



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, |
| Public contact | PM Andre Western, Smerud Medical Research International AS, +47 90526246, andre.western@smerud.com |
| Scientific contact | PM Andre Western, Smerud Medical Research International AS, +47 90526246, andre.western@smerud.com |

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 <ul style="list-style-type: none">+/- 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 <ul style="list-style-type: none">+/- 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 occurrences (all) | 3 / 54 (5.56%) 3 | 1 / 51 (1.96%) 1 | |
| Peripheral swelling subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 1 / 51 (1.96%) 1 | |
| Pyrexia subjects affected / exposed occurrences (all) | 17 / 54 (31.48%) 17 | 1 / 51 (1.96%) 1 | |
| Immune system disorders Kidney transplant rejection subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Renal transplant failure subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 51 (1.96%) 1 | |
| Transplant rejection subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 2 | 1 / 51 (1.96%) 1 | |
| Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 2 | 1 / 51 (1.96%) 1 | |
| Vaginal haematoma subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Choking sensation subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Cough subjects affected / exposed occurrences (all) | 8 / 54 (14.81%) 8 | 1 / 51 (1.96%) 1 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 2 | 0 / 51 (0.00%) 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 occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Transaminases increased subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Urine albumin/creatinine ratio increased subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Weight decreased subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 2 | 0 / 51 (0.00%) 0 | |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Injury, poisoning and procedural complications | | | |
| Cervical vertebral fracture subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Contusion subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 51 (1.96%) 1 | |
| Graft complication subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 2 | 0 / 51 (0.00%) 0 | |
| Head injury subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Humerus fracture subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 51 (1.96%) 1 | |
| Ligament sprain subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 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 | |
| Palpitations | | | |
| 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 occurrences (all) | 1 / 54 (1.85%) 1 | 1 / 51 (1.96%) 1 | |
| Eye disorders | | | |
| Blindness | | | |
| subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Chalazion | | | |
| subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 51 (1.96%) 1 | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Corneal disorder | | | |
| subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 51 (1.96%) 1 | |
| Lens dislocation | | | |
| subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Retinal detachment | | | |
| subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Swollen tear duct | | | |
| subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 51 (1.96%) 1 | |
| Visual acuity reduced | | | |
| subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 1 / 51 (1.96%) 1 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 0 | |
| Abdominal pain | | | |
| subjects affected / exposed occurrences (all) | 9 / 54 (16.67%) 9 | 0 / 51 (0.00%) 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 occurrences (all) | 1 / 54 (1.85%) 1 | 0 / 51 (0.00%) 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 | <p>The substantial amendment included the following changes:</p> <ul style="list-style-type: none">• 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 | <p>The substantial amendment included the following changes:</p> <ul style="list-style-type: none">• 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.<ul style="list-style-type: none">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 | <p>The substantial amendment included the following changes:</p> <ul style="list-style-type: none">• 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