Clinical trial results:
AZD1656 in Transplantation with Diabetes tO PromoTe Immune TOleraNce

Summary

EudraCT number	2019-001587-30
Trial protocol	GB
Global end of trial date	11 September 2023

Results information

Result version number	v1 (current)
This version publication date	05 December 2024
First version publication date	05 December 2024
Summary attachment (see zip file)	Early termination (early termination.pdf)

Trial information

Trial identification

Sponsor protocol code	012657

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05216172
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS: 252155, REC: 19/EE/0209

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Mile End Road, London, United Kingdom, E1 4NS
Public contact	Dr Kieran McCafferty, Diabetic Kidney Disease Centre, kieran.mccafferty4@nhs.net
Scientific contact	Dr Kieran McCafferty, Diabetic Kidney Disease Centre, research.governance@qmul.ac.uk

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	20 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 September 2023
Global end of trial reached?	Yes
Global end of trial date	11 September 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Will treating post-transplant patients with glucokinase activator (AZD1656) compared to placebo for 3 months improve the function of their transplant kidney via a change in the levels of immune cells (regulatory T cells)? We will measure this by measuring the number of regulatory T cells in blood samples taken from the patients.

Protection of trial subjects:

All subjects were under regular clinical and research monitoring.
Trial conduct supervised by regular joint trial steering and data monitoring committee.
All subject data stored as pseudonymised records in either locked research facility or saved on secure servers.

Background therapy:

Standard of care for renal transplant recipients at the site stratifies them into standard and high immunological risk, based on multiple factors. Patients deemed to be at high immunological risk are given antithymocyte globulin (ATG) as induction; patients with standard immunological risk or unsuitable for ATG are given basiliximab (anti-IL-2 receptor mAb).

Living donor recipients are pre-loaded with tacrolimus. All recipients receive induction therapy of either basiliximab or ATG on the day of transplant, in addition to intravenous methylprednisolone, with a second dose of basiliximab or AGT on day 4 post-transplant. Patients receiving ATG are given hydrocortisone and chlorphenamine to mitigate against infusion reactions.

After transplant, all patients are maintained on tacrolimus (Adoport), mycophenolate mofetil and a reducing course of prednisolone. Prednisolone is gradually weaned from 20mg OD to 5mg OD over a period of 12 weeks. Target trough levels are reduced from 8-12 mcg/L after the first 3 months to 5-10mcg/L for the rest of the first year post-transplant. Immunosuppression regimes are individually “fine tuned” depending on renal function, incidence of infection, patient tolerance and any other drug side-effects.

Patients receive antimicrobial prophylaxis for the first 3-6 months: PCP prophylaxis for all patients; CMV prophylaxis for antibody negative recipients who have received an antibody positive graft; and TB prophylaxis for high risk or IGRA positive patients. All patients receive aspirin and atorvastatin as cardiovascular protection, and either proton pump inhibitors or histamine H2 receptor antagonists as gastroprotection.

Patients are reviewed in clinic 2-3 times per week within the first 3 months of transplant; subsequently, monitoring decreases to weekly or fortnightly before moving to monthly to 3 monthly visits at around 6 months post-transplant. Monitoring frequency can be adjusted according to individual circumstances.

Evidence for comparator:

Glucokinase activators (GKA) have been recognised as effective and safe glucose-lowering agents. However, they has not been licensed for clinical use due to their lack of long-term efficacy. AZD1656 is a GKA which has been given to around 960 subjects in phase I-IIB studies. It has recently been shown to increase glucokinase activity in regulatory T cells (Tregs), which switches them from a resting to migratory phenotype, with subsequent migration into sites of injury. Conversely, inhibition of glucokinase resulting in less Treg motility led to increased rejection in a skin transplant model. Tregs have been suggested to mediate tolerance in human renal transplantation.

It was therefore proposed to use AZD1656 in patients undergoing renal transplant with pre-existing Type 2 diabetes in order to both mobilise Tregs as a tolerogenic therapy and to improve glycemic control.

Actual start date of recruitment	30 December 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 26
Worldwide total number of subjects	26
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)	22
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited exclusively from patients undergoing renal transplantation at the Royal London Hospital.

Pre-assignment

Screening details:

Once possible participants were identified by their clinical team, their eligibility was determined by the CI or sub-I: they had to meet all of the inclusion criteria and none of the exclusion criteria.

Period 1

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

Blinding implementation details:

Treatment codes were created via an online generator using a 2:2 block randomisation sequence and written on cards; these were allocated at random into envelopes with 1-50 printed on them. These sealed envelopes were randomly chosen to associate a study ID to the treatment code inside. The linked study ID and treatment code were sent to pharmacy on a prescription to dispense the study drug. The dispensing pharmacist would refer to the spreadsheet which linked treatment code with allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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:

100mg twice daily with or after a meal for 3 months (two 50mg tablets twice daily)

Arm title	AZD1656

Arm description: -

Arm type	Experimental
Investigational medicinal product name	AZD1656
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100mg twice daily with or after a meal for 3 months (two 50mg tablets twice daily)

Number of subjects in period 1	Placebo	AZD1656
Started	13	13
Completed	13	13

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	AZD1656
Reporting group description: -	

Reporting group values	Placebo	AZD1656	Total
Number of subjects	13	13	26
Age categorical Units: Subjects			
Adults	13	13	26
Age continuous Units: years			
arithmetic mean	56.5	57.7	
standard deviation	± 10.4	± 6.6	-
Gender categorical Units: Subjects			
Female	5	3	8
Male	8	10	18
Ethnicity			
participant ethnicity			
Units: Subjects			
Asian/Asian British	8	3	11
Black/Black British	4	6	10
White British	0	3	3
Other	1	1	2
Smoking status			
current/ex-smoker			
Units: Subjects			
Yes	0	2	2
No	13	11	24
Family history of diabetes			
Family history of diabetes			
Units: Subjects			
Yes	10	11	21
No	3	2	5
Previous transplant			
previous renal transplant			
Units: Subjects			
First graft	13	11	24
Second graft	0	2	2
Cause of renal failure			
primary renal diagnosis			
Units: Subjects			
Diabetes	11	10	21
Vascular (HTN)	1	1	2

Glomerular	0	1	1
Obstruction	0	1	1
Unknown	1	0	1
Dialysis modality			
renal replacement modality prior to transplant			
Units: Subjects			
Peritoneal dialysis	2	6	8
Haemodialysis	8	6	14
Transplant	0	1	1
Pre-emptive	3	0	3
Transplant type Units: Subjects			
DBD	7	9	16
DCD	5	2	7
Live unrelated	1	1	2
Live related	0	1	1
ECD	0	0	0
HLA mismatch Units: Subjects			
total 1	1	0	1
total 2	2	1	3
total 3	4	5	9
total 4	1	1	2
total 5	4	5	9
total 6	1	1	2
Donor sex Units: Subjects			
Female	9	10	19
Male	4	3	7
Donor cause of death Units: Subjects			
Vascular	8	10	18
Hypoxia	4	0	4
Other	0	1	1
NA: live donor	1	2	3
CMV status Units: Subjects			
-/-	0	1	1
-/+	4	2	6
+/-	1	3	4
+/+	8	7	15
Induction agent Units: Subjects			
IL-2 (basiliximab)	12	12	24
ATG	1	1	2
Timing of baseline blood sampling Units: Subjects			
Pre-induction	5	6	11
Pre-induction but loaded with tacrolimus	1	2	3
Post-induction	7	5	12

Immunosuppression ciclosporin/Azathioprine Units: Subjects			
Yes	0	0	0
No	13	13	26
Number of anti diabetic medications per patient Units: Subjects			
0 ADMs	2	7	9
1 ADM	7	4	11
2 ADMs	1	2	3
3 ADMs	3	0	3
immunosupression Tacrolimus Units: Subjects			
Yes	11	12	23
No	2	1	3
immunosupression: MMF Units: Subjects			
Yes	11	10	21
No	2	3	5
immunosupression: Prednisolone Units: Subjects			
yes	11	10	21
no	2	3	5
peripheral arterial disease Units: Subjects			
Yes	2	1	3
No	11	12	23
Cardiovascular disease Units: Subjects			
Yes	3	2	5
No	10	11	21
hypertension Units: Subjects			
yes	8	7	15
no	5	6	11
Medication: metformin Units: Subjects			
yes	0	0	0
no	13	13	26
medication gliclazide Units: Subjects			
yes	3	1	4
no	10	12	22
medication linaglyptin Units: Subjects			
yes	5	5	10
no	8	8	16
medication: insulin Units: Subjects			
yes	8	2	10
no	5	11	16

comorbidity: respiratory Units: Subjects			
yes	2	3	5
no	11	10	21
medication: GLP1RA Units: Subjects			
yes	0	0	0
no	13	13	26
comorbidity: urinary Units: Subjects			
yes	3	3	6
no	10	10	20
comorbidity: gastrointestinal Units: Subjects			
yes	2	4	6
no	11	9	20
comorbidity:endocrine Units: Subjects			
yes	0	1	1
no	13	12	25
comorbidity:neurological Units: Subjects			
yes	4	2	6
no	9	11	20
comorbidity:musculoskeletal Units: Subjects			
yes	4	2	6
no	9	11	20
comorbidity: other Units: Subjects			
yes	4	5	9
no	9	8	17
Medication: RAASI Units: Subjects			
yes	2	1	3
no	11	12	23
Medication: statin Units: Subjects			
yes	5	5	10
no	8	8	16
Medication:antiplatelet Units: Subjects			
yes	5	3	8
no	8	10	18
Medication: beta-blocker Units: Subjects			
yes	3	5	8
no	10	8	18
Medication:: diuretic Units: Subjects			
yes	1	0	1

no	12	13	25
Medication: other anthypertensive Units: Subjects			
yes	2	3	5
no	11	10	21
Medication:mineral bone medications Units: Subjects			
yes	2	4	6
no	11	9	20
Medication:: PPI Units: Subjects			
yes	11	10	21
no	2	3	5
Medication:prophylaxis Units: Subjects			
yes	11	10	21
no	2	3	5
Medication:antibiotics Units: Subjects			
yes	0	1	1
no	13	12	25
Medication:valganciclovir Units: Subjects			
yes	4	1	5
no	9	12	21
Medication: other Units: Subjects			
yes	6	8	14
no	7	5	12
diabetes comorbidity: retinopathy Units: Subjects			
yes	6	5	11
no	7	8	15
diabetic complications: neuropathy Units: Subjects			
yes	2	1	3
no	11	12	23
sBP Units: mmHg			
arithmetic mean	128.4	128.8	
standard deviation	± 17.8	± 22.2	-
BMI Units: kg/m2			
median	27.9	30.3	
inter-quartile range (Q1-Q3)	26.7 to 34.4	25.1 to 32.7	-
Weight			
weight (kg)			
Units: kg			
median	80	87.3	
inter-quartile range (Q1-Q3)	71.1 to 91.6	79.6 to 90.8	-
dBP			

Units: mmHg			
arithmetic mean	70.0	67.6	
standard deviation	± 12.0	± 12.9	-
Dialysis vintage			
Units: days			
arithmetic mean	1280.5	1230.6	
standard deviation	± 902.5	± 783.2	-
Duration of diabetes			
Units: years			
arithmetic mean	19.3	17.5	
standard deviation	± 11.3	± 8.5	-
Units of alcohol/week			
Units: units			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 2	-
Time on waitlist			
Units: days			
arithmetic mean	413.3	714.2	
standard deviation	± 287.3	± 441.6	-
Warm ischaemic time (secondary)			
Units: minutes			
arithmetic mean	40.9	43.4	
standard deviation	± 11.8	± 11.2	-
Cold ischaemia time			
Units: minutes			
arithmetic mean	930.3	786.0	
standard deviation	± 353	± 363.8	-
Donor age			
Units: years			
median	45	51	
inter-quartile range (Q1-Q3)	44 to 52	40.5 to 58.5	-
Platelets			
Units: x10^9/L			
arithmetic mean	185.1	169.9	
standard deviation	± 47.7	± 65.1	-
WBC			
Units: x10^9/L			
arithmetic mean	11.3	9.6	
standard deviation	± 5.4	± 4.3	-
Hb			
Units: g/L			
arithmetic mean	97.7	100.8	
standard deviation	± 21.1	± 20.3	-
Sodium			
Units: mmol/L			
median	137	136	
inter-quartile range (Q1-Q3)	134 to 138	134.5 to 139.5	-
Potassium			
Units: mmol/L			
arithmetic mean	5.1	5.1	
standard deviation	± 0.7	± 1.0	-
Bicarbonate			

Units: mmol/L			
arithmetic mean	21.7	23.6	
standard deviation	± 2.1	± 3.3	-
Urea			
Units: mmol/L			
median	19.4	15.0	
inter-quartile range (Q1-Q3)	18.6 to 22	10.7 to 22.4	-
Creatinine			
Units: umol/L			
median	578	654	
inter-quartile range (Q1-Q3)	453 to 850	534.5 to 755.5	-
eGFR			
Units: ml/min/1.73m2			
median	6	7	
inter-quartile range (Q1-Q3)	4.5 to 10.5	6 to 8	-
PO4			
Units: mmol/L			
arithmetic mean	1.60	1.50	
standard deviation	± 0.37	± 0.38	-
cCa			
Units: mmol/L			
arithmetic mean	2.23	2.17	
standard deviation	± 0.13	± 0.25	-
albumin			
Units: g/L			
arithmetic mean	36.3	34.5	
standard deviation	± 6.4	± 6.4	-
ALP			
Units: unit/L			
arithmetic mean	91.8	108.7	
standard deviation	± 42.9	± 55.6	-
ALT			
Units: unit/L			
median	20	15	
inter-quartile range (Q1-Q3)	14.5 to 26.5	12 to 17	-
Bilirubin			
Units: umol/L			
median	4	7	
inter-quartile range (Q1-Q3)	2 to 6	4 to 10	-
Mg			
Units: mmol/L			
arithmetic mean	1.0	1.0	
standard deviation	± 0.1	± 0.2	-
C-peptide			
Units: pmol/L			
arithmetic mean	1748.4	2857.8	
standard deviation	± 837.6	± 859.4	-
HbA1c			
Units: mmol/mol			
arithmetic mean	62	57.4	
standard deviation	± 12.9	± 22.3	-
glucose			

Units: mmol/L			
arithmetic mean	11.5	12.1	
standard deviation	± 6.0	± 4.4	-
triglycerides			
Units: mmol/L			
median	1.72	1.20	
inter-quartile range (Q1-Q3)	1.06 to 2.02	0.89 to 1.93	-
total cholesterol			
Units: mmol/L			
arithmetic mean	3.5	3.4	
standard deviation	± 0.9	± 1.4	-
CRP			
Units: mg/L			
median	10	6	
inter-quartile range (Q1-Q3)	4.5 to 40.5	4 to 17	-
HOMA-IR			
Units: standard units			
median	5.40	7.70	
inter-quartile range (Q1-Q3)	2.9 to 7.3	6.6 to 10.5	-

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	AZD1656
Reporting group description: -	

Primary: Change in pTregs between month 3 and baseline	
End point title	Change in pTregs between month 3 and baseline
End point description: change in number of peripheral Tregs between week 12 and randomisation (ie number of Tregs at week 12 - number of Tregs at baseline)	
End point type	Primary
End point timeframe: 12 weeks	

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: cells				
arithmetic mean (standard deviation)	56.5 (± 91.4)	-50.2 (± 129.9)		

Statistical analyses

Statistical analysis title	student t-test (unpaired)
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05 [1]
Method	t-test, 2-sided

Notes:
[1] - p value 0.023

Primary: Treg count at baseline	
End point title	Treg count at baseline
End point description: number of Treg cells at baseline	
End point type	Primary
End point timeframe: at baseline	

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: cells				
arithmetic mean (standard deviation)	116.2 (± 99.7)	155.1 (± 135.4)		

Statistical analyses

Statistical analysis title	student t test (unpaired)
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.412
Method	t-test, 2-sided

Primary: Treg count at week 12

End point title	Treg count at week 12

End point description:

End point type	Primary

End point timeframe:
at week 12

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: ce				
arithmetic mean (standard deviation)	172.6 (± 113.6)	104.9 (± 71.9)		

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	Placebo v AZD1656

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	ANOVA

Statistical analysis title	student t-test (unpaired)
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.082
Method	t-test, 2-sided

Secondary: Delayed graft function

End point title	Delayed graft function
End point description: need for dialysis within 1 week post-transplant	
End point type	Secondary
End point timeframe: 1 week post-transplant	

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: number of patients				
No	10	11		
Yes	3	2		

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Fisher exact

Secondary: eGFR at month 3

End point title	eGFR at month 3

End point description:

End point type	Secondary

End point timeframe:

3 months/12 weeks

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: ml/min/1.73m2				
median (inter-quartile range (Q1-Q3))	47 (33 to 62)	28 (19 to 48)		

Statistical analyses

Statistical analysis title	Mann-Whitney U
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.005 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - p value 0.039

Secondary: Creatinine at month 3

End point title	Creatinine at month 3

End point description:

End point type	Secondary

End point timeframe:

3 months/12 weeks

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: umol/L				
arithmetic mean (standard deviation)	133.6 (± 40.1)	198.2 (± 74.6)		

Statistical analyses

Statistical analysis title	t-test
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05 [3]
Method	t-test, 2-sided

Notes:
[3] - p value 0.011

Secondary: Urea at month 3

End point title	Urea at month 3

End point description:

End point type	Secondary

End point timeframe:
3 months/12 weeks

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mmol/L				
median (inter-quartile range (Q1-Q3))	8.0 (6.7 to 11.5)	10.7 (8.7 to 13.7)		

Statistical analyses

Statistical analysis title	Mann Whitney U
Comparison groups	Placebo v AZD1656

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.091
Method	Wilcoxon (Mann-Whitney)

Secondary: Incidence of hypoglycaemic episodes at month 3

End point title	Incidence of hypoglycaemic episodes at month 3

End point description:

End point type	Secondary

End point timeframe:

3 months/12 weeks

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: episodes				
No	4	3		
Yes	9	10		

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Fisher exact

Secondary: Number of hypoglycaemic episodes at month 3

End point title	Number of hypoglycaemic episodes at month 3

End point description:

End point type	Secondary

End point timeframe:

3 months/12 weeks

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: no. of episodes				
1 episode	4	4		
2 episodes	4	4		
3 episodes	1	1		
4 episodes	0	1		

Statistical analyses

Statistical analysis title	Chi square
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.813
Method	Chi-squared

Secondary: Incidence of episodes of rejection at month 3

End point title	Incidence of episodes of rejection at month 3

End point description:

End point type	Secondary

End point timeframe:

3 months/12 weeks

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: episodes				
No	13	11		
Yes	0	2		

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.48
Method	Fisher exact

Secondary: Number of episodes of rejection at month 3

End point title	Number of episodes of rejection at month 3

End point description:

End point type	Secondary

End point timeframe:

3 months/12 weeks

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: episodes				
0 episodes	13	11		
1 episode	0	1		
2 episodes	0	1		

Statistical analyses

Statistical analysis title	Chi square
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 [4]
Method	Chi-squared

Notes:

[4] - n/a

Secondary: Incidence of episodes of infection at month 3

End point title	Incidence of episodes of infection at month 3

End point description:

End point type	Secondary

End point timeframe: 3 months/12 weeks

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: episodes				
No	3	2		
Yes	10	11		

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Fisher exact

Secondary: Number of episodes of infection at month 3

End point title	Number of episodes of infection at month 3
End point description:	

End point type	Secondary
End point timeframe: 3 months/12 weeks	

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: episodes				
1 episode	4	2		
2 episodes	6	2		
3 episodes	0	2		
4 episodes	0	1		
5 episodes	0	2		
8 episodes	0	1		
12 episodes	0	1		

Statistical analyses

Statistical analysis title	Chi square
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.141
Method	Chi-squared

Secondary: Delta HbA1c at month 3

End point title	Delta HbA1c at month 3
End point description:	
End point type	Secondary
End point timeframe:	
3 months/12 weeks	

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mmol/mol				
arithmetic mean (standard deviation)	9.8 (± 19.2)	8.4 (± 31.9)		

Statistical analyses

Statistical analysis title	t-test
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.903
Method	t-test, 2-sided

Secondary: HbA1c at month 3	
End point title	HbA1c at month 3
End point description:	

End point type	Secondary
End point timeframe:	
3 months/12 weeks	

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: mmol/mol				
arithmetic mean (standard deviation)	69.5 (± 17.3)	62.9 (± 20.4)		

Statistical analyses

Statistical analysis title	t-test
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.418
Method	t-test, 2-sided

Secondary: HOMA-IR at month 3	
End point title	HOMA-IR at month 3
End point description:	

End point type	Secondary
End point timeframe:	
3 months/12 weeks	

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: standard units				
median (inter-quartile range (Q1-Q3))	1.40 (1.1 to 2.0)	2.30 (1.2 to 3.1)		

Statistical analyses

Statistical analysis title	Mann Whitney U
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.302
Method	Wilcoxon (Mann-Whitney)

Secondary: Number of anti diabetic medications at month 3

End point title	Number of anti diabetic medications at month 3

End point description:

End point type	Secondary

End point timeframe:

3 months/12 weeks

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13[5]		
Units: number of medications				
1 ADM	4	2		
2 ADMs	4	8		
3 ADMs	4	2		
4 ADMs	1	0		

Notes:

[5] - 1 patient MV as on HDx

Statistical analyses

Statistical analysis title	Chi square
Comparison groups	Placebo v AZD1656

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.304
Method	Chi-squared

Secondary: Antidiabetic medications at month 3

End point title	Antidiabetic medications at month 3

End point description:

End point type	Secondary

End point timeframe:

3 months/12 weeks

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13[6]		
Units: type of medication				
Metformin	3	0		
Gliclazide	1	1		
Linagliptin	7	7		
Insulin	12	10		
GLP1RA	0	2		

Notes:

[6] - 1 patient MV as on HDx at month 3

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 [7]
Method	Fisher exact

Notes:

[7] - metformin 0.220
gliclazide 1.000
linagliptin 1.000
insulin 0.593
GLP1RA 0.220

Other pre-specified: ANOVA AZ Bx data

End point title	ANOVA AZ Bx data

End point description:

End point type	Other pre-specified

End point timeframe:
as needed (100 days)

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[8]	6[9]		
Units: %Treg cells				
arithmetic mean (standard deviation)	0.32 (± 0.46)	0.22 (± 0.20)		

Notes:

[8] - not all subjects had paired biopsies

[9] - not all subjects had paired biopsies

Statistical analyses

Statistical analysis title	repeated 2 way ANOVA
Comparison groups	Placebo v AZD1656
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	ANOVA

Other pre-specified: ANOVA migration Tregs	
End point title	ANOVA migration Tregs

End point description:

End point type	Other pre-specified

End point timeframe:
14 weeks

End point values	Placebo	AZD1656		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[10]	6[11]		
Units: delta Treg cells				
arithmetic mean (standard deviation)	0.38 (± 13.5)	7.00 (± 14.3)		

Notes:

[10] - not all subjects had complete data for additional assay

[11] - not all subjects had complete data for additional assay

Statistical analyses

Statistical analysis title	ANOVA repeated 2 way
Comparison groups	Placebo v AZD1656

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	ANOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26

Reporting groups	
Reporting group title	AZD1656
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	AZD1656	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 13 (69.23%)	6 / 13 (46.15%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Investigations			
Biopsy kidney	Additional description: IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Post transplant lymphoproliferative disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (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			
Delayed graft function			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents	Additional description: IP admission		

subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter	Additional description: IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (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			
Nephrostomy	Additional description: IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesicoureteral reflux surgery	Additional description: IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Physical deconditioning	Additional description: Prolonged IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (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			
Transplant rejection	Additional description: IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematemesis	Additional description: IP admission		

subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Perinephric collection	Additional description: IP admissions		
subjects affected / exposed	2 / 13 (15.38%)	2 / 13 (15.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion	Additional description: IP admission		
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Escherichia bacteraemia	Additional description: IP admission		
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysematous pyelonephritis	Additional description: IP admission - graft nephrectomy Possible SUSAR		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia	Additional description: IP admission		
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia	Additional description: IP admissions		
subjects affected / exposed	3 / 13 (23.08%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pseudomonal sepsis	Additional description: IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia	Additional description: Prolonged IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal graft infection	Additional description: Prolonged IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mucormycosis	Additional description: IP admission and death Reported as possible SUSAR		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urosepsis	Additional description: IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia	Additional description: IP admission		
subjects affected / exposed	2 / 13 (15.38%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia	Additional description: IP admission		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (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: 1 %

Non-serious adverse events	AZD1656	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	13 / 13 (100.00%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Diastolic hypertension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	7 / 13 (53.85%)	1 / 13 (7.69%)	
occurrences (all)	8	1	
Hypertension			
subjects affected / exposed	12 / 13 (92.31%)	10 / 13 (76.92%)	
occurrences (all)	17	15	
Orthostatic hypotension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Superficial vein thrombosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Thrombophlebitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Surgical and medical procedures			
Bladder catheter temporary			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Enteral nutrition			

subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nephrostomy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Renal transplant			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	0 / 13 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	6 / 13 (46.15%)	6 / 13 (46.15%)	
occurrences (all)	6	6	
Impaired healing			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Oedema			
subjects affected / exposed	5 / 13 (38.46%)	4 / 13 (30.77%)	
occurrences (all)	5	4	
Oedema peripheral			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Swelling face			

subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Thirst			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Transplant rejection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Penile oedema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Penile swelling			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Prostatism			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pruritus genital			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Scrotal swelling			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Dysphonia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dyspnoea			

subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dyspnoea exertional			
subjects affected / exposed	2 / 13 (15.38%)	5 / 13 (38.46%)	
occurrences (all)	2	5	
Epistaxis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Pulmonary embolism			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pulmonary mass			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Rales			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 13 (7.69%)	3 / 13 (23.08%)	
occurrences (all)	1	3	
Investigations			
Blood magnesium decreased			

subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Blood bicarbonate decreased			
subjects affected / exposed	0 / 13 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Blood bicarbonate increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood calcium decreased			
subjects affected / exposed	3 / 13 (23.08%)	1 / 13 (7.69%)	
occurrences (all)	3	1	
Blood cholesterol increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	7 / 13 (53.85%)	4 / 13 (30.77%)	
occurrences (all)	8	4	
Blood folate decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood iron decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood lactic acid increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood phosphorus decreased			
subjects affected / exposed	2 / 13 (15.38%)	4 / 13 (30.77%)	
occurrences (all)	2	5	
Candida test positive			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Culture positive			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Culture urine positive			

subjects affected / exposed	4 / 13 (30.77%)	8 / 13 (61.54%)	
occurrences (all)	12	18	
Blood potassium increased			
subjects affected / exposed	4 / 13 (30.77%)	4 / 13 (30.77%)	
occurrences (all)	6	5	
Fluid balance negative			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Liver function test abnormal			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Occult blood positive			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Staphylococcus test positive			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Stress echocardiogram abnormal			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Strongyloides test positive			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Troponin T increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Urine output decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	1 / 13 (7.69%)	4 / 13 (30.77%)	
occurrences (all)	1	4	
White blood cell count decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Tracheal aspirate culture			

subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Arteriovenous fistula maturation failure			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Complications of transplant surgery			
subjects affected / exposed	2 / 13 (15.38%)	2 / 13 (15.38%)	
occurrences (all)	2	2	
Contusion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Delayed graft function			
subjects affected / exposed	3 / 13 (23.08%)	5 / 13 (38.46%)	
occurrences (all)	3	5	
Endotracheal intubation complication			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Post procedural persistent drain fluid			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Postoperative ileus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	3 / 13 (23.08%)	3 / 13 (23.08%)	
occurrences (all)	5	3	
Product dose omission in error			
subjects affected / exposed	3 / 13 (23.08%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Product prescribing error			

subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Post procedural haematoma			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Spinal compression fracture			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	1	
Wrong drug			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Transplant dysfunction			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Wound complication			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Wound dehiscence			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Supraventricular tachycardia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Tricuspid valve incompetence			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	2 / 13 (15.38%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Headache			
subjects affected / exposed	1 / 13 (7.69%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Hypoaesthesia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Parosmia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Tremor			

subjects affected / exposed	1 / 13 (7.69%)	4 / 13 (30.77%)	
occurrences (all)	1	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 13 (69.23%)	8 / 13 (61.54%)	
occurrences (all)	12	9	
Iron deficiency anaemia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Lymphopenia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Polycythaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Diabetic retinopathy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Macular oedema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Visual acuity reduced			

subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Abdominal distension			
subjects affected / exposed	3 / 13 (23.08%)	2 / 13 (15.38%)	
occurrences (all)	3	2	
Abdominal pain			
subjects affected / exposed	2 / 13 (15.38%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Abdominal pain upper			
subjects affected / exposed	2 / 13 (15.38%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Anal fissure			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	7 / 13 (53.85%)	
occurrences (all)	2	7	
Dry mouth			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Epigastric discomfort			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	

Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 13 (23.08%)	3 / 13 (23.08%)	
occurrences (all)	3	3	
Diarrhoea			
subjects affected / exposed	5 / 13 (38.46%)	6 / 13 (46.15%)	
occurrences (all)	6	7	
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Odynophagia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Tongue ulceration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 13 (15.38%)	2 / 13 (15.38%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blister			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Night sweats			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Skin hyperpigmentation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Skin hypopigmentation			

subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Skin plaque			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Anuria			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Bladder spasm			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hydronephrosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hypertonic bladder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Perinephric collection			
subjects affected / exposed	1 / 13 (7.69%)	3 / 13 (23.08%)	
occurrences (all)	1	3	
Pollakiuria			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nocturia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Polyuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Proteinuria			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Renal artery stenosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Renal impairment			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Renal mass			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Renal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Urine abnormality			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Endocrine disorders			
Hyperthyroid			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Thyroid mass			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	3 / 13 (23.08%)	
occurrences (all)	0	3	
Back pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Joint swelling			

subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Muscle atrophy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	2 / 13 (15.38%)	4 / 13 (30.77%)	
occurrences (all)	2	4	
Musculoskeletal discomfort			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	3 / 13 (23.08%)	2 / 13 (15.38%)	
occurrences (all)	3	3	
Infections and infestations			
Asymptomatic COVID-19			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
COVID-19			
subjects affected / exposed	2 / 13 (15.38%)	3 / 13 (23.08%)	
occurrences (all)	2	3	
Cystitis			
subjects affected / exposed	1 / 13 (7.69%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Cystitis escherichia			
subjects affected / exposed	3 / 13 (23.08%)	1 / 13 (7.69%)	
occurrences (all)	6	1	
Cystitis klebsiella			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Cystitis pseudomonal			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Cytomegalovirus viraemia			
subjects affected / exposed	7 / 13 (53.85%)	3 / 13 (23.08%)	
occurrences (all)	8	3	

Herpes simplex			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Polyomavirus viraemia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	3 / 13 (23.08%)	1 / 13 (7.69%)	
occurrences (all)	5	1	
Pseudomonal sepsis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Transmission of an infectious agent via transplant			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Wound infection			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Wound infection staphylococcal			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			

Abnormal loss of weight			
subjects affected / exposed	3 / 13 (23.08%)	1 / 13 (7.69%)	
occurrences (all)	3	1	
Diabetes mellitus inadequate control			
subjects affected / exposed	3 / 13 (23.08%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Decreased appetite			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	13 / 13 (100.00%)	12 / 13 (92.31%)	
occurrences (all)	17	18	
Hyperkalaemia			
subjects affected / exposed	2 / 13 (15.38%)	2 / 13 (15.38%)	
occurrences (all)	2	2	
Hypervolaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	10 / 13 (76.92%)	9 / 13 (69.23%)	
occurrences (all)	19	15	
Hypokalaemia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2020	Update PIS for study contact details; leeway for follow-up visits; change in location of sample processing for primary endpoint; clarification of EOT definition; trial will contribute to PhD of sub-I. PI is academic supervisor.
20 November 2020	update definition of acceptable methods of highly effective contraception to remove abstinence also updated latest version of IB and drug label
01 November 2022	Extension of EOT period duration to allow for sample processing; transfer of samples to external laboratory for processing; potential exploratory end-points.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 March 2020	Halt to study recruitment due to COVID-19	20 August 2020
05 January 2021	Halt to study recruitment due to COVID-19	06 April 2021

Notes:

Limitations and caveats

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

192 PD recorded: none sig impacted trial
no protocol Bx - due to COVID
3 patients had IMP held for 9/10/12 days; another 3 not compliant at wk12
1 patient took IMP OD (not BD) for 7 days from day 18-25.
see appendix for early termination note

Notes: