



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
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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 ≥ 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
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
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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 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: 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 (\pm 1.22)	1.83 (\pm 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
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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
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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
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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
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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
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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
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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
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End point description:

episodes of acute rejection

End point type	Secondary
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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
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Comparison groups	Metformin v Placebo
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25
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Reporting groups

Reporting group title	Metformin
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Reporting group description: -

Reporting group title	Placebo
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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 occurrences (all)	1 / 30 (3.33%) 1	3 / 30 (10.00%) 3	
Social circumstances Social problem subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Reproductive system and breast disorders Heavy menstrual bleeding subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Painful erection subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Penile pain subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Perineal pain subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Polycystic ovaries subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Prostatism subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Testicular swelling subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	2 / 30 (6.67%) 3	
Dyspnoea subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	

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

subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Investigations			
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Blood bicarbonate decreased subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	5 / 30 (16.67%) 5	
Blood calcium decreased subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3	0 / 30 (0.00%) 0	
Blood calcium increased subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Blood cholesterol increased subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1	
Blood creatinine increased subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 6	4 / 30 (13.33%) 4	
Blood magnesium decreased subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3	0 / 30 (0.00%) 0	
Blood parathyroid hormone increased subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Blood phosphorus decreased subjects affected / exposed occurrences (all)	11 / 30 (36.67%) 11	4 / 30 (13.33%) 4	
Blood potassium decreased subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 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 occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Postoperative wound complication subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3	1 / 30 (3.33%) 1	
Procedural pain subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	4 / 30 (13.33%) 4	
Product dose omission in error subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Product use issue subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 2	0 / 30 (0.00%) 0	
Road traffic accident subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Vascular access site haemorrhage subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Wound complication subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	3 / 30 (10.00%) 4	
Wound secretion subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Wrist fracture subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Wrong dose subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 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 occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 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: