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 , kieran.mccafferty4@nhs.net
Scientific contact	Dr Kieran McCafferty, Barts Health NHS Trust , 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:

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:

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:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	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 >/= 30ml/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
Arm title	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

Arm title	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

Number of subjects in period 1	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: x10^9			
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: x10^9			
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:	
Patients received 500mg OD metformin	
Reporting group title	Placebo
Reporting group description:	
Patients received placebo	

Primary: Primary: Diagnosis of PTDM

End point title	Primary: Diagnosis of PTDM

End point description:

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 than11.1mmol/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:

Between randomisation visit and month 12 visit

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[1]	30[2]		
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:

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

Statistical analysis title	Chi-square

Statistical analysis description:

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[3]
P-value	> 0.05
Method	Chi-squared

Notes:

[3] - Chi-square test

Secondary: HOMA IR

End point title	HOMA IR

End point description:

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:

from randomisation visit to 12 month visit

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[4]	30[5]		
Units: units				
arithmetic mean (standard deviation)	2.74 (± 1.22)	1.83 (± 1.10)		

Notes:

[4] - intention to treat

[5] - intention to treat

Statistical analyses

Statistical analysis title	2-way repeated measure ANOVA

Statistical analysis description:

2-way repeated measure ANOVA

Comparison groups	Metformin v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	> 0.05 [7]
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

Statistical analysis title	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:

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:

from randomisation to month 12 visit

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

Notes:

[9] - intention to treat

[10] - intention to treat

Statistical analyses

Statistical analysis title	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[11]	30[12]		
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:

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:

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

Statistical analysis title	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	
Strongyloidiasis			
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	
Urinary tract infection			
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	
Urosepsis			
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 %

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

subjects affected / exposed	3 / 30 (10.00%)	5 / 30 (16.67%)	
occurrences (all)	4	5	
Intermittent claudication			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Lymphocele			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Lymphoedema			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Orthostatic hypotension			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Thrombophlebitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Thyroxine therapy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	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			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Social circumstances			
Social problem			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Painful erection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Penile pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Perineal pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Polycystic ovaries			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Prostatism			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Testicular swelling			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	
occurrences (all)	2	3	
Dyspnoea			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	

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

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Blood bicarbonate decreased			
subjects affected / exposed	2 / 30 (6.67%)	5 / 30 (16.67%)	
occurrences (all)	2	5	
Blood calcium decreased			
subjects affected / exposed	3 / 30 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Blood calcium increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol increased			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Blood creatinine increased			
subjects affected / exposed	6 / 30 (20.00%)	4 / 30 (13.33%)	
occurrences (all)	6	4	
Blood magnesium decreased			
subjects affected / exposed	3 / 30 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Blood parathyroid hormone increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Blood phosphorus decreased			
subjects affected / exposed	11 / 30 (36.67%)	4 / 30 (13.33%)	
occurrences (all)	11	4	
Blood potassium decreased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	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			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Postoperative wound complication			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Procedural pain			
subjects affected / exposed	2 / 30 (6.67%)	4 / 30 (13.33%)	
occurrences (all)	2	4	
Product dose omission in error			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Product use issue			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Road traffic accident			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Vascular access site haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Wound complication			
subjects affected / exposed	2 / 30 (6.67%)	3 / 30 (10.00%)	
occurrences (all)	2	4	
Wound secretion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Wrist fracture			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Wrong dose			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
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	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	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. Updated contact details, updated SPC, updated SAP, updated schedule of visits table to more accurately reflect the text. 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). 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: