HALF, CLT, and Vss.

  PK samples were drawn on the following days: pre-dose on Day 1, 30 minutes and 2 hours after start of infusion on Day 1, 2 hours post-dose on Day 1; and Days 8, 15, 29, and 57.

Secondary endpoints:

- Safety Outcome Measures: AE, SAE, and AE leading to early discontinuation. As part of the comprehensive safety evaluation of belatacept, the sponsor identified AEs that may be associated with the use of immunomodulatory drugs. Specific events within the categories of autoimmune disorders and injection site AEs will be identified. Autoimmune disorders, injection site AEs, infections and malignancies will be classified as 'AEs of interest.' These AEs are a subset of all AEs, and include serious and non-serious AEs. Subjects will be followed until 24 weeks after discontinuation for safety evaluation.
- Immunogenicity Measures: Antibody titers against belatacept will be measured using a previously validated electrochemi-luminescence assay method. Immunogenicity samples will be assayed for the presence of anti-belatacept antibody at Baseline/Day 1, Days 15, 29, and 57, at the time of any episode of acute rejection or suspected diagnosis of PTLD (post-transplant lymphoproliferative disorder), and after early discontinuation of study drug. Lack of immunogenicity will be defined as the absence of a positive response.
- Pharmacodynamic Measures: Blood samples collected at selected time points following the SD belatacept infusion will be assessed for CD86 receptor occupancy (RO) and its relationship to belatacept serum concentrations will be explored. Samples will be collected at Baseline/Day1, Day 29 and Day 57 and after early discontinuation of study drug.
- Donor Specific Antibodies: Blood samples collected at selected time points will be assayed for the presence of HLA Class I and Class II donor specific antibodies (DSA), along with the Median Fluorescence Intensity (MFI) levels.

Statistical Methods

The number of subjects that were enrolled and received SD belatacept was not based on statistical power considerations. For all PK, safety, and immunogenicity measures, missing values will not be imputed.

Individual subject PK parameter values were derived by noncompartmental methods.

Measurement of biomarkers and anti-belatacept antibodies

Donor specific antibodies (DSA): A by-subject listing of DSA results were reported by study visit for all treated subjects. Blood samples were collected at screening and at the time of any suspected acute rejection (AR)/PTLD. The listing included particular Class I and Class II DSA detection status, along with the corresponding fluorescence intensity (MFI) levels, at each of the available time points.

CD86 RO: Blood samples collected at selected time points were assessed for CD86 RO and its relationship with belatacept serum concentrations was summarized and explored. Samples were collected at baseline (Day 1 pre-dose), Day 1 (0.5 hours post-dose), Day 29, and Day 57.

Immunogenicity: Anti-belatacept antibody was assessed for the impact on PK and safety. The timing of emergence, persistence and transience was examined for correlation to PK and safety. Immunogenicity response was determined by the comparison of antibody specificity and the corresponding titre relative to their baseline level (prior to infusion on Day 1). A by-subject listing of immunogenicity responses by time was provided. The relationship between immunogenicity response and PK (total body clearance) was explored graphically.

2.3.2.3. Results

Recruitment / Number analysed

Table 1 Subject Disposition - All Enrolled Subjects

	Belatacept
SUBJECTS ENROLLED[a]	16
SUBJECTS ENROLLED BUT NOT TREATED	7 (43.8)
SUBJECTS TREATED	9 (56.3)
SUBJECTS COMPLETED DAY 57	9 (56.3)
SUBJECTS NOT COMPLETING DAY 57	0
SUBJECTS CONTINUING IN THE STUDY (BYOND DAY 57)	9 (56.3)
SUBJECTS NOT CONTINUING IN THE STUDY	0
SUBJECTS COMPLETED THE STUDY (WEEK 24)	9 (56.3)

Seven subjects were not treated: 1 subject withdrew consent, and 6 subjects no longer met study criteria. All 9 treated subjects continued in the study (beyond Day 57) and completed the follow up visit. No subjects that were treated with a SD infusion of belatacept were discontinued from the study.

Assessor's comment:

9/16 enrolled patients were treated. The main reason for not being treated (6/7 subjects) was that study criteria were no longer met. All treated subjects completed the study.

Baseline data

Table 2 Baseline Demographics of Transplant Recipients - All Treated Subjects
(adopted from CSR Table 5.3.1.1-1)

	Belatacept (N=9)
Age (Years) Mean (min; max)	 15.1 (13; 17)
Weight (kg) Mean (min; max)	 59.1 (37.6;103.5)
Gender Male (N; %) Female (N; %)	 5 (55.6) 4 (44.4)
Race White (N; %) Black or African American (N; %)	 5 (55.6) 4 (44.4)
Ethnicity Hispanic or Latino (N; %) Not Hispanic or Latino (N; %)	 4 (44.4) 5 (55.6)
Region North America (N; %)	 9 (100.0)

The mean age of the donor population was 30 years, with a range of 12 to 55 years. Six of the donors were male, 3 were female, 4 were white, and 5 were black or African American.

Five allograft recipients did not have previous transplants, while the remaining 4 had 1 previous transplant. All 9 were at least 6 months post-transplant at the time of study participation. All 9 treated subjects had panel-reactive antibody titers < 20% at the time of transplantation. One subject had a history of type 2 diabetes mellitus, 7 subjects had hypertension, and 1 subject had hypercholesterolemia. The primary causes of end stage renal disease were glomerular disease (N=1); renovascular and other vascular diseases (N=1); congenital, rare familial, and metabolic disorders (N=2); and other (N=3); the cause of end-stage renal disease (ESRD) was missing for 2 subjects.

At the time of transplantation, 5 of the 9 adolescents were CMV seronegative; the donors were CMV-positive in 3, CMV-negative in 1, and CMV serostatus unknown in 1. Of the 4 CMV seropositive adolescents, 3 had received their kidneys from CMV-positive donors, and 1 from a CMV-negative donor. All 9 adolescent transplant recipients were EBV seropositive; for all but 1, the donors were also EBV-positive.

At the time of the screening evaluation, all information from the past medical history, and all physical findings for each subject were consistent with the inclusion/exclusion criteria of the study protocol. Prior and concomitant medications reported for all treated subjects also were acceptable per protocol and consistent with those typically prescribed for adolescent renal transplant recipients. None of the medications prescribed for treatment of AEs reported during the study were prohibited per protocol.

Assessment comment:

All 9 treated subjects were 13 to 17 years of age, with a mean age of 15 years. Five subjects were male, 4 were female; 5 were white, and 4 were black or African American.

The study is small but balanced regarding gender and race. This is acceptable.

Pharmacokinetic results

The results are provided in Table 3.

Table 3 Summary Statistics of Belatacept PK Parameters

Parameter Statistic	Belatacept
Cmax (µg/mL)	
Geo Mean [N]	151 [9]
(CV%)	(20)
Tmax (h)	
Median [N]	0.733 [9]
(Min, Max)	(0.450 - 2.05)
AUC(0-T) (h*µg/mL)	
Geo Mean [N]	15145 [9]
(CV%)	(25)
AUC(INF) (h*µg/mL)	
Geo Mean [N]	15407 [9]
(CV%)	(25)
T-HALF (h)	
Mean [N]	173 [9]
(SD)	(46.8)
CLT (mL/h/kg)	
Geo Mean [N]	0.483 [9]
(CV%)	(27)
Vss (L/kg)	
Geo Mean [N]	0.088 [9]
(CV%)	(30)

Assessment comment:

The MAH put forward that the single dose PK profile seen in the adolescent subjects in this study is similar to the PK disposition of belatacept seen in adults. This is agreed to. In adults, a mean terminal half-life of approximately 8 days, a Vss of 0.099 L/kg and a total body clearance of 0.46 mL/h/kg has previously been reported.

Pharmacodynamic results

DSA Results: Testing for donor-specific antibodies (anti-HLA Class I and Class II) was negative in all 9 subjects prior to single-dose belatacept administration, and was not retested thereafter.

CD86 Receptor Occupancy Levels:

Immediate (0.5-hour) post-infusion CD86 RO levels were available for 7 of 9 subjects, and for 5 subjects on Day 57. The mean percentage CD86 RO of 94.7% (range 87.5% to 98.4%) was similar in

adolescents at 0.5 hours after SD belatacept administration to that observed approximately 4 days after the initial infusion of belatacept to adult renal transplant recipients (mean [min, max] % CD86 RO was 94.1% (86.4%, 101.8%]) prior to the second belatacept infusion on Day 5. As expected, durability of the percent RO remained relatively high through Day 29 despite the observed decrease in serum concentration of belatacept to less than 20 µg/mL for all subjects evaluated.

Efficacy results

N/A

Safety results

Deaths and graft loss

There were no deaths or graft losses reported during the study or follow-up period in this study

Other serious adverse events

During the protocol-specified 6-month reporting period, six serious adverse events (SAEs) were reported for 4 subjects (44.4%), all of which were assessed by the investigator as not related to study drug. All were mild or moderate in intensity, and most occurred after the end of the SAE reporting window. One subject had an SAE of moderate gastroenteritis on Day 52, the SAEs in the remaining 3 subjects were all reported after Day 57.

Table 4 Summary of Serious Adverse Events - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Belatacept N = 9
Total subjects with an Event	4 (44.4)
Infections and Infestations	4 (44.4)
Gastroenteritis	2 (22.2)
Pyelonephritis	1 (11.1)
Pyelonephritis Acute	1 (11.1)
Urinary Tract Infection	1 (11.1)
Investigations	1 (11.1)
Blood Creatinine Increased	1 (11.1)
Renal and Urinary Disorders	1 (11.1)
Acute Kidney Injury	1 (11.1)

Assessment comment:

4/9 subjects reported 6 SAE. All SAEs but one (1) were reports during the follow-up period after Day 57. 4/6 reported SAEs were in SOC Infections and Infestations. This is expected as infections are common in immunosuppressive treatment. The remaining 2 SAEs regards impaired renal function ("Blood creatinine increased" and "Acute renal failure"). One of these events occurred in association with intercurrent urinary tract infection.

All SAE were among those expected in a renal transplant population.

Adverse Events Leading to Discontinuation of Study Therapy

There were no AEs leading to discontinuation

Adverse events of special interest

Events of interest included death, graft loss, PTLD, progressive multifocal leukoencephalopathy (PML), malignancies, autoimmune disorders, central nervous system (CNS) infections, tuberculosis infections, serious infections, infusion related reactions, and injection site reactions.

The following infection-related AEs were reported as SAEs in 4 subjects: acute pyelonephritis (N=1), gastroenteritis (N=2), pyelonephritis (N=1), and urinary tract infection (UTI; N=1). All were mild or moderate in intensity and assessed by the investigator as not related to study drug. All events resolved prior to study completion. Treatment was prescribed for each event but no further action was taken. The SAEs of gastroenteritis were considered likely to be viral in aetiology. The SAEs of acute pyelonephritis, pyelonephritis, and UTI were most likely bacterial rather than viral in aetiology, and as such, did not meet the protocol criteria for events of special interest.

Assessment comment:

Four subjects reported five AE of special interest, all in the area serious infections. Three of the events did not meet the protocol criteria for events of special interest.

All AEs of special interest concerned common infections. Infections are expected in the renal transplant population.

Overall adverse events

A total of 35 AEs were reported by 7 subjects up to Day 168. Three (33.3%) subjects had 8 AEs during the 57-day protocol-specified reporting period following belatacept administration (Table 5).

Table 5 Summary of Adverse Events up to Day 75 (study period) - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Belatacept N = 9
Total subjects with an Event	3 (33.3)
Infections and Infestations	2 (22.2)
Gastroenteritis	1 (11.1)
Urinary Tract Infection	1 (11.1)
Nervous System Disorders	2 (22.2)
Headache	2 (22.2)
Gastrointestinal Disorders	1 (11.1)
Abdominal Pain Upper	1 (11.1)
Vomiting	1 (11.1)
General Disorders and Administration Site Conditions	1 (11.1)
Asthenia	1 (11.1)

All AEs resolved, except for an AE of headache that was intermittent in occurrence and assessed by the investigator as mild in intensity; the event was continuing at study completion.

Assessment comment:

No unexpected adverse events have emerged during the study.

Clinical laboratory evaluations

No marked clinical laboratory abnormalities were reported during the study up to Day 57.

Serum creatinine concentrations were collected for all 9 treated subjects during the screening period and/or on Day 1 of the SD belatacept infusion, and were used to estimate glomerular filtration rate (GFR) per the updated Schwartz formula. The estimated GFR at baseline (Screening and/or Study Day 1) for all subjects ranged from 53.6 to 109.8 mL/min/1.73 m2, which is consistent with the corresponding protocol eligibility criterion.

Three subjects had non-protocol specified creatinine determinations performed at the time of intercurrent AEs. The higher serum creatinine concentrations/correspondingly lower estimated GFRs noted after Day 1 for these subjects either occurred in association with an acute intercurrent illness or after completion of the protocol-specified period of follow-up. In each of the episodes of renal function deterioration for which a concomitant AE was reported, the investigator assessed the events as not related to the SD infusion of belatacept.

Testing was performed at the screening visit for blood levels of CMV IgG. Qualitative testing for anti-CMV IgG was positive in 7 of 9 subjects, indicating pre-existing exposure to cytomegalovirus prior to study participation.
All subjects had BK virus (BKV) and EBV viral DNA values that were below the lower limit of quantitation (LLQ) at baseline and at Day 57. One subject had a CMV value that was detectable, but at a level below the LLQ (31.2 IU/mL) at baseline, and a CMV value reported as negative (“target not detected”) at Day 57. Another subject had a CMV value of 38 IU/mL at baseline, and a CMV value reported as negative (“target not detected”) at Day 57. Seven subjects had CMV values reported as negative (“target not detected”) at both baseline and Day 57.

Assessment comment:

No remarkable laboratory abnormalities, except two events of impaired renal function (“Blood creatinine increased” and “Acute renal failure”) discussed above as SAEs, were reported.

Vital Signs and Physical Findings

Vital signs were determined prior to and post-belatacept infusion in all 9 subjects. Mean (SD) heart rates and systolic (SD) and diastolic (SD) blood pressures pre- and post-belatacept infusion were 82 (17) and 88 (18) per minute, and 122 (9) / 74 (7) and 118 (11) / 70 (8) mm Hg, respectively. In one subject, heart rate and blood pressure were 76 per minute and 116/73 mm Hg before belatacept infusion and 100 per minute and 102/62 mm Hg post-dose, changes that were not associated with any reported adverse events. Single-dose IV administration of belatacept had no clinically meaningful effect on temperature or respiratory rate in any patient. Physical examinations, performed during Screening, were unremarkable for findings other than those consistent with each subject’s underlying cause of chronic kidney disease.

Assessment comment:

No remarkable abnormalities in vital signs and physical findings were reported.

Acute Rejection

There were no biopsy-proven events of AR reported in the 9 subjects during the protocol-specified, 57-day post-belatacept infusion study period

Immunogenicity results

Testing for anti-belatacept antibodies, performed using a validated assay at baseline and protocol-specified time points post-dose, was negative in all 9 subjects. As no belatacept serum samples with concentrations ≤1 µg/mL were positive to the LEA29Y (antigen-binding) portion of the molecule in tier 2, no neutralizing antibody (Nab) analyses were performed.

2.3.3. Discussion on clinical aspects

This is the first of two planned clinical studies in a paediatric development program.
In this PK, safety and tolerability study 9 subjects (five males and four females), 13 to 17 years of age, received a single dose infusion with belatacept, followed by an 8 week (Day 57) post dose follow-up visit and a 24 week (safety follow-up/end of study) telephone or clinic visit. All subjects treated completed the study.

The single dose PK profile seen in the adolescent subjects in this study is similar to the PK disposition of belatacept seen in adults.

There were no deaths, biopsy proven acute rejections and graft losses reported during the study or follow-up periods in this study, and no subjects discontinued the study due to adverse events.

No unexpected AEs emerged during study.
6 serious AEs were reported. Only 1/6 SAE was reported during the follow-up period after Day 57. 4/6 reported SAEs were in SOC Infections and Infestations. This is expected as infections are common in immunosuppressive treatment. The remaining 2 SAEs regards impaired renal function ("Blood creatinine increased" and "Acute renal failure"). One of these events occurred in association with intercurrent urinary tract infection. None of the SAE was deemed related to the study drug by the Investigator. This is agreed, as all events occurred >50 days after the SD infusion and as all SAE represented medical conditions expected to occur in a renal transplant population.

No remarkable laboratory abnormalities, except two events of impaired renal function ("Blood creatinine increased" and "Acute renal failure"), discussed as SAEs or abnormalities in vital signs and physical findings were reported during the course.

3. Overall conclusion and recommendation

This is a small safety, tolerability and pharmacokinetic study, including only 9 subjects, on single-dose administration of belatacept on adolescents. No new or unexpected safety data emerged during the study. The MAH has not suggested any further regulatory actions. This is agreed.

The paediatric development program also includes a multi-centre, randomized conversion study to evaluate the safety, efficacy and pharmacokinetics of belatacept administered to adolescents aged 12 to less than 18 years with a stable renal transplant. This study has not yet been initiated.

The benefit/risk balance for belatacept remains unchanged.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled**

4. Additional clarification requested

None

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Nulojix Active substance: belatacept

Study title	Study number	Date of completion	Date of submission of final study
Three-month intermittent dose intravenous immunotoxicity study in rats	DS07166	04 Mar 2008	Submitted with initial MAA (eCTD sequence
Thirteen-week subcutaneous/intravenous toxicity study in juvenile	DN07013	9 June 2008	Submitted with initial MAA (eCTD sequence
In vitro evaluation of CD86 receptor occupancy in paediatric blood	930036341	Receptor occupancy in paediatric blood completed on 21 November 2008	Submitted with initial MAA (eCTD sequence 0000)
Three-month intermittent dose subcutaneous and intravenous immunotoxicity study in juvenile rats	DS07165	12 January 2009	Submitted with initial MAA (eCTD sequence 0000)
Three-month intermittent-dose subcutaneous investigative immunotoxicity study in juvenile rats	DN11153	01 Oct 2012	Submitted in parallel to the PSUR covering the period from 15 June 2012 to 14 December 2012.

Clinical studies

Product Name: Nulojix Active substance: belatacept

Study title	Study number	Date of completion	Date of submission of final study report
Single-dose PK study in stable renal transplant recipients (from 12 to less than 18 years of age) receiving a calcineurin inhibitor (CNI)-based	IM103144	06 Dec 2016	Final study report provided with this submission.
Multi-center, randomized conversion study to evaluate the safety, efficacy and pharmacokinetics of belatacept administered to adolescents aged 12 to less than 18 years with a stable	IM103XXX	To be initiated	N/A