Clinical trial results:
Cardiovascular (CV) risk prediction and CV biomarkers in renal transplant recipients treated with belatacept compared to calcineurin inhibitors (CNI).
Open randomized 12 month study.

Summary

EudraCT number	2013-001178-20
Trial protocol	SE DK NL
Global end of trial date	13 September 2018

Results information

Result version number	v1 (current)
This version publication date	18 September 2020
First version publication date	18 September 2020
Summary attachment (see zip file)	Study synopsis (2729_CSR_synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	IM103-307,SMR-2729

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Uppsala University Hospital
Sponsor organisation address	MHT, Dept. of Nephrology, Uppsala, Sweden,
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2018
Global end of trial reached?	Yes
Global end of trial date	13 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare cardiovascular(CV) risk estimated by a renal transplant specific CV calculator in renal transplant recipients (RTR) randomized to belatacept or CNI-based immunosuppression.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to withdraw at any time. All patients were informed about the study both orally and in writing, and signed the informed consent prior to any study related procedures took place. Patients were treated in the clinic with standard care for this population.

Background therapy:

No treatments that were not test or comparator was used across the two arms in the trial.

Evidence for comparator:

Standard treatment for renal transplant recipients is the use of CNI. Half of the population remained on this treatment as a comparator and the other half received belatacept.

Actual start date of recruitment	18 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 32
Country: Number of subjects enrolled	Norway: 16
Country: Number of subjects enrolled	Sweden: 37
Country: Number of subjects enrolled	Denmark: 20
Worldwide total number of subjects	105
EEA total number of subjects	105

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	61
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 4 countries, and 11 recruiting sites. Denmark 2 sites, The Netherlands: 1 site, Norway: 1 site, and Sweden 5 sites. A total of 111 were randomized, but 6 of the subject never received any treatment, leaving 105 subject in the study. Of these, 54 received belatacept and 51 received CNI.

Pre-assignment

Screening details:

- Signed Written Informed Consent
- Renal transplant recipients of living donor or deceased donor kidney transplant.
- Stable renal graft with no need for exploratory examination eGFR > 20 ml/min)
- Tacrolimus or CsA (cyclosporine A) standard treatment since transplantation
- 3 – 60 months post-transplantation
- Men and women, aged 18 to 80

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

CNIs are administered orally as a daily dose of tablets, while belatacept is administered as monthly IV infusion, hence an open study design was chosen.

Arms

Are arms mutually exclusive?	Yes
Arm title	Belatacept arm

Arm description:

Belatacept (Nulojix) is administered as IV infusion on day 1, 15, 29, 43, 57 and then every month thereafter, for a total of 11 months, i.e. 14 infusions.
Both groups had the same underlying immunosuppressive regimen, consisting of

- +/- mycophenolic acid, as mycophenolate mofetil or enteric coated mycophenolate sodium
- +/- corticosteroids

Arm type	Experimental
Investigational medicinal product name	Belatacept
Investigational medicinal product code	L04A A28
Other name	Nulojix
Pharmaceutical forms	Powder for concentrate
Routes of administration	Intravenous use

Dosage and administration details:

Belatacept was administered at a dose of 5 mg/kg body weight. IV infusion took place on day 1, 15, 29, 43, 57 and then every month thereafter, for a total of 14 infusions. The CNI product was down-titrated and finally stopped on Day 28.

Arm title	CNI arm

Arm description:

Standard immunosuppressive regimen with CNI (cyclosporin or tacrolimus).
Both groups had the same underlying immunosuppressive regimen, consisting of

- +/- mycophenolic acid, as mycophenolate mofetil or enteric coated mycophenolate sodium
- +/- corticosteroids

Arm type	Active comparator

Investigational medicinal product name	Tacrolimus/Ciclosporin
Investigational medicinal product code	L04A
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to the CNI arm continued their regulated treatment with the CNI product for 12 month in the study.

Number of subjects in period 1	Belatacept arm	CNI arm
Started	54	51
Completed	49	49
Not completed	5	2
Consent withdrawn by subject	1	1
Adverse event, non-fatal	3	1
Moved out of the country	1	-

Baseline characteristics

Reporting groups

Reporting group title	Belatacept arm

Reporting group description:

Belatacept (Nulojix) is administered as IV infusion on day 1, 15, 29, 43, 57 and then every month thereafter, for a total of 11 months, i.e. 14 infusions.
Both groups had the same underlying immunosuppressive regimen, consisting of

- +/- mycophenolic acid, as mycophenolate mofetil or enteric coated mycophenolate sodium
- +/- corticosteroids

Reporting group title	CNI arm

Reporting group description:

Standard immunosuppressive regimen with CNI (cyclosporin or tacrolimus).
Both groups had the same underlying immunosuppressive regimen, consisting of

- +/- mycophenolic acid, as mycophenolate mofetil or enteric coated mycophenolate sodium
- +/- corticosteroids

Reporting group values	Belatacept arm	CNI arm	Total
Number of subjects	54	51	105
Age categorical			
A total of 112 patients signed the informed consent form. Of these, 1 patient was a screen failure and was never randomized. Of the 111 randomized patients, 6 withdrew consent before any study drug was given, of which 4 were in the belatacept arm and 2 in the CNI arm. Thus, 105 patients were randomized; 54 to the belatacept arm and 51 to the CNI arm. In the belatacept arm 5 patients were withdrawn prematurely from the study; 3 due to AEs, 1 withdrew consent and 1 moved out of the country. Similarly, there were 2 prematurely withdrawals in the CNI arm; 1 due to AE and 1 withdrew consent.			
Units: Subjects			
Adults (18-64 years)	29	32	61
From 65-84 years	25	19	44
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	13	13	26
Male	41	38	79

End points

End points reporting groups

Reporting group title	Belatacept arm

Reporting group description:

Belatacept (Nulojix) is administered as IV infusion on day 1, 15, 29, 43, 57 and then every month thereafter, for a total of 11 months, i.e. 14 infusions.
Both groups had the same underlying immunosuppressive regimen, consisting of
- +/- mycophenolic acid, as mycophenolate mofetil or enteric coated mycophenolate sodium
- +/- corticosteroids

Reporting group title	CNI arm

Reporting group description:

Standard immunosuppressive regimen with CNI (cyclosporin or tacrolimus).
Both groups had the same underlying immunosuppressive regimen, consisting of
- +/- mycophenolic acid, as mycophenolate mofetil or enteric coated mycophenolate sodium
- +/- corticosteroids

Primary: MACE

End point title	MACE

End point description:

In order to evaluate the cardiovascular benefit of belatacept, the CVD risk calculation was chosen as the primary endpoint, i.e. the estimated risk of major adverse cardiovascular events (MACE) and mortality at one year. The MACE is calculated as a linear combination of the following variables: age, previous coronary heart disease, previous smoker, current smoker, creatinine, diabetes mellitus, low-density lipoprotein (LDL) and number of transplants.

End point type	Primary

End point timeframe:

Belatacept versus CNI after one year of treatment

End point values	Belatacept arm	CNI arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54[1]	51[2]		
Units: Predicted risk for MACE				
arithmetic mean (standard deviation)	0.15 (± 0.15)	0.15 (± 0.15)		

Notes:

[1] - The value is the estimated risk for MACE in the Belatacept group after Month 12.

[2] - The value is the estimated risk for MACE in the CNI group after Month 12.

Statistical analyses

Statistical analysis title	Primary analysis for MACE after Month 12

Statistical analysis description:

The primary endpoint was the estimated risk of MACE and mortality as per the risk calculator generated by Soveri et al., a calculator which is based on an observation period of 7 years. Here is shows the estimated risk prediction at 7 years by using the data collected in this study at one year.

Comparison groups	CNI arm v Belatacept arm

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Log means
Point estimate	0.064089
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.043106
upper limit	0.171284
Variability estimate	Standard deviation

Primary: Mortality

End point title	Mortality

End point description:

In order to evaluate the cardiovascular benefit of belatacept, the CVD risk calculation was chosen as the primary endpoint, i.e. the estimated risk of major adverse cardiovascular events (MACE) and mortality at one year. The MACE is calculated as a linear combination of the following variables: age, previous coronary heart disease, previous smoker, current smoker, creatinine, diabetes mellitus, low-density lipoprotein (LDL) and number of transplants.

End point type	Primary

End point timeframe:

From baseline to Month 12

End point values	Belatacept arm	CNI arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54[3]	51[4]		
Units: Predicted risk for mortality				
arithmetic mean (standard deviation)	0.23 (± 0.20)	0.21 (± 0.20)		

Notes:

[3] - The value is the estimated risk for Mortality in the Belatacept group after Month 12.

[4] - The value is the estimated risk for Mortality in the CNI group after Month 12.

Statistical analyses

Statistical analysis title	Analysis for mortality after Month 12

Statistical analysis description:

The primary endpoint was the estimated risk of MACE and mortality as per the risk calculator generated by Soveri et al., a calculator which is based on an observation period of 7 years. Here is shows the estimated risk prediction at 7 years by using the data collected in this study at one year. There was no difference between the treatment groups in terms of change in predicted risk.

Comparison groups	Belatacept arm v CNI arm

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Log means
Point estimate	0.043051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.055602
upper limit	0.141705
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to Month 12	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	Belatacept

Reporting group description:

Belatacept (Nulojix) is administered as IV infusion on day 1, 15, 29, 43, 57 and then every month thereafter, for a total of 11 months, i.e. 14 infusions.
Both groups had the same underlying immunosuppressive regimen, consisting of
- +/- mycophenolic acid, as mycophenolate mofetil or enteric coated mycophenolate sodium
- +/ corticosteroids

Reporting group title	CNI arm

Reporting group description:

Standard immunosuppressive regimen with CNI (cyclosporin or tacrolimus).
Both groups had the same underlying immunosuppressive regimen, consisting of
- +/- mycophenolic acid, as mycophenolate mofetil or enteric coated mycophenolate sodium
- +/ corticosteroids

Serious adverse events	Belatacept	CNI arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 54 (29.63%)	8 / 51 (15.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Incisional hernia repair			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula operation			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Transplant rejection			
subjects affected / exposed	3 / 54 (5.56%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Biopsy kidney			

subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haemorrhage			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Lacunar infarction			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Lens dislocation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			

subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal arteritis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Localised infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Belatacept	CNI arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 54 (100.00%)	51 / 51 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Basal cell carcinoma			
subjects affected / exposed	1 / 54 (1.85%)	2 / 51 (3.92%)	
occurrences (all)	1	2	
Bowen's disease			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Lung neoplasm malignant			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	

Neoplasm			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Skin papilloma			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Arterial occlusive disease			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Embolism			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	14 / 54 (25.93%)	9 / 51 (17.65%)	
occurrences (all)	14	9	
Hypotension			
subjects affected / exposed	0 / 54 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Intermittent claudication			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Peripheral coldness			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Arteriovenous fistula operation			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Ileocolectomy			

subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Incisional hernia repair			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Knee arthroplasty			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Skin neoplasm excision			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Toe operation			
subjects affected / exposed	0 / 54 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Cyst			
subjects affected / exposed	1 / 54 (1.85%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	4 / 54 (7.41%)	1 / 51 (1.96%)	
occurrences (all)	4	1	
Instillation site warmth			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Local swelling			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	1 / 54 (1.85%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Oedema peripheral			

subjects affected / exposed	3 / 54 (5.56%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Peripheral swelling			
subjects affected / exposed	1 / 54 (1.85%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	17 / 54 (31.48%)	1 / 51 (1.96%)	
occurrences (all)	17	1	
Immune system disorders			
Kidney transplant rejection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Renal transplant failure			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Transplant rejection			
subjects affected / exposed	2 / 54 (3.70%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	2 / 54 (3.70%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Vaginal haematoma			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Choking sensation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	8 / 54 (14.81%)	1 / 51 (1.96%)	
occurrences (all)	8	1	
Dyspnoea			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Dyspnoea exertional			

subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Productive cough			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Pulmonary embolism			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Rales			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Investigations			
Biopsy kidney			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Blood calcium increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol increased			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Blood creatinine increased			
subjects affected / exposed	15 / 54 (27.78%)	2 / 51 (3.92%)	
occurrences (all)	15	2	
Blood parathyroid hormone decreased			

subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
C-reactive protein increased			
subjects affected / exposed	6 / 54 (11.11%)	0 / 51 (0.00%)	
occurrences (all)	6	0	
Cardiac murmur			
subjects affected / exposed	2 / 54 (3.70%)	3 / 51 (5.88%)	
occurrences (all)	2	3	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Heart rate irregular			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Low density lipoprotein increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Nitrite urine present			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Prostatic specific antigen increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	

Renal function test abnormal			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Urine albumin/creatinine ratio increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Weight increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Graft complication			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Head injury			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Humerus fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Meniscus injury			

subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Skin wound			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Subdural haemorrhage			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Synovial rupture			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Atrial flutter			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Atrioventricular block first degree			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Palpitaions			
subjects affected / exposed	1 / 54 (1.85%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Tachycardia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Areflexia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	4 / 54 (7.41%)	0 / 51 (0.00%)	
occurrences (all)	4	0	
Headache			

subjects affected / exposed	4 / 54 (7.41%)	1 / 51 (1.96%)	
occurrences (all)	4	1	
Hyporeflexia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Lacunar infarction			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Motor dysfunction			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	2 / 54 (3.70%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Sciatica			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	5 / 54 (9.26%)	1 / 51 (1.96%)	
occurrences (all)	5	1	
Leukopenia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Normochromic normocytic anaemia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Polycythaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Tinnitus			

subjects affected / exposed	1 / 54 (1.85%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Eye disorders			
Blindness			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Chalazion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Conjunctival haemorrhage			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Corneal disorder			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Lens dislocation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Retinal detachment			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Swollen tear duct			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Visual acuity reduced			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	9 / 54 (16.67%)	0 / 51 (0.00%)	
occurrences (all)	9	0	
Abdominal pain upper			

subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Aphthous ulcer			
subjects affected / exposed	3 / 54 (5.56%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Colitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Colitis ischaemic			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	5 / 54 (9.26%)	2 / 51 (3.92%)	
occurrences (all)	5	2	
Dry mouth			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Hiatus hernia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Large intestine polyp			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Melaena			

subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 54 (5.56%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Oesophageal spasm			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Oesophagitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Pancreatic cyst			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 54 (3.70%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Spider naevus			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 54 (1.85%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Dysuria			

subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
IgA nephropathy			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Lower urinary tract symptoms			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Microalbuminuria			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Postrenal failure			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Prerenal failure			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Renal arteritis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Renal artery stenosis			
subjects affected / exposed	0 / 54 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Proteinuria			
subjects affected / exposed	7 / 54 (12.96%)	1 / 51 (1.96%)	
occurrences (all)	7	1	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Urethral pain			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Urine odour abnormal			

subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Hyperparathyroidism			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 54 (3.70%)	3 / 51 (5.88%)	
occurrences (all)	2	3	
Back pain			
subjects affected / exposed	0 / 54 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Bone pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Bursitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Groin pain			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Muscle disorder			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Muscular weakness			

subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	3 / 54 (5.56%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Osteoarthritis			
subjects affected / exposed	2 / 54 (3.70%)	2 / 51 (3.92%)	
occurrences (all)	2	2	
Osteopenia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 54 (1.85%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Plantar fasciitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 54 (1.85%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	1 / 54 (1.85%)	2 / 51 (3.92%)	
occurrences (all)	1	2	
Cytomegalovirus infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	

Fungal skin infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	1 / 54 (1.85%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Gingivitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Haemophilus infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Hepatitis E			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	3 / 54 (5.56%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Influenza			
subjects affected / exposed	1 / 54 (1.85%)	2 / 51 (3.92%)	
occurrences (all)	1	2	
Localised infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	10 / 54 (18.52%)	8 / 51 (15.69%)	
occurrences (all)	10	8	
Oral candidiasis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	3 / 54 (5.56%)	4 / 51 (7.84%)	
occurrences (all)	3	4	

Respiratory tract infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	4 / 54 (7.41%)	0 / 51 (0.00%)	
occurrences (all)	4	0	
Urinary tract infection			
subjects affected / exposed	16 / 54 (29.63%)	2 / 51 (3.92%)	
occurrences (all)	16	2	
Urosepsis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Varicella			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Fluid retention			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Gout			

subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Hypercalcaemia			
subjects affected / exposed	2 / 54 (3.70%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Hypercholesterolaemia			
subjects affected / exposed	2 / 54 (3.70%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Hypoglycaemia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Hypophosphataemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Iron deficiency			
subjects affected / exposed	1 / 54 (1.85%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 54 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2014	The substantial amendment included the following changes: • Blood samples to be collected at 0, 6 and 12 months for evaluation of biomarkers for CV risk factors. • Changes in number of patients to be enrolled. The reason for the change was due to the estimated reduction in MACE CV risk score had been downgraded from 40% to 30%, which lead to the need of increasing sample size from 50 to 110. • For patients discontinuing the study before one year, the last available estimate of CV risk was used in the analysis of the ITT population.
12 December 2014	The substantial amendment included the following changes: • Specifications in the inclusion/exclusion criteria. • Addition of traditional CV biomarkers; ApoB and ApoA1. The ratio for ApoB/ApoA1 added because it has been shown as an efficient test for predicting risk for CV disease. • With the start of the study at three Swedish sites, a need for additional criteria for exclusion from the study as well as clarifications of existing inclusion/exclusion criteria had been discovered. o Exclusion criterion 4b; Previous/on-going use of rituximab has been added to the protocol since the use of rituximab in renal transplants is always an "off-label" (i.e. unapproved) related to humoral rejection. Previous in-label use may be related to treatment of CD20+ B-cell lymphomas, which in turn should be an exclusion criterion, taken into account the increased risk of PTLD with belatacept. Therefore, patients with previous use of rituximab due to e.g. treatment of B-cell lymphoma might not be candidates for conversion to belatacept. o Exclusion criterion 3b; History of tuberculosis has been added to avoid re-activation of tuberculosis as tuberculosis (along with PTLD) has previously been reported as a principal safety finding associated with belatacept.
23 May 2017	The substantial amendment included the following changes: • Sponsor has updated the calculation of infusion dose in order to be in alignment with the SmPC of belatacept. Infusion doses will be based on the patient's body weight at baseline. If weight later changes more than +/- 10% a new dose was to be calculate. • Clarification of the exclusion criteria regarding tuberculosis and the use of rituximab was made. • Clarification of the term "Discontinuation of Patients from Treatment" was made, and also included a description of the follow up of patients who were withdrawn from the study. • An update regarding risk monitoring was made. • The different heart diseases were described in more detail.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported