



## Clinical trial results:

**A single site, placebo controlled, double blind randomised clinical trial evaluating the effectiveness of metformin to prevent post-transplant diabetes in a cohort of patients undergoing renal transplantation.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2017-004880-11 |
| Trial protocol           | GB             |
| Global end of trial date | 30 May 2022    |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 18 June 2023 |
| First version publication date | 18 June 2023 |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 012280 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |                               |
|------------------------------------|-------------------------------|
| ISRCTN number                      | -                             |
| ClinicalTrials.gov id (NCT number) | NCT05240274                   |
| WHO universal trial number (UTN)   | -                             |
| Other trial identifiers            | REC: 18/LO/0958, IRAS: 203080 |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Barts Health NHS Trust  |
| Sponsor organisation address | Joint Research and Management Office, Dept. W, 69-89 Mile End Rd, London , London, United Kingdom, E1 4UJ |
| Public contact               | Dr Kieran McCafferty, Barts Health NHS Trust<br>, kieran.mccafferty4@nhs.net                              |
| Scientific contact           | Dr Kieran McCafferty, Barts Health NHS Trust<br>, kieran.mccafferty4@nhs.net                              |

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:

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## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 06 October 2022 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 30 May 2022     |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 30 May 2022     |
| Was the trial ended prematurely?                     | No              |

Notes:

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## General information about the trial

Main objective of the trial:

To determine whether treating post-renal transplant patients with metformin as compared with placebo for 3 months lead to a long term reduction in post transplant diabetes mellitus, as defined by a positive 2 hour oral glucose tolerance test 1 year post transplant.

Protection of trial subjects:

Participants were given a minimum 24 hours after being invited to take part in the clinical trial prior to being consented. They were encouraged to ask questions and were made aware that they could withdraw consent and stop participation in the trial at any time.

Every effort was made to minimise any additional burden on the participants by synchronising trial visits with clinical visits and taking trial blood samples at the same time as clinical blood samples.

Data protection and pseudonymisation were performed in line with recognised standards: the trial was performed in adherence to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and all subsequent amendments of the clinical trial regulations, current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

Background therapy:

All participants received standard clinical care post-transplantation. This included triple immunosuppression (i.e. tacrolimus, mycophenolate mofetil and prednisolone). Clinicians were able to alter participants' medical therapies per clinical indication. If the IMP was thought to be responsible or contributing to an adverse event or serious adverse event, it could be held after discussion with the trial PI. If participants were thought to have developed hyperglycaemia, then their case should be discussed with the trial PI who would request an oral glucose tolerance test. Should it be found to be positive, the initiation of anti-diabetic medication would be determined on a case by case basis, with discussion between the PI and the clinical team.

Evidence for comparator:

Kidney transplantation is widely held to be the optimal form of renal replacement therapy for patients with end-stage renal disease, leading to a longer survival and improved quality of life in patients receiving a renal transplant compared to those that remain on dialysis. However renal transplantation brings with it a new set of challenges for the clinician. One of the most important of these is post-transplant diabetes mellitus (PTDM). The prevalence of PTDM has increased over time and may occur in up to a third of all post-transplant patients making it a critical challenge for transplant physicians.

PTDM tends to occur early post-transplant, with most patients developing PTDM within the first 3-6 months. A reason for this is the higher doses of immunosuppressive medication used during the early transplant period. Thus, the early post-transplant period represents a crucial window to intervene to reduce the incidence of PTDM.

Recent evidence suggests that basal insulin may protect the pancreas from the pro-diabetogenic stimuli in the first months post-transplantation, thus preventing PTDM. However, insulin with its risks of hypoglycaemia and weight gain may not be the ideal therapy for this patient group.

Metformin is a biguanide which leads to a reduction in hyperglycaemia by reducing the expression of gluconeogenesis genes, enhancing the uptake of glucose into cells and reducing free fatty acids which are the substrate for gluconeogenesis. It is recommended as the first line treatment for patients with type 2 diabetes.

Our hypothesis is that treatment with metformin is safe and will significantly reduce the incidence of diabetes in a post renal transplant cohort of patients in a London Transplant unit.

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 22 January 2019 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

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### Population of trial subjects

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#### Subjects enrolled per country

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|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 60 |
| Worldwide total number of subjects   | 60                 |
| EEA total number of subjects         | 0                  |

Notes:

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#### Subjects enrolled per age group

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|   |    |
|---|----|
| 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)                      | 56 |
| From 65 to 84 years                       | 4  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment took place at the Royal London Hospital from Jan 2019 to April 2021. There were two pauses to recruitment from March-July 2020 and from Dec 2020-March 2021 due to the COVID-19 pandemic: transplantation activity was halted and trial staff redeployed.

### Pre-assignment

Screening details:

Eligible patients needed to be consented and have a negative OGTT and eGFR  $\geq 30$  ml/min within 10 days of transplant. Of 190 people approached: 39 declined, 30 did not meet criteria, already met target for 4; 30 screen-fail eGFR, 24 screen-fail OGTT; 2 screen-fail both; 1 started anti-diabetic drug; 60 enrolled and randomised.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Investigator, Carer, Subject   |

Blinding implementation details:

A spreadsheet of treatment codes (linked to either active substance or placebo) was created using an online generator using a block randomisation sequence and stored in the pharmacy dispensary. Each treatment code (for example A1, A2,...A60), was written on a card and sealed in an envelope. At randomisation, one envelope was chosen at random to associate study IDs with treatment codes. Only pharmacy and sponsor team had access to the treatment code matched to the treatment allocation.

### Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | Metformin |

Arm description:

Patients received 500mg OD metformin

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Metformin    |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

500mg once daily

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Patients received placebo

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Placebo 500mg once daily

| <b>Number of subjects in period 1</b> | Metformin | Placebo |
|---------------------------------------|-----------|---------|
| Started                               | 30        | 30      |
| Completed                             | 30        | 30      |

## Baseline characteristics

### Reporting groups

|                                      |           |
|--------------------------------------|-----------|
| Reporting group title                | Metformin |
| Reporting group description:         |           |
| Patients received 500mg OD metformin |           |
| Reporting group title                | Placebo   |
| Reporting group description:         |           |
| Patients received placebo            |           |

| Reporting group values                                     | Metformin | Placebo | Total |
|--|-----------|---------|-------|
| Number of subjects   | 30        | 30      | 60    |
| Age categorical  |           |         |       |
| Units: Subjects  |           |         |       |
| In utero   |           |         | 0     |
| Preterm newborn infants (gestational age < 37 wks)         |           |         | 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)                                       |           |         | 0     |
| From 65-84 years   |           |         | 0     |
| 85 years and over  |           |         | 0     |
| Age continuous   |           |         |       |
| age of patients  |           |         |       |
| Units: years   |           |         |       |
| arithmetic mean  | 41.5      | 46.6    |       |
| standard deviation   | ± 12.6    | ± 15.5  | -     |
| Gender categorical   |           |         |       |
| Units: Subjects  |           |         |       |
| Female   | 11        | 12      | 23    |
| Male   | 19        | 18      | 37    |
| Patient ethnicity  |           |         |       |
| patient ethnicity  |           |         |       |
| Units: Subjects  |           |         |       |
| Asian  | 10        | 4       | 14    |
| Black  | 5         | 12      | 17    |
| White  | 15        | 13      | 28    |
| Other  | 0         | 1       | 1     |
| Family history of diabetes mellitus                        |           |         |       |
| Family history of diabetes mellitus                        |           |         |       |
| Units: Subjects  |           |         |       |
| Yes  | 13        | 9       | 22    |
| No   | 17        | 21      | 38    |
| Dialysis modality  |           |         |       |
| Type of renal replacement therapy prior to transplantation |           |         |       |
| Units: Subjects  |           |         |       |

|   |    |    |    |
|---|----|----|----|
| Peritoneal dialysis   | 6  | 9  | 15 |
| Haemodialysis   | 17 | 14 | 31 |
| Pre-dialysis (pre-emptive transplant)   | 7  | 7  | 14 |
| Cause of end-stage renal disease  |    |    |    |
| Cause of ESRF (broad categories)  |    |    |    |
| Units: Subjects   |    |    |    |
| Glomerular  | 11 | 11 | 22 |
| Vascular  | 5  | 12 | 17 |
| Tubulointerstitial  | 0  | 0  | 0  |
| Polycystic kidney disease   | 6  | 0  | 6  |
| Unknown   | 6  | 3  | 9  |
| Other   | 2  | 4  | 6  |
| Previous transplant   |    |    |    |
| History of previous transplant (no recipient had had more than one previous transplant) |    |    |    |
| Units: Subjects   |    |    |    |
| No  | 25 | 25 | 50 |
| Yes   | 5  | 5  | 10 |
| Smoking status  |    |    |    |
| Smoking status  |    |    |    |
| Units: Subjects   |    |    |    |
| No  | 29 | 30 | 59 |
| Yes   | 1  | 0  | 1  |
| Type of transplant  |    |    |    |
| Type of renal transplant  |    |    |    |
| Units: Subjects   |    |    |    |
| DBD   | 15 | 19 | 34 |
| DCD   | 0  | 2  | 2  |
| live unrelated  | 6  | 4  | 10 |
| live related  | 9  | 5  | 14 |
| Extended criteria donor   |    |    |    |
| Extended criteria donor   |    |    |    |
| Units: Subjects   |    |    |    |
| No  | 15 | 19 | 34 |
| Yes   | 0  | 2  | 2  |
| Not applicable (live donor)   | 15 | 9  | 24 |
| Donor cause of death  |    |    |    |
| Donor cause of death (broad categories)   |    |    |    |
| Units: Subjects   |    |    |    |
| Vascular  | 9  | 11 | 20 |
| Trauma  | 1  | 3  | 4  |
| Hypoxic   | 5  | 4  | 9  |
| Infective   | 0  | 1  | 1  |
| Other   | 0  | 2  | 2  |
| Not available   | 15 | 9  | 24 |
| Donor sex   |    |    |    |
| Donor sex   |    |    |    |
| Units: Subjects   |    |    |    |
| Female  | 16 | 11 | 27 |
| Male  | 14 | 19 | 33 |
| CMV serology match  |    |    |    |

|  |              |                |    |
|--|--------------|----------------|----|
| Donor to recipient CMV status                                  |              |                |    |
| Units: Subjects  |              |                |    |
| -/-  | 5            | 6              | 11 |
| -/+  | 8            | 8              | 16 |
| +/-  | 2            | 3              | 5  |
| +/+  | 15           | 13             | 28 |
| HLA mismatch (total)   |              |                |    |
| Number of HLA mismatches (total)                               |              |                |    |
| Units: Subjects  |              |                |    |
| 0 MM   | 2            | 1              | 3  |
| 1 MM   | 3            | 3              | 6  |
| 2 MM   | 4            | 7              | 11 |
| 3 MM   | 12           | 11             | 23 |
| 4 MM   | 5            | 3              | 8  |
| 5 MM   | 3            | 5              | 8  |
| 6 MM   | 1            | 0              | 1  |
| Time on dialysis (vintage)                                     |              |                |    |
| number of days spent on dialysis                               |              |                |    |
| Units: days  |              |                |    |
| median   | 662          | 882            |    |
| inter-quartile range (Q1-Q3)                                   | 410 to 1992  | 515 to 1522    | -  |
| Time on transplant waitlist                                    |              |                |    |
| number of days on transplant waiting list                      |              |                |    |
| Units: days  |              |                |    |
| median   | 251.5        | 336.5          |    |
| inter-quartile range (Q1-Q3)                                   | 51.3 to 421  | 161.5 to 800.5 | -  |
| Height of patient  |              |                |    |
| patient height in metres                                       |              |                |    |
| Units: metre   |              |                |    |
| arithmetic mean  | 1.72         | 1.70           |    |
| standard deviation   | ± 0.10       | ± 0.13         | -  |
| Weight at screening  |              |                |    |
| patient weight in kg at screening visit                        |              |                |    |
| Units: kilograms   |              |                |    |
| median   | 79.5         | 73.5           |    |
| inter-quartile range (Q1-Q3)                                   | 68.6 to 87.3 | 62.2 to 81.9   | -  |
| BMI at screening   |              |                |    |
| patient BMI at screening visit in kilograms per metres squared |              |                |    |
| Units: kg/m2   |              |                |    |
| median   | 26.2         | 24.9           |    |
| inter-quartile range (Q1-Q3)                                   | 23.9 to 29.1 | 22.1 to 27.3   | -  |
| Donor age  |              |                |    |
| age of kidney donor  |              |                |    |
| Units: years   |              |                |    |
| arithmetic mean  | 43.5         | 47.9           |    |
| standard deviation   | ± 14.1       | ± 16.5         | -  |
| Transplant CIT   |              |                |    |
| cold ischaemia time of transplant in minutes                   |              |                |    |
| Units: minutes   |              |                |    |
| median   | 404.5        | 588.5          |    |
| inter-quartile range (Q1-Q3)                                   | 236 to 765   | 277.5 to 866.3 | -  |
| Transplant WIT   |              |                |    |



|  |              |                |   |
|--|--------------|----------------|---|
| secondary warm ischaemia time of transplant in minutes |              |                |   |
| Units: minutes   |              |                |   |
| median   | 31.5         | 32.5           |   |
| inter-quartile range (Q1-Q3)                           | 27.8 to 44.3 | 28.5 to 42.8   | - |
| Units of alcohol/week                                  |              |                |   |
| Units of alcohol consumed per week                     |              |                |   |
| Units: units   |              |                |   |
| median   | 0            | 0              |   |
| inter-quartile range (Q1-Q3)                           | 0 to 0       | 0 to 0         | - |
| Systolic BP at screening                               |              |                |   |
| Systolic BP at screening                               |              |                |   |
| Units: mmHg  |              |                |   |
| arithmetic mean  | 147          | 152            |   |
| standard deviation                                     | ± 16.4       | ± 21.8         | - |
| Diastolic BP at screening                              |              |                |   |
| Diastolic BP at screening                              |              |                |   |
| Units: mmHg  |              |                |   |
| arithmetic mean  | 89           | 87             |   |
| standard deviation                                     | ± 10.8       | ± 10.1         | - |
| Hb at screening  |              |                |   |
| Haemoglobin at screening                               |              |                |   |
| Units: g/L   |              |                |   |
| arithmetic mean  | 95.4         | 89.5           |   |
| standard deviation                                     | ± 15.2       | ± 11.5         | - |
| WBC at screening                                       |              |                |   |
| White blood cell count at screening                    |              |                |   |
| Units: x10 <sup>9</sup>                                |              |                |   |
| median   | 6.9          | 7.4            |   |
| inter-quartile range (Q1-Q3)                           | 5.3 to 8.2   | 5.8 to 9.3     | - |
| Plts at screening                                      |              |                |   |
| Platelet count at screening                            |              |                |   |
| Units: x10 <sup>9</sup>                                |              |                |   |
| median   | 166          | 167            |   |
| inter-quartile range (Q1-Q3)                           | 132.8 to 195 | 138.3 to 235.3 | - |
| Na at screening  |              |                |   |
| Serum sodium at screening                              |              |                |   |
| Units: mmol/L  |              |                |   |
| median   | 139          | 139            |   |
| inter-quartile range (Q1-Q3)                           | 137 to 140   | 137 to 141     | - |
| K at screening   |              |                |   |
| Serum potassium at screening                           |              |                |   |
| Units: mmol/L  |              |                |   |
| arithmetic mean  | 4.4          | 4.4            |   |
| standard deviation                                     | ± 0.5        | ± 0.4          | - |
| Bicarb at screening                                    |              |                |   |
| Serum bicarbonate at screening                         |              |                |   |
| Units: mmol/L  |              |                |   |
| arithmetic mean  | 23           | 22             |   |
| standard deviation                                     | ± 2.7        | ± 2.9          | - |
| Urea at screening                                      |              |                |   |
| Serum urea at screening                                |              |                |   |
| Units: mmol/L  |              |                |   |

|   |              |              |   |
|---|--------------|--------------|---|
| median  | 8.0          | 8.9          |   |
| inter-quartile range (Q1-Q3)                    | 6.0 to 9.2   | 5.3 to 11.0  | - |
| Creatinine at screening                         |              |              |   |
| Serum creatinine at screening                   |              |              |   |
| Units: umol/L                                   |              |              |   |
| arithmetic mean                                 | 143          | 156          |   |
| standard deviation                              | ± 40.8       | ± 42.3       | - |
| eGFR at screening                               |              |              |   |
| Estimated glomerular function rate at screening |              |              |   |
| Units: ml/min                                   |              |              |   |
| median  | 42           | 35           |   |
| inter-quartile range (Q1-Q3)                    | 36 to 55     | 32 to 52     | - |
| ALT at screening                                |              |              |   |
| Serum alanine transaminase at screening         |              |              |   |
| Units: unit/L                                   |              |              |   |
| median  | 25           | 28           |   |
| inter-quartile range (Q1-Q3)                    | 15.8 to 35   | 17 to 46.8   | - |
| ALP at screening                                |              |              |   |
| Serum alkaline phosphatase at screening         |              |              |   |
| Units: unit/L                                   |              |              |   |
| median  | 60           | 61           |   |
| inter-quartile range (Q1-Q3)                    | 48 to 72     | 48.8 to 77.8 | - |
| cCa at screening                                |              |              |   |
| Serum corrected calcium at screening            |              |              |   |
| Units: mmol/L                                   |              |              |   |
| arithmetic mean                                 | 2.34         | 2.29         |   |
| standard deviation                              | ± 0.2        | ± 0.2        | - |
| PO4 at screening                                |              |              |   |
| Serum phosphate at screening                    |              |              |   |
| Units: mmol/L                                   |              |              |   |
| median  | 0.63         | 0.82         |   |
| inter-quartile range (Q1-Q3)                    | 0.55 to 0.76 | 0.52 to 0.96 | - |
| CRP at screening                                |              |              |   |
| Serum C-reactive protein at screening           |              |              |   |
| Units: mg/L                                     |              |              |   |
| median  | 7            | 11.5         |   |
| inter-quartile range (Q1-Q3)                    | 5 to 14.5    | 8 to 14      | - |
| Triglycerides at screening                      |              |              |   |
| Serum triglycerides at screening                |              |              |   |
| Units: mmol/L                                   |              |              |   |
| median  | 1.83         | 1.43         |   |
| inter-quartile range (Q1-Q3)                    | 1.33 to 2.25 | 1.11 to 1.69 | - |
| Mg at screening                                 |              |              |   |
| Serum magnesium at screening                    |              |              |   |
| Units: mmol/L                                   |              |              |   |
| median  | 0.8          | 0.9          |   |
| inter-quartile range (Q1-Q3)                    | 0.7 to 0.9   | 0.7 to 1.0   | - |
| Glucose at screening                            |              |              |   |
| Serum glucose at screening                      |              |              |   |
| Units: mmol/L                                   |              |              |   |
| median  | 4.9          | 5.0          |   |
| inter-quartile range (Q1-Q3)                    | 4.5 to 5.4   | 4.6 to 5.5   | - |

|   |               |               |   |
|---|---------------|---------------|---|
| HbA1c at screening  |               |               |   |
| Glycated haemoglobin at screening (mmol/mol)                                  |               |               |   |
| Units: mmol/mol   |               |               |   |
| arithmetic mean   | 33            | 33            |   |
| standard deviation  | ± 4.4         | ± 4.2         | - |
| UPCR at screening   |               |               |   |
| Urine protein:creatinine ratio at screening                                   |               |               |   |
| Units: mg/mmol  |               |               |   |
| median  | 46.6          | 57.1          |   |
| inter-quartile range (Q1-Q3)  | 31.4 to 63.0  | 31.7 to 76.0  | - |
| C-peptide at screening  |               |               |   |
| Serum C-peptide at screening  |               |               |   |
| Units: pmol/L   |               |               |   |
| median  | 1136          | 1143          |   |
| inter-quartile range (Q1-Q3)  | 872 to 1379.5 | 860.5 to 1444 | - |
| HOMA-IR at screening  |               |               |   |
| HOMA-IR (calculated measure of insulin resistance) at screening               |               |               |   |
| Units: units  |               |               |   |
| median  | 2.5           | 2.58          |   |
| inter-quartile range (Q1-Q3)  | 1.86 to 2.94  | 1.80 to 3.23  | - |
| Tacrolimus level at screening   |               |               |   |
| Serum tacrolimus level at screening   |               |               |   |
| Units: mcg/L  |               |               |   |
| arithmetic mean   | 8.9           | 7.6           |   |
| standard deviation  | ± 4.0         | ± 4.4         | - |
| OGTT time 0 at screening  |               |               |   |
| Glucose level at time 0 of oral glucose tolerance test at screening           |               |               |   |
| Units: mmol/L   |               |               |   |
| arithmetic mean   | 4.7           | 4.8           |   |
| standard deviation  | ± 0.6         | ± 0.6         | - |
| OGTT time 2 at screening  |               |               |   |
| Glucose level at time 2 (2 hours) of oral glucose tolerance test at screening |               |               |   |
| Units: mmol/L   |               |               |   |
| arithmetic mean   | 7.8           | 8.5           |   |
| standard deviation  | ± 1.7         | ± 1.3         | - |
| CMV at screening  |               |               |   |
| Cytomegalovirus DNA viral load at screening                                   |               |               |   |
| Units: log units  |               |               |   |
| median  | 0             | 0             |   |
| inter-quartile range (Q1-Q3)  | 0 to 0        | 0 to 0        | - |
| BKV at screening  |               |               |   |
| BK virus DNA viral load at screening  |               |               |   |
| Units: log units  |               |               |   |
| median  | 0             | 0             |   |
| inter-quartile range (Q1-Q3)  | 0 to 0        | 0 to 0        | - |

## End points

### End points reporting groups

|  |           |
|--|-----------|
| Reporting group title  | Metformin |
| Reporting group description:<br>Patients received 500mg OD metformin |           |
| Reporting group title  | Placebo   |
| Reporting group description:<br>Patients received placebo            |           |

### Primary: Primary: Diagnosis of PTDM

|  |                            |
|--|----------------------------|
| End point title  | Primary: Diagnosis of PTDM |
| End point description:<br>The primary end point is the diagnosis of diabetes following a 3 month course of metformin or placebo, defined as a positive 2-hour Oral Glucose tolerance (blood sugar greater than 11.1mmol/l) test at 3, 6, or 12 months post-transplant, or following an OGTT due to suspected new diabetes at other routine clinical visits |                            |
| End point type   | Primary                    |
| End point timeframe:<br>Between randomisation visit and month 12 visit   |                            |

| End point values            | Metformin         | Placebo           |  |  |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type          | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed | 30 <sup>[1]</sup> | 30 <sup>[2]</sup> |  |  |
| Units: proportion           |                   |                   |  |  |
| PTDM                        | 7                 | 5                 |  |  |
| No PTDM                     | 23                | 25                |  |  |

Notes:

[1] - intention to treat

[2] - intention to treat

### Statistical analyses

|  |                       |
|--|-----------------------|
| Statistical analysis title   | Kaplan-Meier survival |
| Statistical analysis description:<br>Survival curve where event was defined as a diagnosis of PTDM by OGTT at any point between randomisation visit and 12 month visit |                       |
| Comparison groups  | Metformin v Placebo   |
| Number of subjects included in analysis  | 60                    |
| Analysis specification   | Pre-specified         |
| Analysis type  | equivalence           |
| P-value  | > 0.05                |
| Method   | Logrank               |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>   | Chi-square                 |
| Statistical analysis description:<br>Diagnosis of PTDM as defined by positive OGTT at 3, 6 or 12 month visits |                            |
| Comparison groups   | Metformin v Placebo        |
| Number of subjects included in analysis   | 60                         |
| Analysis specification  | Pre-specified              |
| Analysis type   | equivalence <sup>[3]</sup> |
| P-value   | > 0.05                     |
| Method  | Chi-squared                |

Notes:

[3] - Chi-square test

## Secondary: HOMA IR

|   |           |
|---|-----------|
| End point title   | HOMA IR   |
| End point description:<br>The effect of 3/12 metformin on markers of pancreatic beta cell function using the HOMA-IR test (a calculation of insulin resistance) at 3,6, and 12 months |           |
| End point type  | Secondary |
| End point timeframe:<br>from randomisation visit to 12 month visit  |           |

| End point values                     | Metformin          | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 30 <sup>[4]</sup>  | 30 <sup>[5]</sup>  |  |  |
| Units: units                         |                    |                    |  |  |
| arithmetic mean (standard deviation) | 2.74 ( $\pm$ 1.22) | 1.83 ( $\pm$ 1.10) |  |  |

Notes:

[4] - intention to treat

[5] - intention to treat

## Statistical analyses

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>                                 | 2-way repeated measure ANOVA |
| Statistical analysis description:<br>2-way repeated measure ANOVA |                              |
| Comparison groups   | Metformin v Placebo          |
| Number of subjects included in analysis                           | 60                           |
| Analysis specification  | Pre-specified                |
| Analysis type   | equivalence <sup>[6]</sup>   |
| P-value   | > 0.05 <sup>[7]</sup>        |
| Method  | ANOVA                        |

Notes:

[6] - within subject = time; between subject = treatment allocation

[7] - no significant difference caused by treatment allocation

## Secondary: HbA1c

|                 |       |
|-----------------|-------|
| End point title | HbA1c |
|-----------------|-------|

End point description:

2 way repeated measure ANOVA on the effect of 3 months of metformin on HbA1c at 3, 6 and 12 months from baseline

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

End point timeframe:

from randomisation visit to month 12 visit

| End point values                     | Metformin       | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 30              | 30              |  |  |
| Units: mmol/mol                      |                 |                 |  |  |
| arithmetic mean (standard deviation) | 39.4 (± 6.8)    | 36.4 (± 4.5)    |  |  |

### Statistical analyses

|   |                               |
|---|-------------------------------|
| Statistical analysis title              | 2-way repeated measures ANOVA |
| Comparison groups                       | Placebo v Metformin           |
| Number of subjects included in analysis | 60                            |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | equivalence                   |
| P-value                                 | > 0.05 [8]                    |
| Method                                  | ANOVA                         |

Notes:

[8] - change was significant over time but not by treatment allocation

### Secondary: IGTT

|                 |      |
|-----------------|------|
| End point title | IGTT |
|-----------------|------|

End point description:

Chi-Square and Kaplan-Meier survival analysis on whether participants developed impaired glucose tolerance or post-transplant diabetes mellitus

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

End point timeframe:

from randomisation visit to 12 month visit

| End point values            | Metformin       | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 30              | 30              |  |  |
| Units: proportion/patients  |                 |                 |  |  |
| No                          | 18              | 16              |  |  |
| IGT or OGTT                 | 12              | 14              |  |  |

### Statistical analyses

|   |                     |
|---|---------------------|
| <b>Statistical analysis title</b>       | Kaplan-Meier        |
| Comparison groups                       | Metformin v Placebo |
| Number of subjects included in analysis | 60                  |
| Analysis specification                  | Pre-specified       |
| Analysis type                           | equivalence         |
| P-value                                 | > 0.05              |
| Method                                  | Logrank             |

### Secondary: Renal function at 12 months

|   |                             |
|---|-----------------------------|
| End point title   | Renal function at 12 months |
| End point description:<br>renal function as measured by eGFR: difference between randomisation to 12 month (last eGFR carried forward if missing value) |                             |
| End point type  | Secondary                   |
| End point timeframe:<br>from randomisation to month 12 visit  |                             |

|                                      |                   |                    |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| <b>End point values</b>              | Metformin         | Placebo            |  |  |
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 30 <sup>[9]</sup> | 30 <sup>[10]</sup> |  |  |
| Units: ml/min                        |                   |                    |  |  |
| arithmetic mean (standard deviation) | 56 (± 18.3)       | 51 (± 15.2)        |  |  |

Notes:

[9] - intention to treat

[10] - intention to treat

### Statistical analyses

|   |                     |
|---|---------------------|
| <b>Statistical analysis title</b>       | t-test              |
| Comparison groups                       | Metformin v Placebo |
| Number of subjects included in analysis | 60                  |
| Analysis specification                  | Pre-specified       |
| Analysis type                           | equivalence         |
| P-value                                 | > 0.05              |
| Method                                  | t-test, 2-sided     |

**Secondary: Patient/graft survival**

|                 |                        |
|-----------------|------------------------|
| End point title | Patient/graft survival |
|-----------------|------------------------|

End point description:

patient or graft survival over 12 months - all patients and grafts survived hence no further statistical analysis completed

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

End point timeframe:

from randomisation to month 12 visit

| End point values               | Metformin          | Placebo            |  |  |
|--------------------------------|--------------------|--------------------|--|--|
| Subject group type             | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed    | 30 <sup>[11]</sup> | 30 <sup>[12]</sup> |  |  |
| Units: proportion/participants |                    |                    |  |  |
| Graft survived                 | 30                 | 30                 |  |  |
| Patient survived               | 30                 | 30                 |  |  |

Notes:

[11] - intention to treat

[12] - intention to treat

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Episodes of acute rejection**

|                 |                             |
|-----------------|-----------------------------|
| End point title | Episodes of acute rejection |
|-----------------|-----------------------------|

End point description:

episodes of acute rejection

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

End point timeframe:

from randomisation to month 12 visit

| End point values               | Metformin       | Placebo         |  |  |
|--------------------------------|-----------------|-----------------|--|--|
| Subject group type             | Reporting group | Reporting group |  |  |
| Number of subjects analysed    | 30              | 30              |  |  |
| Units: proportion/participants |                 |                 |  |  |
| Rejection                      | 2               | 3               |  |  |
| No rejection                   | 28              | 27              |  |  |

**Statistical analyses**

|                            |                       |
|----------------------------|-----------------------|
| Statistical analysis title | Kaplan-Meier survival |
|----------------------------|-----------------------|

|                   |                     |
|-------------------|---------------------|
| Comparison groups | Metformin v Placebo |
|-------------------|---------------------|



|   |               |
|---|---------------|
| Number of subjects included in analysis | 60            |
| Analysis specification                  | Pre-specified |
| Analysis type                           | equivalence   |
| P-value                                 | > 0.05        |
| Method                                  | Logrank       |

## Secondary: AE events

|   |           |
|---|-----------|
| End point title   | AE events |
| End point description:<br>rate of AEs (inc SAEs) as per MedDRA system organ class - no adjustment for multiple events per subject |           |
| End point type  | Secondary |
| End point timeframe:<br>from screening visit to month 12 visit  |           |

| End point values                  | Metformin       | Placebo         |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 30              | 30              |  |  |
| Units: proportion/participants    |                 |                 |  |  |
| Blood & Lymphatic AE              | 14              | 19              |  |  |
| Cardiac AE                        | 2               | 2               |  |  |
| ENT AE                            | 0               | 2               |  |  |
| Endocrine AE                      | 1               | 0               |  |  |
| Eye AE                            | 4               | 3               |  |  |
| Gastro AE                         | 14              | 22              |  |  |
| General Disorders AE              | 20              | 9               |  |  |
| Immune System AE                  | 2               | 3               |  |  |
| Infections & Infestations AE      | 27              | 29              |  |  |
| Injury, Poisoning & Procedural AE | 18              | 16              |  |  |
| Investigations AE                 | 25              | 22              |  |  |
| Metabolism & Nutrition AE         | 9               | 8               |  |  |
| Musculoskeletal AE                | 10              | 15              |  |  |
| Neoplasms AE                      | 2               | 3               |  |  |
| Nervous System AE                 | 17              | 13              |  |  |
| Psych AE                          | 2               | 5               |  |  |
| Renal & GU AE                     | 15              | 20              |  |  |
| Reproductive & Breast AE          | 5               | 1               |  |  |
| Resp AE                           | 8               | 6               |  |  |
| Skin AE                           | 10              | 12              |  |  |
| Social AE                         | 1               | 0               |  |  |
| Surgical & Medical Procedures AE  | 1               | 4               |  |  |
| Vascular AE                       | 24              | 21              |  |  |

## Statistical analyses

|   |                         |
|---|-------------------------|
| <b>Statistical analysis title</b>       | Mann Whitney U          |
| Comparison groups                       | Metformin v Placebo     |
| Number of subjects included in analysis | 60                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | equivalence             |
| P-value                                 | > 0.05                  |
| Method                                  | Wilcoxon (Mann-Whitney) |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

from consent to 12 months after randomisation

Adverse event reporting additional description:

AE collected at each study visit

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 25 |
|--------------------|----|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Metformin |
|-----------------------|-----------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events  | Metformin       | Placebo         |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events                   |                 |                 |  |
| subjects affected / exposed   | 7 / 30 (23.33%) | 9 / 30 (30.00%) |  |
| 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) |                 |                 |  |
| Post transplant lymphoproliferative disorder                        |                 |                 |  |
| subjects affected / exposed   | 1 / 30 (3.33%)  | 0 / 30 (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                      |                 |                 |  |
| Post-procedural urine leak  |                 |                 |  |
| subjects affected / exposed   | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                                     |                 |                 |  |
| Arteriovenous fistula operation                                     |                 |                 |  |
| subjects affected / exposed   | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Inguinal hernia repair                          |                |                |  |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal artery stent placement                    |                |                |  |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |
| Febrile neutropenia                             |                |                |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 30 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Immune system disorders                         |                |                |  |
| Kidney transplant rejection                     |                |                |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 30 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Abdominal pain                                  |                |                |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vomiting  |                |                |  |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                           |                |                |  |
| Confusional state                               |                |                |  |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Perinephric collection                          |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Campylobacter gastroenteritis                   |                |                |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 30 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Clostridium difficile colitis                   |                |                |  |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| COVID-19  |                |                |  |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cytomegalovirus viraemia                        |                |                |  |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 2 / 30 (6.67%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Escherichia bacteraemia                         |                |                |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 30 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumocystis jiroveci pneumonia                 |                |                |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 30 (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                     | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia pseudomonal                           |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Strongyloidiasis</b>                         |                |                |  |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Urinary tract infection</b>                  |                |                |  |
| subjects affected / exposed                     | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Urosepsis</b>                                |                |                |  |
| subjects affected / exposed                     | 1 / 30 (3.33%) | 0 / 30 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 3 %

| <b>Non-serious adverse events</b>  | Metformin         | Placebo           |  |
|--|-------------------|-------------------|--|
| <b>Total subjects affected by non-serious adverse events</b>               |                   |                   |  |
| subjects affected / exposed  | 30 / 30 (100.00%) | 30 / 30 (100.00%) |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                   |                   |  |
| <b>Skin papilloma</b>  |                   |                   |  |
| subjects affected / exposed  | 1 / 30 (3.33%)    | 2 / 30 (6.67%)    |  |
| occurrences (all)  | 1                 | 2                 |  |
| <b>Vascular disorders</b>  |                   |                   |  |
| <b>Blood pressure fluctuation</b>  |                   |                   |  |
| subjects affected / exposed  | 1 / 30 (3.33%)    | 0 / 30 (0.00%)    |  |
| occurrences (all)  | 1                 | 0                 |  |
| <b>Hypertension</b>  |                   |                   |  |
| subjects affected / exposed  | 20 / 30 (66.67%)  | 16 / 30 (53.33%)  |  |
| occurrences (all)  | 23                | 17                |  |
| <b>Hypotension</b>   |                   |                   |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 3 / 30 (10.00%)<br>4 | 5 / 30 (16.67%)<br>5 |  |
| Intermittent claudication<br>subjects affected / exposed<br>occurrences (all)   | 0 / 30 (0.00%)<br>0  | 1 / 30 (3.33%)<br>1  |  |
| Lymphocele<br>subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1  | 0 / 30 (0.00%)<br>0  |  |
| Lymphoedema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 30 (0.00%)<br>0  | 1 / 30 (3.33%)<br>1  |  |
| Orthostatic hypotension<br>subjects affected / exposed<br>occurrences (all)   | 1 / 30 (3.33%)<br>1  | 0 / 30 (0.00%)<br>0  |  |
| Pelvic venous thrombosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 30 (0.00%)<br>0  | 1 / 30 (3.33%)<br>1  |  |
| Thrombophlebitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 30 (0.00%)<br>0  | 1 / 30 (3.33%)<br>1  |  |
| Surgical and medical procedures<br>Thyroxine therapy<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 30 (0.00%)<br>0  | 1 / 30 (3.33%)<br>1  |  |
| Tooth extraction<br>subjects affected / exposed<br>occurrences (all)  | 0 / 30 (0.00%)<br>0  | 1 / 30 (3.33%)<br>1  |  |
| General disorders and administration<br>site conditions<br>Catheter site pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1  | 0 / 30 (0.00%)<br>0  |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)  | 2 / 30 (6.67%)<br>2  | 0 / 30 (0.00%)<br>0  |  |
| Fatigue   |                      |                      |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 7 / 30 (23.33%) | 2 / 30 (6.67%)  |  |
| occurrences (all)           | 7               | 2               |  |
| Gait disturbance            |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Malaise                     |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)           | 1               | 1               |  |
| Oedema                      |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Oedema peripheral           |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Pain                        |                 |                 |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Peripheral swelling         |                 |                 |  |
| subjects affected / exposed | 3 / 30 (10.00%) | 4 / 30 (13.33%) |  |
| occurrences (all)           | 3               | 5               |  |
| Puncture site haemorrhage   |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Pyrexia                     |                 |                 |  |
| subjects affected / exposed | 4 / 30 (13.33%) | 1 / 30 (3.33%)  |  |
| occurrences (all)           | 5               | 2               |  |
| Suprapubic pain             |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Swelling                    |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Swelling face               |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Immune system disorders     |                 |                 |  |



|  |                     |                      |  |
|--|---------------------|----------------------|--|
| Kidney transplant rejection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1 | 3 / 30 (10.00%)<br>3 |  |
| Social circumstances<br>Social problem<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0  |  |
| Reproductive system and breast disorders<br>Heavy menstrual bleeding<br>subjects affected / exposed<br>occurrences (all) | 0 / 30 (0.00%)<br>0 | 1 / 30 (3.33%)<br>1  |  |
| Painful erection<br>subjects affected / exposed<br>occurrences (all)   | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0  |  |
| Penile pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0  |  |
| Perineal pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0  |  |
| Polycystic ovaries<br>subjects affected / exposed<br>occurrences (all)   | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0  |  |
| Prostatism<br>subjects affected / exposed<br>occurrences (all)   | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0  |  |
| Testicular swelling<br>subjects affected / exposed<br>occurrences (all)  | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)             | 2 / 30 (6.67%)<br>2 | 2 / 30 (6.67%)<br>3  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0  |  |

|   |                      |                     |  |
|---|----------------------|---------------------|--|
| Dyspnoea exertional<br>subjects affected / exposed<br>occurrences (all)               | 3 / 30 (10.00%)<br>3 | 1 / 30 (3.33%)<br>1 |  |
| Increased bronchial secretion<br>subjects affected / exposed<br>occurrences (all)     | 0 / 30 (0.00%)<br>0  | 1 / 30 (3.33%)<br>1 |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 30 (3.33%)<br>1  | 0 / 30 (0.00%)<br>0 |  |
| Obstructive sleep apnoea syndrome<br>subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1  | 0 / 30 (0.00%)<br>0 |  |
| Productive cough<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 30 (3.33%)<br>1  | 2 / 30 (6.67%)<br>2 |  |
| Upper airway cough syndrome<br>subjects affected / exposed<br>occurrences (all)       | 0 / 30 (0.00%)<br>0  | 1 / 30 (3.33%)<br>1 |  |
| Psychiatric disorders   |                      |                     |  |
| Depressed mood<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 30 (3.33%)<br>1  | 0 / 30 (0.00%)<br>0 |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 30 (0.00%)<br>0  | 1 / 30 (3.33%)<br>1 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 30 (0.00%)<br>0  | 2 / 30 (6.67%)<br>2 |  |
| Irritability<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 30 (3.33%)<br>1  | 0 / 30 (0.00%)<br>0 |  |
| Paramnesia<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 30 (0.00%)<br>0  | 1 / 30 (3.33%)<br>1 |  |
| Paranoia  |                      |                     |  |

|  |                        |                      |  |
|--|------------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 30 (0.00%)<br>0    | 1 / 30 (3.33%)<br>1  |  |
| Investigations   |                        |                      |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 30 (3.33%)<br>1    | 0 / 30 (0.00%)<br>0  |  |
| Blood bicarbonate decreased<br>subjects affected / exposed<br>occurrences (all)            | 2 / 30 (6.67%)<br>2    | 5 / 30 (16.67%)<br>5 |  |
| Blood calcium decreased<br>subjects affected / exposed<br>occurrences (all)                | 3 / 30 (10.00%)<br>3   | 0 / 30 (0.00%)<br>0  |  |
| Blood calcium increased<br>subjects affected / exposed<br>occurrences (all)                | 1 / 30 (3.33%)<br>1    | 0 / 30 (0.00%)<br>0  |  |
| Blood cholesterol increased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 30 (3.33%)<br>1    | 1 / 30 (3.33%)<br>1  |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)             | 6 / 30 (20.00%)<br>6   | 4 / 30 (13.33%)<br>4 |  |
| Blood magnesium decreased<br>subjects affected / exposed<br>occurrences (all)              | 3 / 30 (10.00%)<br>3   | 0 / 30 (0.00%)<br>0  |  |
| Blood parathyroid hormone<br>increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1    | 0 / 30 (0.00%)<br>0  |  |
| Blood phosphorus decreased<br>subjects affected / exposed<br>occurrences (all)             | 11 / 30 (36.67%)<br>11 | 4 / 30 (13.33%)<br>4 |  |
| Blood potassium decreased<br>subjects affected / exposed<br>occurrences (all)              | 1 / 30 (3.33%)<br>1    | 0 / 30 (0.00%)<br>0  |  |
| Blood potassium increased  |                        |                      |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                    | 1 / 30 (3.33%)   | 0 / 30 (0.00%)   |  |
| occurrences (all)                              | 1                | 0                |  |
| Blood uric acid increased                      |                  |                  |  |
| subjects affected / exposed                    | 1 / 30 (3.33%)   | 0 / 30 (0.00%)   |  |
| occurrences (all)                              | 1                | 0                |  |
| Culture urine positive                         |                  |                  |  |
| subjects affected / exposed                    | 15 / 30 (50.00%) | 12 / 30 (40.00%) |  |
| occurrences (all)                              | 22               | 21               |  |
| Heart rate irregular                           |                  |                  |  |
| subjects affected / exposed                    | 0 / 30 (0.00%)   | 1 / 30 (3.33%)   |  |
| occurrences (all)                              | 0                | 1                |  |
| Liver function test abnormal                   |                  |                  |  |
| subjects affected / exposed                    | 2 / 30 (6.67%)   | 6 / 30 (20.00%)  |  |
| occurrences (all)                              | 2                | 6                |  |
| Staphylococcus test positive                   |                  |                  |  |
| subjects affected / exposed                    | 0 / 30 (0.00%)   | 1 / 30 (3.33%)   |  |
| occurrences (all)                              | 0                | 1                |  |
| Streptococcus test positive                    |                  |                  |  |
| subjects affected / exposed                    | 0 / 30 (0.00%)   | 1 / 30 (3.33%)   |  |
| occurrences (all)                              | 0                | 1                |  |
| Strongyloides test positive                    |                  |                  |  |
| subjects affected / exposed                    | 1 / 30 (3.33%)   | 1 / 30 (3.33%)   |  |
| occurrences (all)                              | 1                | 1                |  |
| Weight decreased                               |                  |                  |  |
| subjects affected / exposed                    | 1 / 30 (3.33%)   | 1 / 30 (3.33%)   |  |
| occurrences (all)                              | 1                | 1                |  |
| Weight increased                               |                  |                  |  |
| subjects affected / exposed                    | 7 / 30 (23.33%)  | 6 / 30 (20.00%)  |  |
| occurrences (all)                              | 7                | 6                |  |
| Blood pressure diastolic increased             |                  |                  |  |
| subjects affected / exposed                    | 0 / 30 (0.00%)   | 2 / 30 (6.67%)   |  |
| occurrences (all)                              | 0                | 2                |  |
| Injury, poisoning and procedural complications |                  |                  |  |
| Abdominal wound dehiscence                     |                  |                  |  |

|   |                 |                 |
|---|-----------------|-----------------|
| subjects affected / exposed             | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |
| occurrences (all)                       | 1               | 0               |
| Arteriovenous fistula aneurysm          |                 |                 |
| subjects affected / exposed             | 1 / 30 (3.33%)  | 1 / 30 (3.33%)  |
| occurrences (all)                       | 1               | 1               |
| Arteriovenous fistula site complication |                 |                 |
| subjects affected / exposed             | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                       | 0               | 1               |
| Arteriovenous fistula thrombosis        |                 |                 |
| subjects affected / exposed             | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                       | 0               | 1               |
| Complications of transplant surgery     |                 |                 |
| subjects affected / exposed             | 7 / 30 (23.33%) | 5 / 30 (16.67%) |
| occurrences (all)                       | 7               | 5               |
| Foot fracture                           |                 |                 |
| subjects affected / exposed             | 2 / 30 (6.67%)  | 0 / 30 (0.00%)  |
| occurrences (all)                       | 2               | 0               |
| Incisional hernia                       |                 |                 |
| subjects affected / exposed             | 1 / 30 (3.33%)  | 1 / 30 (3.33%)  |
| occurrences (all)                       | 1               | 1               |
| Joint dislocation                       |                 |                 |
| subjects affected / exposed             | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |
| occurrences (all)                       | 1               | 0               |
| Penile contusion                        |                 |                 |
| subjects affected / exposed             | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |
| occurrences (all)                       | 1               | 0               |
| Post lumbar puncture syndrome           |                 |                 |
| subjects affected / exposed             | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |
| occurrences (all)                       | 1               | 0               |
| Post procedural contusion               |                 |                 |
| subjects affected / exposed             | 2 / 30 (6.67%)  | 0 / 30 (0.00%)  |
| occurrences (all)                       | 2               | 0               |
| Post procedural haematoma               |                 |                 |
| subjects affected / exposed             | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                       | 0               | 1               |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| Post procedural urine leak<br>subjects affected / exposed<br>occurrences (all)       | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0  |  |
| Postoperative wound complication<br>subjects affected / exposed<br>occurrences (all) | 2 / 30 (6.67%)<br>3 | 1 / 30 (3.33%)<br>1  |  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 30 (6.67%)<br>2 | 4 / 30 (13.33%)<br>4 |  |
| Product dose omission in error<br>subjects affected / exposed<br>occurrences (all)   | 0 / 30 (0.00%)<br>0 | 1 / 30 (3.33%)<br>1  |  |
| Product use issue<br>subjects affected / exposed<br>occurrences (all)                | 1 / 30 (3.33%)<br>2 | 0 / 30 (0.00%)<br>0  |  |
| Road traffic accident<br>subjects affected / exposed<br>occurrences (all)            | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0  |  |
| Vascular access site haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 0 / 30 (0.00%)<br>0 | 1 / 30 (3.33%)<br>1  |  |
| Wound complication<br>subjects affected / exposed<br>occurrences (all)               | 2 / 30 (6.67%)<br>2 | 3 / 30 (10.00%)<br>4 |  |
| Wound secretion<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 30 (0.00%)<br>0 | 1 / 30 (3.33%)<br>1  |  |
| Wrist fracture<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 30 (0.00%)<br>0 | 1 / 30 (3.33%)<br>1  |  |
| Wrong dose<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0  |  |
| Cardiac disorders<br>Bradycardia   |                     |                      |  |

|                             |                 |                |  |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 30 (3.33%)  | 1 / 30 (3.33%) |  |
| occurrences (all)           | 1               | 1              |  |
| Sinus node dysfunction      |                 |                |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Sinus tachycardia           |                 |                |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 1 / 30 (3.33%) |  |
| occurrences (all)           | 0               | 1              |  |
| Nervous system disorders    |                 |                |  |
| Ataxia                      |                 |                |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Burning sensation           |                 |                |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Cerebral venous thrombosis  |                 |                |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Dizziness                   |                 |                |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 1 / 30 (3.33%) |  |
| occurrences (all)           | 1               | 1              |  |
| Dizziness postural          |                 |                |  |
| subjects affected / exposed | 3 / 30 (10.00%) | 0 / 30 (0.00%) |  |
| occurrences (all)           | 3               | 0              |  |
| Formication                 |                 |                |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 1 / 30 (3.33%) |  |
| occurrences (all)           | 0               | 1              |  |
| Headache                    |                 |                |  |
| subjects affected / exposed | 6 / 30 (20.00%) | 1 / 30 (3.33%) |  |
| occurrences (all)           | 7               | 1              |  |
| Hypoaesthesia               |                 |                |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 2 / 30 (6.67%) |  |
| occurrences (all)           | 0               | 2              |  |
| Migraine                    |                 |                |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 1 / 30 (3.33%) |  |
| occurrences (all)           | 1               | 1              |  |

|                                      |                  |                  |  |
|--------------------------------------|------------------|------------------|--|
| Neuralgia                            |                  |                  |  |
| subjects affected / exposed          | 1 / 30 (3.33%)   | 0 / 30 (0.00%)   |  |
| occurrences (all)                    | 1                | 0                |  |
| Neuropathy peripheral                |                  |                  |  |
| subjects affected / exposed          | 0 / 30 (0.00%)   | 1 / 30 (3.33%)   |  |
| occurrences (all)                    | 0                | 1                |  |
| Post herpetic neuralgia              |                  |                  |  |
| subjects affected / exposed          | 0 / 30 (0.00%)   | 1 / 30 (3.33%)   |  |
| occurrences (all)                    | 0                | 1                |  |
| Presyncope                           |                  |                  |  |
| subjects affected / exposed          | 0 / 30 (0.00%)   | 1 / 30 (3.33%)   |  |
| occurrences (all)                    | 0                | 1                |  |
| Tremor                               |                  |                  |  |
| subjects affected / exposed          | 10 / 30 (33.33%) | 9 / 30 (30.00%)  |  |
| occurrences (all)                    | 11               | 9                |  |
| Blood and lymphatic system disorders |                  |                  |  |
| Anaemia                              |                  |                  |  |
| subjects affected / exposed          | 7 / 30 (23.33%)  | 11 / 30 (36.67%) |  |
| occurrences (all)                    | 7                | 11               |  |
| Leukocytosis                         |                  |                  |  |
| subjects affected / exposed          | 0 / 30 (0.00%)   | 1 / 30 (3.33%)   |  |
| occurrences (all)                    | 0                | 1                |  |
| Leukopenia                           |                  |                  |  |
| subjects affected / exposed          | 6 / 30 (20.00%)  | 5 / 30 (16.67%)  |  |
| occurrences (all)                    | 6                | 6                |  |
| Neutropenia                          |                  |                  |  |
| subjects affected / exposed          | 1 / 30 (3.33%)   | 3 / 30 (10.00%)  |  |
| occurrences (all)                    | 1                | 3                |  |
| Polycythaemia                        |                  |                  |  |
| subjects affected / exposed          | 1 / 30 (3.33%)   | 1 / 30 (3.33%)   |  |
| occurrences (all)                    | 1                | 1                |  |
| Thrombocytopenia                     |                  |                  |  |
| subjects affected / exposed          | 1 / 30 (3.33%)   | 1 / 30 (3.33%)   |  |
| occurrences (all)                    | 1                | 1                |  |
| Thrombocytosis                       |                  |                  |  |



|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 30 (3.33%)<br>1 | 0 / 30 (0.00%)<br>0 |  |
| Ear and labyrinth disorders                      |                     |                     |  |
| Ear pain   |                     |                     |  |
| subjects affected / exposed                      | 0 / 30 (0.00%)      | 1 / 30 (3.33%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Vertigo  |                     |                     |  |
| subjects affected / exposed                      | 0 / 30 (0.00%)      | 1 / 30 (3.33%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Eye disorders                                    |                     |                     |  |
| Eye swelling                                     |                     |                     |  |
| subjects affected / exposed                      | 1 / 30 (3.33%)      | 0 / 30 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Ocular hyperaemia                                |                     |                     |  |
| subjects affected / exposed                      | 1 / 30 (3.33%)      | 0 / 30 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Periorbital swelling                             |                     |                     |  |
| subjects affected / exposed                      | 0 / 30 (0.00%)      | 1 / 30 (3.33%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Photophobia                                      |                     |                     |  |
| subjects affected / exposed                      | 0 / 30 (0.00%)      | 1 / 30 (3.33%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Vision blurred                                   |                     |                     |  |
| subjects affected / exposed                      | 1 / 30 (3.33%)      | 1 / 30 (3.33%)      |  |
| occurrences (all)                                | 1                   | 1                   |  |
| Visual impairment                                |                     |                     |  |
| subjects affected / exposed                      | 1 / 30 (3.33%)      | 0 / 30 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Vitreous floaters                                |                     |                     |  |
| subjects affected / exposed                      | 1 / 30 (3.33%)      | 0 / 30 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Gastrointestinal disorders                       |                     |                     |  |
| Abdominal distension                             |                     |                     |  |
| subjects affected / exposed                      | 2 / 30 (6.67%)      | 1 / 30 (3.33%)      |  |
| occurrences (all)                                | 2                   | 1                   |  |
| Abdominal pain                                   |                     |                     |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed            | 0 / 30 (0.00%)  | 5 / 30 (16.67%) |  |
| occurrences (all)                      | 0               | 5               |  |
| Abdominal pain upper                   |                 |                 |  |
| subjects affected / exposed            | 1 / 30 (3.33%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                      | 1               | 1               |  |
| Constipation                           |                 |                 |  |
| subjects affected / exposed            | 3 / 30 (10.00%) | 6 / 30 (20.00%) |  |
| occurrences (all)                      | 3               | 6               |  |
| Diarrhoea                              |                 |                 |  |
| subjects affected / exposed            | 7 / 30 (23.33%) | 9 / 30 (30.00%) |  |
| occurrences (all)                      | 11              | 9               |  |
| Dyspepsia                              |                 |                 |  |
| subjects affected / exposed            | 2 / 30 (6.67%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                      | 2               | 1               |  |
| Gastritis                              |                 |                 |  |
| subjects affected / exposed            | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                      | 0               | 1               |  |
| Gastrointestinal disorder              |                 |                 |  |
| subjects affected / exposed            | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                      | 0               | 1               |  |
| Gastrooesophageal reflux disease       |                 |                 |  |
| subjects affected / exposed            | 3 / 30 (10.00%) | 4 / 30 (13.33%) |  |
| occurrences (all)                      | 3               | 4               |  |
| Inguinal hernia                        |                 |                 |  |
| subjects affected / exposed            | 0 / 30 (0.00%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                      | 0               | 2               |  |
| Nausea                                 |                 |                 |  |
| subjects affected / exposed            | 2 / 30 (6.67%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                      | 2               | 2               |  |
| Rectal bleeding                        |                 |                 |  |
| subjects affected / exposed            | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                      | 0               | 1               |  |
| Vomiting                               |                 |                 |  |
| subjects affected / exposed            | 4 / 30 (13.33%) | 3 / 30 (10.00%) |  |
| occurrences (all)                      | 4               | 3               |  |
| Skin and subcutaneous tissue disorders |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Acanthosis nigricans                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Acne  |                 |                 |  |
| subjects affected / exposed                     | 3 / 30 (10.00%) | 2 / 30 (6.67%)  |  |
| occurrences (all)                               | 4               | 3               |  |
| Alopecia  |                 |                 |  |
| subjects affected / exposed                     | 4 / 30 (13.33%) | 2 / 30 (6.67%)  |  |
| occurrences (all)                               | 4               | 2               |  |
| Hypertrophic scar                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Keloid scar                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Night sweats                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                               | 2               | 2               |  |
| Palisaded neutrophilic granulomatous dermatitis |                 |                 |  |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Pruritus  |                 |                 |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Rash  |                 |                 |  |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 3 / 30 (10.00%) |  |
| occurrences (all)                               | 0               | 3               |  |
| Rash papular                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Rash pruritic                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Scar pain                                       |                 |                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Seborrhoeic dermatitis      |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Seborrhoeic keratosis       |                 |                 |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Skin depigmentation         |                 |                 |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Renal and urinary disorders |                 |                 |  |
| Acute kidney injury         |                 |                 |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Dysuria                     |                 |                 |  |
| subjects affected / exposed | 5 / 30 (16.67%) | 4 / 30 (13.33%) |  |
| occurrences (all)           | 6               | 5               |  |
| Haematuria                  |                 |                 |  |
| subjects affected / exposed | 4 / 30 (13.33%) | 5 / 30 (16.67%) |  |
| occurrences (all)           | 5               | 5               |  |
| Nocturia                    |                 |                 |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Perinephric collection      |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)           | 1               | 2               |  |
| Pollakiuria                 |                 |                 |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)           | 0               | 2               |  |
| Polyuria                    |                 |                 |  |
| subjects affected / exposed | 2 / 30 (6.67%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 2               | 0               |  |
| Proteinuria                 |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)           | 1               | 2               |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Renal artery stenosis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Renal haematoma                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Renal impairment                                |                 |                 |  |
| subjects affected / exposed                     | 4 / 30 (13.33%) | 5 / 30 (16.67%) |  |
| occurrences (all)                               | 4               | 5               |  |
| Renal mass                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                               | 0               | 2               |  |
| Renal tubular necrosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Urethral pain                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Hydronephrosis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                               | 0               | 2               |  |
| Endocrine disorders                             |                 |                 |  |
| Hyperparathyroidism secondary                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 4 / 30 (13.33%) | 3 / 30 (10.00%) |  |
| occurrences (all)                               | 4               | 4               |  |
| Arthritis reactive                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Back pain                                       |                 |                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 30 (3.33%)  | 3 / 30 (10.00%) |  |
| occurrences (all)           | 1               | 3               |  |
| Flank pain                  |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)           | 1               | 2               |  |
| Groin pain                  |                 |                 |  |
| subjects affected / exposed | 2 / 30 (6.67%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 2               | 0               |  |
| Joint swelling              |                 |                 |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 3 / 30 (10.00%) |  |
| occurrences (all)           | 0               | 3               |  |
| Limb mass                   |                 |                 |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Muscle spasms               |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)           | 1               | 1               |  |
| Muscle twitching            |                 |                 |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Musculoskeletal chest pain  |                 |                 |  |
| subjects affected / exposed | 0 / 30 (0.00%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)           | 0               | 2               |  |
| Myalgia                     |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)           | 1               | 1               |  |
| Osteoarthritis              |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Pain in extremity           |                 |                 |  |
| subjects affected / exposed | 3 / 30 (10.00%) | 4 / 30 (13.33%) |  |
| occurrences (all)           | 3               | 4               |  |
| Infections and infestations |                 |                 |  |
| Body tinea                  |                 |                 |  |
| subjects affected / exposed | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |

|                                     |                 |                 |
|-------------------------------------|-----------------|-----------------|
| Cellulitis                          |                 |                 |
| subjects affected / exposed         | 1 / 30 (3.33%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 1               | 1               |
| COVID-19                            |                 |                 |
| subjects affected / exposed         | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |
| occurrences (all)                   | 1               | 0               |
| Cystitis klebsiella                 |                 |                 |
| subjects affected / exposed         | 1 / 30 (3.33%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 1               | 1               |
| Cytomegalovirus viraemia            |                 |                 |
| subjects affected / exposed         | 7 / 30 (23.33%) | 7 / 30 (23.33%) |
| occurrences (all)                   | 8               | 7               |
| Escherichia urinary tract infection |                 |                 |
| subjects affected / exposed         | 6 / 30 (20.00%) | 5 / 30 (16.67%) |
| occurrences (all)                   | 8               | 5               |
| Fungal foot infection               |                 |                 |
| subjects affected / exposed         | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 0               | 1               |
| Gastroenteritis                     |                 |                 |
| subjects affected / exposed         | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 0               | 1               |
| Gastroenteritis Escherichia coli    |                 |                 |
| subjects affected / exposed         | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 0               | 1               |
| Gastroenteritis norovirus           |                 |                 |
| subjects affected / exposed         | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 0               | 1               |
| Genital candidiasis                 |                 |                 |
| subjects affected / exposed         | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 0               | 1               |
| Genital herpes                      |                 |                 |
| subjects affected / exposed         | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 0               | 1               |
| Genital herpes simplex              |                 |                 |
| subjects affected / exposed         | 0 / 30 (0.00%)  | 2 / 30 (6.67%)  |
| occurrences (all)                   | 0               | 2               |

|                                     |                 |                 |
|-------------------------------------|-----------------|-----------------|
| Herpes simplex                      |                 |                 |
| subjects affected / exposed         | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |
| occurrences (all)                   | 1               | 0               |
| Herpes simplex viraemia             |                 |                 |
| subjects affected / exposed         | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 0               | 1               |
| Lower respiratory tract infection   |                 |                 |
| subjects affected / exposed         | 1 / 30 (3.33%)  | 2 / 30 (6.67%)  |
| occurrences (all)                   | 1               | 2               |
| Oral candidiasis                    |                 |                 |
| subjects affected / exposed         | 4 / 30 (13.33%) | 3 / 30 (10.00%) |
| occurrences (all)                   | 4               | 3               |
| Oral herpes                         |                 |                 |
| subjects affected / exposed         | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |
| occurrences (all)                   | 1               | 0               |
| Orchitis                            |                 |                 |
| subjects affected / exposed         | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 0               | 1               |
| Otitis media                        |                 |                 |
| subjects affected / exposed         | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 0               | 1               |
| Paronychia                          |                 |                 |
| subjects affected / exposed         | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |
| occurrences (all)                   | 1               | 0               |
| Pneumonia                           |                 |                 |
| subjects affected / exposed         | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |
| occurrences (all)                   | 0               | 1               |
| Polyomavirus viraemia               |                 |                 |
| subjects affected / exposed         | 7 / 30 (23.33%) | 7 / 30 (23.33%) |
| occurrences (all)                   | 7               | 7               |
| Polyomavirus-associated nephropathy |                 |                 |
| subjects affected / exposed         | 2 / 30 (6.67%)  | 2 / 30 (6.67%)  |
| occurrences (all)                   | 2               | 2               |
| Proteus infection                   |                 |                 |



|                                      |                 |                 |  |
|--------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed          | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                    | 0               | 1               |  |
| Pustular rash                        |                 |                 |  |
| subjects affected / exposed          | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Renal graft infection                |                 |                 |  |
| subjects affected / exposed          | 2 / 30 (6.67%)  | 3 / 30 (10.00%) |  |
| occurrences (all)                    | 2               | 3               |  |
| Rhinitis                             |                 |                 |  |
| subjects affected / exposed          | 6 / 30 (20.00%) | 5 / 30 (16.67%) |  |
| occurrences (all)                    | 7               | 5               |  |
| Rhinovirus infection                 |                 |                 |  |
| subjects affected / exposed          | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Sinusitis                            |                 |                 |  |
| subjects affected / exposed          | 2 / 30 (6.67%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                    | 2               | 0               |  |
| Tinea versicolour                    |                 |                 |  |
| subjects affected / exposed          | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                    | 0               | 1               |  |
| Tooth infection                      |                 |                 |  |
| subjects affected / exposed          | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                    | 0               | 1               |  |
| Urinary tract infection              |                 |                 |  |
| subjects affected / exposed          | 2 / 30 (6.67%)  | 5 / 30 (16.67%) |  |
| occurrences (all)                    | 2               | 6               |  |
| Urinary tract infection enterococcal |                 |                 |  |
| subjects affected / exposed          | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                    | 0               | 1               |  |
| Wound infection                      |                 |                 |  |
| subjects affected / exposed          | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                    | 0               | 1               |  |
| Herpes zoster                        |                 |                 |  |
| subjects affected / exposed          | 3 / 30 (10.00%) | 1 / 30 (3.33%)  |  |
| occurrences (all)                    | 3               | 1               |  |
| Metabolism and nutrition disorders   |                 |                 |  |

|                                      |                 |                 |  |
|--------------------------------------|-----------------|-----------------|--|
| Appetite disorder                    |                 |                 |  |
| subjects affected / exposed          | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Decreased appetite                   |                 |                 |  |
| subjects affected / exposed          | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Diabetes mellitus inadequate control |                 |                 |  |
| subjects affected / exposed          | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                    | 0               | 1               |  |
| Gout                                 |                 |                 |  |
| subjects affected / exposed          | 0 / 30 (0.00%)  | 3 / 30 (10.00%) |  |
| occurrences (all)                    | 0               | 3               |  |
| Hypervolaemia                        |                 |                 |  |
| subjects affected / exposed          | 3 / 30 (10.00%) | 1 / 30 (3.33%)  |  |
| occurrences (all)                    | 3               | 1               |  |
| Increased appetite                   |                 |                 |  |
| subjects affected / exposed          | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Iron deficiency                      |                 |                 |  |
| subjects affected / exposed          | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                    | 0               | 1               |  |
| Malnutrition                         |                 |                 |  |
| subjects affected / exposed          | 0 / 30 (0.00%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                    | 0               | 1               |  |
| Vitamin D deficiency                 |                 |                 |  |
| subjects affected / exposed          | 1 / 30 (3.33%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Hyperglycaemia                       |                 |                 |  |
| subjects affected / exposed          | 3 / 30 (10.00%) | 2 / 30 (6.67%)  |  |
| occurrences (all)                    | 3               | 2               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment  |
|--------------|--|
| 22 June 2020 | New secondary outcome to follow-up patients who screen-fail for positive OGTT: review of records at 1 year post-transplant.<br>Updated contact details, updated SPC, updated SAP, updated schedule of visits table to more accurately reflect the text.<br>Extension to screening period from 7 to 10 days (COVID-19), and leeway for 3 month visit extended to 2 weeks, leeway for month 6 and 12 visits extended to 1 month (COVID-19).<br>Study forms part of sub-I's PhD; CI is academic supervisor. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date             | Interruption   | Restart date  |
|------------------|--|---------------|
| 16 March 2020    | Recruitment interrupted due to cessation of transplant programme March-July 2020 and redeployment of research staff in response to the COVID-19 pandemic     | 13 July 2020  |
| 21 December 2020 | Recruitment interrupted due to cessation of transplant programme Dec 2020-March 2021 and redeployment of research staff in response to the COVID-19 pandemic | 15 March 2021 |

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to COVID-19, follow-up visits were late/missing (immunosuppressed patients declined to attend): missing 29 OGTTs total.  
6 patients did not return IMP so unable to verify compliance; 4 patients had <80% adherence on return of IMP.

Notes: