



Clinical trial results:

6 month, multi-center, open-label, prospective, randomized trial, investigating a standard regimen of an advagraf based immunosuppressive regimen in de-novo renal transplant patients versus a slower dose tapering and lower starting dose of Advagraf
Summary

EudraCT number	2013-001770-19
Trial protocol	DE
Global end of trial date	10 November 2023

Results information

Result version number	v1 (current)
This version publication date	30 January 2026
First version publication date	30 January 2026
Summary attachment (see zip file)	2013-001770-19_Report (SplusL_FinalStudyReport.pdf)

Trial information

Trial identification

Sponsor protocol code	TUD-SplusL-061
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Technische Universität Dresden
Sponsor organisation address	MommSENstraße 11, Dresden, Germany, 01069
Public contact	Koordinierungszentrum für Klinische Studien, Medizinische Fakultät C. G. Carus, 0049 351455160, kks@ukdd.de
Scientific contact	Koordinierungszentrum für Klinische Studien, Medizinische Fakultät C. G. Carus, 0049 351455160, kks@ukdd.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2023
Global end of trial reached?	Yes
Global end of trial date	10 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of biopsy-proven rejection of Banff class Ia or higher and/or graft loss and/or patient death in the study group with slower dose tapering and lower starting dose of Advagraf compared with an standard Advagraf based immunosuppressive regimen.

Protection of trial subjects:

Regular IDMC meetings to monitor safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 July 2014
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	Germany: 398
Worldwide total number of subjects	398
EEA total number of subjects	398

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)	293
From 65 to 84 years	105
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Screening for patients planned for kidney transplantation in fourteen German transplantation centres.

Pre-assignment

Screening details:

see inclusion / exclusion criteria.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Slow and low

Arm description: -

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

Dosage and administration details:

preoperative at day of transplantation: 1 x 5 mg; day 1 (first day after transplantation): 1 x 5 mg; day 2 to 6: 1 x 5 mg.

Arm title	Standard care
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

preoperative at day of transplantation: 1x0,2 mg/kg BW; day 1 (first day after transplantation): 1x0,2 mg/kg BW; day 2 to 6: tacrolimus trough levels of 7-9 ng/ml.

Number of subjects in period 1	Slow and low	Standard care
Started	196	202
Completed	196	202

Period 2	
Period 2 title	Intervention
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Slow and low

Arm description: -

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

Dosage and administration details:

preoperative at day of transplantation: 1 x 5 mg; day 1 (first day after transplantation): 1 x 5 mg; day 2 to 6: 1 x 5 mg.

Arm title	Standard care
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

preoperative at day of transplantation: 1x0,2 mg/kg BW; day 1 (first day after transplantation): 1x0,2 mg/kg BW; day 2 to 6: tacrolimus trough levels of 7-9 ng/ml.

Number of subjects in period 2	Slow and low	Standard care
Started	196	202
Completed	179	187
Not completed	17	15
Insufficient compliance	-	1
Consent withdrawn by subject	5	7
Physician decision	1	-
Graft loss	8	5
Death	2	2
Violation of I/E criteria	1	-

Period 3	
Period 3 title	Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Slow and low
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Dose adjustment according to standard of care.	
Arm title	Standard care
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Dose adjustment according to standard of care.	

Number of subjects in period 3	Slow and low	Standard care
Started	179	187
Completed	130	134
Not completed	49	53
Consent withdrawn by subject	1	-
Graft loss	13	17
Death	17	20
Lost to follow-up	18	16

Baseline characteristics

Reporting groups

Reporting group title	Slow and low
Reporting group description: -	
Reporting group title	Standard care
Reporting group description: -	

Reporting group values	Slow and low	Standard care	Total
Number of subjects	196	202	398
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	146	147	293
From 65-84 years	50	55	105
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	55	54	
standard deviation	± 12	± 13	-
Gender categorical			
Units: Subjects			
Female	68	71	139
Male	128	131	259
Type of donor			
Type of donor			
Units: Subjects			
Deceased	163	167	330
Living	33	35	68
Donor with expanded criteria			
Donor with expanded criteria			
Units: Subjects			
Yes	107	105	212
No	89	97	186

Subject analysis sets

Subject analysis set title	Intent to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intention-to-treat population consisted of all patients who received at least one dose of a study drug and underwent successful renal transplantation.	
Subject analysis set title	Per protocol

Subject analysis set type	Per protocol
Subject analysis set description: The per-protocol population was defined, including only patients who received treatment without severe protocol violations (see Supplementary Methods of main paper; PubMed ID 38152417) throughout the study period.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population consisted of all patients who received at least one dose of a study drug and underwent successful renal transplantation.	

Reporting group values	Intent to treat	Per protocol	Safety set
Number of subjects	398	315	398
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	293	241	293
From 65-84 years	105	74	105
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	55	54	55
standard deviation	± 13	± 12	± 13
Gender categorical Units: Subjects			
Female	139	117	139
Male	259	198	259
Type of donor			
Type of donor			
Units: Subjects			
Deceased	330	256	330
Living	68	59	68
Donor with expanded criteria			
Donor with expanded criteria			
Units: Subjects			
Yes	212	158	212
No	186	157	186

End points

End points reporting groups

Reporting group title	Slow and low
Reporting group description: -	
Reporting group title	Standard care
Reporting group description: -	
Reporting group title	Slow and low
Reporting group description: -	
Reporting group title	Standard care
Reporting group description: -	
Reporting group title	Slow and low
Reporting group description: -	
Reporting group title	Standard care
Reporting group description: -	
Subject analysis set title	Intent to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intention-to-treat population consisted of all patients who received at least one dose of a study drug and underwent successful renal transplantation.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description: The per-protocol population was defined, including only patients who received treatment without severe protocol violations (see Supplementary Methods of main paper; PubMed ID 38152417) throughout the study period.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population consisted of all patients who received at least one dose of a study drug and underwent successful renal transplantation.	

Primary: BPAR, Graft loss or death

End point title	BPAR, Graft loss or death
End point description: The primary efficacy outcome was the combined end point of the incidence of BPAR including borderline rejection, graft failure, and death within the first 6 months after renal transplantation. All suspected episodes of acute rejection were confirmed by biopsy, with histologic characteristics described according to the Banff criteria of 2013.	
End point type	Primary
End point timeframe: Day zero to day 180.	

End point values	Slow and low	Standard care	Intent to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	190	193	383	
Units: Patients	42	40	82	

Statistical analyses

Statistical analysis title	Primary end point
Statistical analysis description:	
Primary endpoint was tested by one-sided test of equivalence with a non-inferiority margin of 12.5% and a significance level of 5 percent. Accordingly, two-sided 90 percent confidence interval is presented for the absolute risk difference in primary endpoint.	
Comparison groups	Standard care v Slow and low
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.004
Method	noninferiority for risk difference
Parameter estimate	Risk difference (RD)
Point estimate	1.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.5
upper limit	8.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day one to day 180.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Slow and low
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Reporting group description: -

Reporting group title	Standard care
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Reporting group description: -

Serious adverse events	Slow and low	Standard care	
Total subjects affected by serious adverse events			
subjects affected / exposed	136 / 196 (69.39%)	134 / 202 (66.34%)	
number of deaths (all causes)	19	22	
number of deaths resulting from adverse events	1	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastrointestinal neoplasms malignant and unspecified			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphomas non-Hodgkin's unspecified histology			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (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 tract neoplasms malignant and unspecified			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive neoplasms male malignant and unspecified			

subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin neoplasms malignant and unspecified			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aneurysms and artery dissections			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis, stenosis, vascular insufficiency and necrosis			
subjects affected / exposed	3 / 196 (1.53%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased and nonspecific blood pressure disorders and shock			
subjects affected / exposed	0 / 196 (0.00%)	3 / 202 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism and thrombosis			
subjects affected / exposed	3 / 196 (1.53%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphatic vessel disorders			
subjects affected / exposed	11 / 196 (5.61%)	7 / 202 (3.47%)	
occurrences causally related to treatment / all	0 / 15	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular haemorrhagic disorders			
subjects affected / exposed	6 / 196 (3.06%)	6 / 202 (2.97%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular inflammations			
subjects affected / exposed	0 / 196 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Vascular therapeutic procedures			
subjects affected / exposed	1 / 196 (0.51%)	3 / 202 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal therapeutic procedures			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (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 tract therapeutic procedures			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Therapeutic procedures and supportive care NEC			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (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			
Administration site reactions			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature conditions			
subjects affected / exposed	0 / 196 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tissue disorders NEC			

subjects affected / exposed	2 / 196 (1.02%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General system disorders NEC			
subjects affected / exposed	1 / 196 (0.51%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications associated with device			
subjects affected / exposed	2 / 196 (1.02%)	3 / 202 (1.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic conditions			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune disorders NEC			
subjects affected / exposed	37 / 196 (18.88%)	34 / 202 (16.83%)	
occurrences causally related to treatment / all	7 / 49	7 / 41	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatic disorders (excl infections and inflammations)			
subjects affected / exposed	0 / 196 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Thoracic disorders (excl lung and pleura)			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract disorders (excl obstruction and infection)			

subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural disorders			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary vascular disorders			
subjects affected / exposed	4 / 196 (2.04%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorders NEC			
subjects affected / exposed	3 / 196 (1.53%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract disorders (excl infections)			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Deliria (incl confusion)			
subjects affected / exposed	0 / 196 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed mood disorders and disturbances			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbances in thinking and perception			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Product issues			
Device issues			
subjects affected / exposed	0 / 196 (0.00%)	3 / 202 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haematology investigations (incl blood groups)			
subjects affected / exposed	0 / 196 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic, nutritional and blood gas investigations			
subjects affected / exposed	1 / 196 (0.51%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Protein and chemistry analyses NEC			
subjects affected / exposed	0 / 196 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary tract investigations and urinalyses			
subjects affected / exposed	22 / 196 (11.22%)	21 / 202 (10.40%)	
occurrences causally related to treatment / all	8 / 28	5 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory and pulmonary investigations (excl blood gases)			
subjects affected / exposed	0 / 196 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Physical examination and organ system status topics			
subjects affected / exposed	1 / 196 (0.51%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Bone and joint injuries			
subjects affected / exposed	2 / 196 (1.02%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injuries NEC			
subjects affected / exposed	0 / 196 (0.00%)	3 / 202 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural related injuries and complications NEC			
subjects affected / exposed	40 / 196 (20.41%)	50 / 202 (24.75%)	
occurrences causally related to treatment / all	8 / 50	10 / 65	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exposures, chemical injuries and poisoning			
subjects affected / exposed	1 / 196 (0.51%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrhythmias			
subjects affected / exposed	2 / 196 (1.02%)	4 / 202 (1.98%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disorders			
subjects affected / exposed	3 / 196 (1.53%)	4 / 202 (1.98%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failures			
subjects affected / exposed	1 / 196 (0.51%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Central nervous system vascular disorders			

subjects affected / exposed	0 / 196 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headaches			
subjects affected / exposed	2 / 196 (1.02%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological disorders NEC			
subjects affected / exposed	1 / 196 (0.51%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral neuropathies			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizures (incl subtypes)			
subjects affected / exposed	0 / 196 (0.00%)	1 / 202 (0.50%)	
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			
Anaemias nonhaemolytic and marrow depression			
subjects affected / exposed	3 / 196 (1.53%)	4 / 202 (1.98%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell disorders			
subjects affected / exposed	4 / 196 (2.04%)	4 / 202 (1.98%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathies and bleeding diatheses (excl thrombocytopenic)			
subjects affected / exposed	0 / 196 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Hearing disorders			
subjects affected / exposed	0 / 196 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernias and other abdominal wall conditions			
subjects affected / exposed	0 / 196 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhages NEC			
subjects affected / exposed	0 / 196 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammatory conditions			
subjects affected / exposed	2 / 196 (1.02%)	3 / 202 (1.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal motility and defaecation conditions			
subjects affected / exposed	2 / 196 (1.02%)	6 / 202 (2.97%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal signs and symptoms			
subjects affected / exposed	4 / 196 (2.04%)	5 / 202 (2.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulceration and perforation			
subjects affected / exposed	2 / 196 (1.02%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular conditions			

subjects affected / exposed	0 / 196 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal and retroperitoneal conditions			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Gallbladder disorders			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic and hepatobiliary disorders			
subjects affected / exposed	1 / 196 (0.51%)	0 / 202 (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			
Genitourinary tract disorders NEC			
subjects affected / exposed	1 / 196 (0.51%)	7 / 202 (3.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathies			
subjects affected / exposed	0 / 196 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorders (excl nephropathies)			
subjects affected / exposed	3 / 196 (1.53%)	4 / 202 (1.98%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric disorders			
subjects affected / exposed	2 / 196 (1.02%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract signs and symptoms subjects affected / exposed	2 / 196 (1.02%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Parathyroid gland disorders subjects affected / exposed	2 / 196 (1.02%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders NEC subjects affected / exposed	3 / 196 (1.53%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial infectious disorders subjects affected / exposed	5 / 196 (2.55%)	6 / 202 (2.97%)	
occurrences causally related to treatment / all	2 / 6	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infectious disorders subjects affected / exposed	2 / 196 (1.02%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections - pathogen unspecified subjects affected / exposed	41 / 196 (20.92%)	44 / 202 (21.78%)	
occurrences causally related to treatment / all	8 / 59	12 / 80	
deaths causally related to treatment / all	0 / 0	1 / 3	
Viral infectious disorders subjects affected / exposed	19 / 196 (9.69%)	14 / 202 (6.93%)	
occurrences causally related to treatment / all	8 / 21	5 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Bone, calcium, magnesium and phosphorus metabolism disorders			

subjects affected / exposed	1 / 196 (0.51%)	4 / 202 (1.98%)	
occurrences causally related to treatment / all	0 / 1	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte and fluid balance conditions			
subjects affected / exposed	2 / 196 (1.02%)	5 / 202 (2.48%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucose metabolism disorders (incl diabetes mellitus)			
subjects affected / exposed	2 / 196 (1.02%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Slow and low	Standard care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	189 / 196 (96.43%)	198 / 202 (98.02%)	
Investigations			
Blood calcium increased			
subjects affected / exposed	11 / 196 (5.61%)	7 / 202 (3.47%)	
occurrences (all)	11	7	
Blood creatinine increased			
subjects affected / exposed	35 / 196 (17.86%)	39 / 202 (19.31%)	
occurrences (all)	45	54	
Blood glucose increased			
subjects affected / exposed	6 / 196 (3.06%)	15 / 202 (7.43%)	
occurrences (all)	8	18	
Blood potassium increased			
subjects affected / exposed	32 / 196 (16.33%)	27 / 202 (13.37%)	
occurrences (all)	38	32	
C-reactive protein increased			
subjects affected / exposed	11 / 196 (5.61%)	9 / 202 (4.46%)	
occurrences (all)	11	12	
Hepatic enzyme increased			

subjects affected / exposed occurrences (all)	12 / 196 (6.12%) 12	8 / 202 (3.96%) 8	
Haemoglobin decreased subjects affected / exposed occurrences (all)	12 / 196 (6.12%) 12	10 / 202 (4.95%) 11	
Injury, poisoning and procedural complications			
Complications of transplanted kidney subjects affected / exposed occurrences (all)	25 / 196 (12.76%) 26	33 / 202 (16.34%) 35	
Wound complication subjects affected / exposed occurrences (all)	25 / 196 (12.76%) 25	29 / 202 (14.36%) 32	
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	20 / 196 (10.20%) 21	22 / 202 (10.89%) 22	
Lymphocele subjects affected / exposed occurrences (all)	19 / 196 (9.69%) 20	29 / 202 (14.36%) 29	
Hypertensive crisis subjects affected / exposed occurrences (all)	25 / 196 (12.76%) 36	24 / 202 (11.88%) 32	
Hypotension subjects affected / exposed occurrences (all)	10 / 196 (5.10%) 10	10 / 202 (4.95%) 10	
Nervous system disorders			
Tremor subjects affected / exposed occurrences (all)	16 / 196 (8.16%) 16	23 / 202 (11.39%) 23	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	22 / 196 (11.22%) 22	27 / 202 (13.37%) 28	
Leukocytosis subjects affected / exposed occurrences (all)	18 / 196 (9.18%) 22	21 / 202 (10.40%) 27	

Leukopenia subjects affected / exposed occurrences (all)	46 / 196 (23.47%) 47	42 / 202 (20.79%) 46	
Nephrogenic anaemia subjects affected / exposed occurrences (all)	24 / 196 (12.24%) 24	18 / 202 (8.91%) 20	
General disorders and administration site conditions			
Oedema subjects affected / exposed occurrences (all)	13 / 196 (6.63%) 13	23 / 202 (11.39%) 25	
Oedema peripheral subjects affected / exposed occurrences (all)	25 / 196 (12.76%) 26	23 / 202 (11.39%) 24	
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	3 / 196 (1.53%) 3	11 / 202 (5.45%) 11	
Abdominal pain subjects affected / exposed occurrences (all)	8 / 196 (4.08%) 9	12 / 202 (5.94%) 13	
Diarrhoea subjects affected / exposed occurrences (all)	26 / 196 (13.27%) 27	41 / 202 (20.30%) 46	
Dyspepsia subjects affected / exposed occurrences (all)	4 / 196 (2.04%) 5	13 / 202 (6.44%) 15	
Nausea subjects affected / exposed occurrences (all)	16 / 196 (8.16%) 18	23 / 202 (11.39%) 24	
Vomiting subjects affected / exposed occurrences (all)	6 / 196 (3.06%) 7	14 / 202 (6.93%) 18	
Constipation subjects affected / exposed occurrences (all)	15 / 196 (7.65%) 20	21 / 202 (10.40%) 21	
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	12 / 196 (6.12%) 12	6 / 202 (2.97%) 6	
Dyspnoea subjects affected / exposed occurrences (all)	10 / 196 (5.10%) 10	10 / 202 (4.95%) 14	
Dyspnoea exertional subjects affected / exposed occurrences (all)	11 / 196 (5.61%) 11	2 / 202 (0.99%) 2	
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	9 / 196 (4.59%) 10	11 / 202 (5.45%) 11	
Proteinuria subjects affected / exposed occurrences (all)	15 / 196 (7.65%) 15	12 / 202 (5.94%) 12	
Leukocyturia subjects affected / exposed occurrences (all)	7 / 196 (3.57%) 7	13 / 202 (6.44%) 13	
Renal impairment subjects affected / exposed occurrences (all)	17 / 196 (8.67%) 20	17 / 202 (8.42%) 23	
Psychiatric disorders			
Sleep disorder subjects affected / exposed occurrences (all)	7 / 196 (3.57%) 7	11 / 202 (5.45%) 12	
Infections and infestations			
Cytomegalovirus infection subjects affected / exposed occurrences (all)	17 / 196 (8.67%) 19	30 / 202 (14.85%) 33	
Nasopharyngitis subjects affected / exposed occurrences (all)	13 / 196 (6.63%) 15	13 / 202 (6.44%) 13	
Urinary tract infection subjects affected / exposed occurrences (all)	46 / 196 (23.47%) 65	53 / 202 (26.24%) 71	
Polyomavirus viraemia			

subjects affected / exposed	27 / 196 (13.78%)	34 / 202 (16.83%)	
occurrences (all)	28	36	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	11 / 196 (5.61%)	12 / 202 (5.94%)	
occurrences (all)	14	12	
Glucose tolerance impaired			
subjects affected / exposed	12 / 196 (6.12%)	10 / 202 (4.95%)	
occurrences (all)	12	10	
Hypercholesterolaemia			
subjects affected / exposed	13 / 196 (6.63%)	7 / 202 (3.47%)	
occurrences (all)	13	7	
Hyperkalaemia			
subjects affected / exposed	19 / 196 (9.69%)	24 / 202 (11.88%)	
occurrences (all)	20	28	
Hypophosphataemia			
subjects affected / exposed	30 / 196 (15.31%)	34 / 202 (16.83%)	
occurrences (all)	30	34	
Metabolic acidosis			
subjects affected / exposed	26 / 196 (13.27%)	29 / 202 (14.36%)	
occurrences (all)	26	34	
Hyperlipidaemia			
subjects affected / exposed	10 / 196 (5.10%)	17 / 202 (8.42%)	
occurrences (all)	10	17	
New onset diabetes after transplantation			
subjects affected / exposed	33 / 196 (16.84%)	33 / 202 (16.34%)	
occurrences (all)	33	33	
Folate deficiency			
subjects affected / exposed	12 / 196 (6.12%)	16 / 202 (7.92%)	
occurrences (all)	12	17	
Hypokalaemia			
subjects affected / exposed	11 / 196 (5.61%)	8 / 202 (3.96%)	
occurrences (all)	12	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2017	Addition to the definition of screening failures and expansion of the sample collection for the substudy.
11 January 2018	Revision and correction of inaccuracies, as well as addition of secondary objectives and endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/38152417>