



Clinical trial results:

The ONE Study: A Unified Approach to Evaluating Cellular Immunotherapy in Solid Organ Transplantation – Reference Group Trial Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2011-004301-24 |
| Trial protocol | DE FR IT |
| Global end of trial date | 29 December 2015 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 08 January 2017 |
| First version publication date | 08 January 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | ONErGT11 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01656135 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Free State of Bavaria, represented by the University of Regensburg, represented by Prof. Edward K. Geissler |
| Sponsor organisation address | Franz-Josef-Strauss-Allee 11, Regensburg, Germany, 93053 |
| Public contact | Clinical Study Center Surgery, University Hospital Regensburg, +49 9419444895, theonestudy@klinik.uni-regensburg.de |
| Scientific contact | Clinical Study Center Surgery, University Hospital Regensburg, +49 9419444895, theonestudy@klinik.uni-regensburg.de |

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 | 07 December 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 December 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 December 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To confirm the rate of acute kidney graft rejection in the study population under standard immunosuppressive therapy in order to corroborate historical renal transplantation statistics and generate reference ranges for future clinical research within The ONE Study.

The Reference Group Trial is the first clinical trial planned within the context of The ONE Study, an international, non-commercial research project that ultimately aims in subsequent trials to test several alternative GMP cell products as adjunct immunosuppressive treatments in kidney transplantation. Future trials will assess whether immunoregulatory cell infusion could allow for a reduction in the use of pharmacological maintenance therapy in transplant recipients and alleviate the drawbacks associated with traditional immunosuppressive agents.

Protection of trial subjects:

Patients in the Reference Group Trial were treated with a standard immunosuppressive regimen that represented current best practice in preventing renal allograft rejection. Nevertheless, graft rejection is a potentially life-threatening condition. Therefore, no patient was denied anti-rejection therapy that was deemed necessary by the local Investigator. Optimal clinical care for all patients enrolled in the study was paramount. Investigators acted in the patients' best interests at all times by protecting allograft function, even if this resulted in a protocol deviation. Investigators reserved the right to alter the specified regimen in response to intolerable adverse drug reactions or sub-optimal immunosuppression and dose tapering was not mandatory if graft rejection had occurred or if renal dysfunction was observed. Upon completion of the trial protocol for individual patients, immunosuppressive treatment proceeded at the discretion of the local clinical team.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 11 December 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Germany: 21 |
| Country: Number of subjects enrolled | Italy: 4 |
| Country: Number of subjects enrolled | United Kingdom: 22 |
| Country: Number of subjects enrolled | United States: 14 |
| Worldwide total number of subjects | 70 |
| EEA total number of subjects | 56 |

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 | 9 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled on 11th December 2012 and patient recruitment was completed on 25th September 2014. Recruitment took place at six investigative sites in four European countries (Germany, United Kingdom, France and Italy) and at two investigative sites in the USA.

Pre-assignment

Screening details:

A total of 272 patients (across all study sites) were screened against the inclusion and exclusion criteria for the trial. Potential participants were identified by trial Investigators from information readily available during work-up procedures for living-donor kidney transplantation. 70 patients were enrolled.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|------------------------------------|
| Arm title | Standard immunosuppressive regimen |
|-----------|------------------------------------|

Arm description:

Living-donor renal transplant recipients treated with a standard immunosuppressive regimen consisting of basiliximab + prednisolone (IV and oral) + MMF/MPA + tacrolimus

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Simulect |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Day 0: 20mg IV \leq 2h prior to surgery; Day 4: 20mg IV

| | |
|--|--|
| Investigational medicinal product name | Prednisolone IV |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Day 0: 500mg IV (250mg pre-op, 250mg intra-op); Day 1: 125mg IV

| | |
|--|-------------------|
| Investigational medicinal product name | Prednisolone oral |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Day 2 – 14: 20mg/day oral; Week 3 – 4: 15mg/day oral; Week 5 – 8: 10mg/day oral; Week 9 – 12: 5mg/day oral; Week 13 – 14: 2.5mg/day oral; Week 15 – Study End: Cessation

| | |
|--|---------------|
| Investigational medicinal product name | Tacrolimus |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |

| | |
|---|------------------------------|
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Doses were adjusted as necessary to achieve whole blood drug trough levels within the following concentration ranges during the specified time frames: Day -4 – 14: 3-12ng/ml; Week 3 – 12: 3-10ng/ml; Week 13 – 36: 3-8ng/ml; Week 37 – Study End: 3-6ng/ml | |
| Investigational medicinal product name | Mycophenolate mofetil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard, Coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Day -1 – 14: 2g/day oral; Day 15 – Study End: 1.5g/day oral (750mg twice daily) | |
| Investigational medicinal product name | Mycophenolic acid |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Doses that are biologically equivalent to those specified for mycophenolate mofetil. | |

| Number of subjects in period 1 | Standard immunosuppressive regimen |
|---------------------------------------|------------------------------------|
| Started | 70 |
| Completed | 61 |
| Not completed | 9 |
| Consent withdrawn by subject | 3 |
| Physician decision | 3 |
| Lost to follow-up | 1 |
| Protocol deviation | 2 |

Baseline characteristics

Reporting groups

| | |
|--|---------------|
| Reporting group title | Overall trial |
| Reporting group description: Living-donor renal transplant recipients treated with a standard immunosuppressive regimen consisting of basiliximab + prednisolone (IV and oral) + MMF/MPA + tacrolimus | |

| Reporting group values | Overall trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 70 | 70 | |
| Age categorical | | | |
| Age at time of informed consent was calculated using an exact algorithm (date of consent – date of birth / 365.25). Dates of birth with missing day information were set to the first of the respective month, i.e. 01mmmyyyy. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 61 | 61 | |
| From 65-84 years | 9 | 9 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Age at time of informed consent was calculated using an exact algorithm (date of consent – date of birth / 365.25). Dates of birth with missing day information were set to the first of the respective month, i.e. 01mmmyyyy. | | | |
| Units: years | | | |
| arithmetic mean | 48.4 | | |
| standard deviation | ± 13.3 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 20 | 20 | |
| Male | 50 | 50 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| White | 62 | 62 | |
| Asian | 7 | 7 | |
| Other | 1 | 1 | |

Subject analysis sets

| | |
|--|-------------------------------|
| Subject analysis set title | Safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All patients who signed informed consent and received at least one dose of study-specific medication. | |
| Subject analysis set title | Intention-to-treat population |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All patients included in the safety population who underwent kidney transplantation.

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Per-protocol population |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All patients included in the safety population who were treated according to protocol specifications (acceptable limits defined in the PP criteria).

| Reporting group values | Safety population | Intention-to-treat population | Per-protocol population |
|--|-------------------|-------------------------------|-------------------------|
| Number of subjects | 67 | 66 | 47 |
| Age categorical | | | |
| Age at time of informed consent was calculated using an exact algorithm (date of consent – date of birth / 365.25). Dates of birth with missing day information were set to the first of the respective month, i.e. 01mmmyyyy. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 60 | 59 | 43 |
| From 65-84 years | 7 | 7 | 4 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Age at time of informed consent was calculated using an exact algorithm (date of consent – date of birth / 365.25). Dates of birth with missing day information were set to the first of the respective month, i.e. 01mmmyyyy. | | | |
| Units: years | | | |
| arithmetic mean | 47.6 | 47.4 | 47.7 |
| standard deviation | ± 13.1 | ± 13.1 | ± 12.3 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 18 | 18 | 11 |
| Male | 49 | 48 | 36 |
| Ethnicity | | | |
| Units: Subjects | | | |
| White | 60 | 59 | 41 |
| Asian | 6 | 6 | 5 |
| Other | 1 | 1 | 1 |

End points

End points reporting groups

| | |
|--|------------------------------------|
| Reporting group title | Standard immunosuppressive regimen |
| Reporting group description: Living-donor renal transplant recipients treated with a standard immunosuppressive regimen consisting of basiliximab + prednisolone (IV and oral) + MMF/MPA + tacrolimus | |
| Subject analysis set title | Safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All patients who signed informed consent and received at least one dose of study-specific medication. | |
| Subject analysis set title | Intention-to-treat population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients included in the safety population who underwent kidney transplantation. | |
| Subject analysis set title | Per-protocol population |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All patients included in the safety population who were treated according to protocol specifications (acceptable limits defined in the PP criteria). | |

Primary: Incidence of biopsy-confirmed acute rejection (BCAR)

| | |
|--|---|
| End point title | Incidence of biopsy-confirmed acute rejection (BCAR) ^[1] |
| End point description: Kidney graft biopsies were assessed by a nominated Central Pathologist. A patient was deemed to have reached the primary endpoint only if the Central Pathologist issued a histological confirmation of rejection. Therefore, BCAR required a clinical diagnosis from the local Investigator plus a histopathological confirmation from a for-cause biopsy evaluated by the Central Pathologist. A biopsy was considered to be 'for-cause' if there were overt clinical signs of rejection at the time of sampling. Patients with subclinical rejection detected by a protocol biopsy did not register a primary endpoint. Patients who were diagnosed with acute rejection by the local Investigator, but whose for-cause biopsy did not reveal histopathological evidence of rejection according to the Central Pathologist, also did not register a primary endpoint. | |
| End point type | Primary |
| End point timeframe: Within 60 weeks following renal transplantation. | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was a single-armed trial with no comparator arm. Therefore, all endpoints were analysed descriptively and it was not possible to apply any statistical testing to the primary endpoint.

| End point values | Intention-to-treat population | Per-protocol population | | |
|-----------------------------|-------------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 66 | 47 | | |
| Units: Patients | 8 | 8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first BCAR episode

| | |
|-----------------|----------------------------|
| End point title | Time to first BCAR episode |
|-----------------|----------------------------|

End point description:

For each patient who registered a primary endpoint, the time interval between the date of transplantation ("Day 0") and the date of first BCAR was calculated. The date of first BCAR was defined as the earliest date when both criteria for the primary endpoint (clinical diagnosis and biopsy confirmation from the Central Pathologist) were fulfilled. Therefore, in case the timings of clinical diagnosis and biopsy confirmation did not coincide, the later date was used to measure the time interval. For patients who experienced more than one BCAR, episodes subsequent to the first diagnosis were disregarded. Considering only those patients who registered a primary endpoint, the median and full range are presented here. Time to first BCAR was also analysed by Kaplan-Meier method (results not shown here).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 60 weeks following renal transplantation.

| End point values | Intention-to-treat population | | | |
|-------------------------------|-------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 8 | | | |
| Units: Days | | | | |
| median (full range (min-max)) | 6 (4 to 326) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of first BCAR episode (based on response to treatment)

| | |
|-----------------|---|
| End point title | Severity of first BCAR episode (based on response to treatment) |
|-----------------|---|

End point description:

The severity of BCAR was assessed according to clinical criteria. Investigators were asked to grade the severity of a clinically-diagnosed rejection episode according to the response of the patient to anti-rejection therapy. In the eCRF, severity was classified as: "Spontaneously resolving", "Glucocorticoid-responsive", "Responsive to depleting antibody treatment", "Unresponsive to rescue therapy" or "Not applicable". The option "Not applicable" was available in case no additional anti-rejection treatment was initiated and the patient could be treated by modulating the doses of the study drugs. For each patient who registered a primary endpoint, severity grades from the first BCAR episode were collected for analysis. For patients who experienced more than one episode of BCAR, episodes subsequent to the first diagnosis were disregarded.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 60 weeks following renal transplantation.

| End point values | Intention-to-treat population | Per-protocol population | | |
|--|-------------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 66 | 47 | | |
| Units: Patients | | | | |
| Glucocorticoid-responsive | 4 | 4 | | |
| Responsive to depleting antibody treatment | 3 | 3 | | |
| Not applicable | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of first BCAR episode (based on biopsy histopathology)

| | |
|-----------------|---|
| End point title | Severity of first BCAR episode (based on biopsy histopathology) |
|-----------------|---|

End point description:

The severity of BCAR was evaluated according to the histopathological grading provided by the Central Pathologist. In the eCRF, the options for grading acute rejection pathology were: "Antibody-mediated changes (ABMR)", "Acute T cell-mediated rejection (TCMR) IA", "Acute TCMR IB", "Acute TCMR IIA", "Acute TCMR IIB", "Acute TCMR III" and "Borderline changes". These options were not necessarily mutually exclusive. It was possible for the pathologist to select "Mixed ABMR + TCMR" and specify both ABMR and TCMR sub-classifications. For each patient who registered a primary endpoint, severity grades from the first BCAR episode were collected for analysis. For patients who experienced more than one episode of BCAR, episodes subsequent to the first diagnosis were disregarded.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 60 weeks following renal transplantation.

| End point values | Intention-to-treat population | Per-protocol population | | |
|-----------------------------|-------------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 66 | 47 | | |
| Units: Patients | | | | |
| Acute TCMR IIA | 3 | 3 | | |
| Borderline changes | 3 | 3 | | |
| Acute TCMR IA | 1 | 1 | | |
| Acute TCMR IB | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse drug reactions (ADRs)

| | |
|-----------------|--|
| End point title | Incidence of adverse drug reactions (ADRs) |
|-----------------|--|

End point description:

An ADR was defined as any AE with a reasonable possibility of a causal relationship to any of the study-specific drugs (basiliximab, IV prednisolone, oral prednisolone, MMF/MPA, tacrolimus), as judged by the reporting Investigator. Investigator-reported terms (verbatim) were coded using MedDRA version 19.0. To calculate the prevalence of ADRs, multiple occurrences of the same event (Preferred Term) in one individual were counted only once. For the purposes of this study, graft rejection was exempt from AE reporting.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The observation period was from the date of administration of the first dose of study-specific medication until 28 days after the date of final trial visit or date of withdrawal. Events starting before this period of observation were excluded.

| End point values | Safety population | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 67 | | | |
| Units: Patients | | | | |
| ADRs | 53 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of major infections

| | |
|-----------------|-------------------------------|
| End point title | Incidence of major infections |
|-----------------|-------------------------------|

End point description:

Infections were assessed by systematically collecting information on Serious Adverse Events (SAEs) and Adverse Events (AEs) at the regular trial follow-up visits. Viral loads of CMV, EBV and BKV were measured at Visits 4, 5 and 6 or at 4 week intervals after anti-viral chemoprophylaxis had been completed. The patients were also screened for clinical evidence of bacterial, viral and fungal infections at these three time points. Investigator-reported terms (verbatim) were coded using MedDRA version 19.0. The number of patients who experienced at least one AE belonging to the MedDRA SOC: "Infections and infestations" is reported here.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The observation period was from the date of administration of the first dose of study-specific medication until 28 days after the date of final trial visit or date of withdrawal. Events starting before this period of observation were excluded.

| End point values | Safety population | | | |
|---|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 67 | | | |
| Units: Patients | | | | |
| MedDRA SOC: Infections and infestations | 52 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of neoplasia

| | |
|-----------------|------------------------|
| End point title | Incidence of neoplasia |
|-----------------|------------------------|

End point description:

Neoplasms were assessed by systematically collecting information on Serious Adverse Events (SAEs) and Adverse Events (AEs) at the regular trial follow-up visits. The trial protocol recommended a formal dermatological assessment at Visit 10 (final visit) to screen for signs of skin malignancy. Investigator-reported terms (verbatim) were coded using MedDRA version 19.0. The number of patients who experienced at least one AE belonging to the MedDRA SOC: "Neoplasms benign, malignant and unspecified" is reported here.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The observation period was from the date of administration of the first dose of study-specific medication until 28 days after the date of final trial visit or date of withdrawal. Events starting before this period of observation were excluded.

| End point values | Safety population | | | |
|--|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 67 | | | |
| Units: Patients | | | | |
| MedDRA SOC: Neoplasms benign, malignant, unspec. | 6 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For analysis, the observation period for AEs was defined as the date of administration of the first dose of study-specific medication until 28 days after the date of final trial visit or date of withdrawal. Only these treatment-emergent AEs were included.

Adverse event reporting additional description:

Information on AEs was collected systematically by the study teams at regular trial follow-up visits. It was the responsibility of the Investigator to assess the seriousness and causality of every AE. All reported terms (verbatim) were monitored by source data verification and then coded using MedDRA version 19.0.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

Reporting groups

| | |
|-----------------------|------------------------------------|
| Reporting group title | Standard immunosuppressive regimen |
|-----------------------|------------------------------------|

Reporting group description:

Living-donor renal transplant recipients treated with a standard immunosuppressive regimen consisting of basiliximab + prednisolone (IV and oral) + MMF/MPA + tacrolimus. For analysis, SAEs and non-serious AEs were summarised for the safety population (N=67).

| Serious adverse events | Standard immunosuppressive regimen | | |
|---|------------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 36 / 67 (53.73%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anticonvulsant drug level therapeutic | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Complications of transplanted kidney | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arteriovenous fistula thrombosis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Lymphocele | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Air embolism | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|--|---|----------------|--|--|
| Atrial fibrillation | subjects affected / exposed | 1 / 67 (1.49%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | subjects affected / exposed | 1 / 67 (1.49%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | | |
| Methaemoglobinaemia | subjects affected / exposed | 1 / 67 (1.49%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Nephrogenic anaemia | subjects affected / exposed | 1 / 67 (1.49%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | | |
| Hyperpyrexia | subjects affected / exposed | 1 / 67 (1.49%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Vascular stent thrombosis | subjects affected / exposed | 1 / 67 (1.49%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | | |
| Chronic gastritis | subjects affected / exposed | 1 / 67 (1.49%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal impairment | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal artery stenosis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract obstruction | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Varicella zoster virus infection | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cytomegalovirus colitis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia sepsis | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 1 / 67 (1.49%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Escherichia urinary tract infection | | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Febrile infection | | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fungal oesophagitis | | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster disseminated | | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infected lymphocele | | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection | | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nasal abscess | | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Perirectal abscess | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Polyomavirus-associated nephropathy | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Relapsing fever | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rotavirus infection | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Standard immunosuppressive regimen | | |
|---|------------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 64 / 67 (95.52%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 7 / 67 (10.45%) | | |
| occurrences (all) | 7 | | |
| Hypotension | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | | |
| occurrences (all) | 5 | | |
| Lymphocele | | | |
| subjects affected / exposed | 11 / 67 (16.42%) | | |
| occurrences (all) | 11 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 7 / 67 (10.45%) | | |
| occurrences (all) | 7 | | |
| Fatigue | | | |
| subjects affected / exposed | 8 / 67 (11.94%) | | |
| occurrences (all) | 9 | | |
| Oedema | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | | |
| occurrences (all) | 5 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 11 / 67 (16.42%) | | |
| occurrences (all) | 12 | | |
| Pain | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | | |
| occurrences (all) | 7 | | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 67 (11.94%) | | |
| occurrences (all) | 8 | | |
| Reproductive system and breast disorders | | | |

| | | | |
|--|---|--|--|
| Genital pain subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 4 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Dyspnoea exertional subjects affected / exposed occurrences (all) Increased bronchial secretion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) | 12 / 67 (17.91%) 12 7 / 67 (10.45%) 7 5 / 67 (7.46%) 5 4 / 67 (5.97%) 5 6 / 67 (8.96%) 6 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all) | 10 / 67 (14.93%) 14 7 / 67 (10.45%) 12 | | |
| Investigations Blood creatine increased subjects affected / exposed occurrences (all) Blood pressure increased subjects affected / exposed occurrences (all) C-reactive protein increased subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 5 4 / 67 (5.97%) 5 5 / 67 (7.46%) 5 | | |

| | | | |
|--|------------------------|--|--|
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 6 / 67 (8.96%) 8 | | |
| Polyomavirus test positive subjects affected / exposed occurrences (all) | 8 / 67 (11.94%) 9 | | |
| Injury, poisoning and procedural complications | | | |
| Incision site pain subjects affected / exposed occurrences (all) | 6 / 67 (8.96%) 6 | | |
| Post procedural haematoma subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 4 | | |
| Procedural pain subjects affected / exposed occurrences (all) | 10 / 67 (14.93%) 10 | | |
| Seroma subjects affected / exposed occurrences (all) | 5 / 67 (7.46%) 6 | | |
| Wound complication subjects affected / exposed occurrences (all) | 11 / 67 (16.42%) 16 | | |
| Cardiac disorders | | | |
| Tachycardia subjects affected / exposed occurrences (all) | 4 / 67 (5.97%) 4 | | |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 16 / 67 (23.88%) 26 | | |
| Paraesthesia subjects affected / exposed occurrences (all) | 6 / 67 (8.96%) 6 | | |
| Tremor subjects affected / exposed occurrences (all) | 23 / 67 (34.33%) 23 | | |

| | | | |
|--------------------------------------|------------------|--|--|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 10 / 67 (14.93%) | | |
| occurrences (all) | 10 | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | | |
| occurrences (all) | 4 | | |
| Leukocytosis | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | | |
| occurrences (all) | 6 | | |
| Leukopenia | | | |
| subjects affected / exposed | 21 / 67 (31.34%) | | |
| occurrences (all) | 26 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | | |
| occurrences (all) | 4 | | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | | |
| occurrences (all) | 4 | | |
| Vertigo | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | | |
| occurrences (all) | 6 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 11 / 67 (16.42%) | | |
| occurrences (all) | 13 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 67 (7.46%) | | |
| occurrences (all) | 6 | | |
| Constipation | | | |
| subjects affected / exposed | 23 / 67 (34.33%) | | |
| occurrences (all) | 32 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 21 / 67 (31.34%) | | |
| occurrences (all) | 34 | | |
| Dyspepsia | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Flatulence</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>9 / 67 (13.43%)</p> <p>12</p> <p>7 / 67 (10.45%)</p> <p>10</p> <p>24 / 67 (35.82%)</p> <p>33</p> <p>14 / 67 (20.90%)</p> <p>15</p> | | |
| <p>Hepatobiliary disorders</p> <p>Cholestasis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 67 (5.97%)</p> <p>4</p> | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Acne</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Alopecia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Night sweats</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 67 (7.46%)</p> <p>5</p> <p>5 / 67 (7.46%)</p> <p>6</p> <p>8 / 67 (11.94%)</p> <p>13</p> <p>5 / 67 (7.46%)</p> <p>8</p> | | |
| <p>Renal and urinary disorders</p> <p>Dysuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Haematuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leukocyturia</p> | <p>8 / 67 (11.94%)</p> <p>9</p> <p>7 / 67 (10.45%)</p> <p>7</p> | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Proteinuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urinary retention</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 67 (5.97%)</p> <p>6</p> <p>10 / 67 (14.93%)</p> <p>10</p> <p>4 / 67 (5.97%)</p> <p>4</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Joint swelling</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Muscle spasms</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>7 / 67 (10.45%)</p> <p>8</p> <p>11 / 67 (16.42%)</p> <p>13</p> <p>5 / 67 (7.46%)</p> <p>5</p> <p>7 / 67 (10.45%)</p> <p>11</p> <p>7 / 67 (10.45%)</p> <p>8</p> | | |
| <p>Infections and infestations</p> <p>BK virus infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cytomegalovirus infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cytomegalovirus viraemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasopharyngitis</p> | <p>9 / 67 (13.43%)</p> <p>9</p> <p>5 / 67 (7.46%)</p> <p>5</p> <p>6 / 67 (8.96%)</p> <p>11</p> | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 16 / 67 (23.88%) | | |
| occurrences (all) | 20 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 67 (13.43%) | | |
| occurrences (all) | 11 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 14 / 67 (20.90%) | | |
| occurrences (all) | 18 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | | |
| occurrences (all) | 4 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 7 / 67 (10.45%) | | |
| occurrences (all) | 7 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 7 / 67 (10.45%) | | |
| occurrences (all) | 9 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 10 / 67 (14.93%) | | |
| occurrences (all) | 11 | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | | |
| occurrences (all) | 4 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 8 / 67 (11.94%) | | |
| occurrences (all) | 8 | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | | |
| occurrences (all) | 7 | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | | |
| occurrences (all) | 6 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 08 January 2013 | There was only one substantial amendment of the trial protocol during the course of this clinical trial. The trial eligibility criteria were modified to accelerate the rate of patient recruitment, the Visit 3 protocol graft biopsy was changed from mandatory to optional to enable Investigators to perform protocol biopsies at their discretion, the definition of the primary endpoint was simplified, and the overall volume of blood collected from trial patients for a scientific subproject was reduced. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported