Clinical trial results:
Envarsus® tablets administered once daily in combination with everolimus in elderly de-novo kidney transplant recipients: open-label, multicentre, single-arm, pharmacokinetic and clinical study

Summary

EudraCT number	2015-005640-34
Trial protocol	IT
Global end of trial date	22 February 2018

Results information

Result version number	v1 (current)
This version publication date	28 February 2019
First version publication date	28 February 2019

Trial information

Trial identification

Sponsor protocol code	DFIDM-1501

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02970630
WHO universal trial number (UTN)	-
Other trial identifiers	NA: NA

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Trasparency, Clinical Trial Trasparency, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Trasparency, Clinical Trial Trasparency, clinicaltrials_info@chiesi.com

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	22 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate tacrolimus (Envarsus®) pharmacokinetic parameters (AUC24, Cmin, Cmin/daily dose and AUC24/daily dose) in elderly de-novo kidney transplant recipients of ECD kidney grafts treated with Envarsus® prolonged release tablets in combination with everolimus tablets (Certican®).

Protection of trial subjects:

The protocol, together with all required clinical trial documentation, was submitted to the appropriate independent ethics committee (IEC) in all participating sites. A copy of the favourable opinion from the IEC had to be received before the trial could be initiated at an investigational site. The membership of each IEC was also obtained.
The study was performed in compliance with the 'Declaration of Helsinki', International Conference of Harmonization Tripartite Guidelines Guideline for Good Clinical Practice (ICH GCP), current international and national regulations, the study protocol and current Standard Operating Procedures (SOPs) of Chiesi Farmaceutici S.p.A.
The consent document met all applicable local laws and provided the patient with information regarding the purpose, procedures, requirements and restrictions of the study, along with any known risks and potential benefits associated with the investigational product and the established provisions for maintaining the confidentiality of personal information. Subject's written informed consent obtained prior to transplant intervention and prior to any study-related procedures.

Background therapy:

Envarsus® is a new tacrolimus tablet formulation approved by the European Medicines Agency (EMA). Envarsus®, designed for once-daily administration, was developed utilising the MeltDoseTM drug delivery technology, which increases the bioavailability of poorly water-soluble compounds via solid formulation at molecular state. For this reason, the daily dose should be reduced by 30% in comparison with standard tacrolimus (with the exclusion of black patients), in order to reach the therapeutic exposure to tacrolimus.

Evidence for comparator: -

Actual start date of recruitment	09 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	9
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty-eight (28) patients were enrolled in the study in four (4) Italian sites. There were no screening failures. Of the 28 enrolled patients, 22 (78.6%) completed the study and 6 (21.4%) were discontinued (all due to adverse events).

Pre-assignment

Screening details:

The screening visit (V1) embraced a period of 24 hours before and after kidney transplantation (Tx). In case of unsuccessful transplantation, transplant failure or if the patient was withdrawn from study before the first dose of study treatments, the subject was to be classified as screening failure and replaced.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Study Treatment

Arm description:

all the subjects receiving the study drugs (Envarsus® and everolimus)

Arm type	Experimental
Investigational medicinal product name	1_Envarsus®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Reference product: Envarsus® prolonged-release tablets, oral formulation.

Active ingredient: tacrolimus monohydrate.

Dose:
IMP dosage form: 0.75 mg, 1.0 mg and 4.0 mg dosage strengths.
Oral administration once daily
Starting dose: 0.07 mg/kg/day
The dose of Envarsus® was maintained constant until Day 3. Starting from Day 4, the initial tacrolimus dose was adjusted in order to maintain tacrolimus Ctrough within the following target: 4-7 ng/ml until end of Month 3, then 3-6 ng/ml.

Investigational medicinal product name	2_Certican®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Reference product: Certican® tablets, oral formulation.

Active ingredient: everolimus

Dose:
IMP dosage form: 0.25 mg and 0.75 mg dosage strengths.
Oral administration twice daily
Starting dose: 2 mg/day
The dose of everolimus was maintained constant until Day 3. Starting from Day 4, the initial dose was adjusted in order to maintain everolimus Ctrough within the following target: 3-8 ng/ml (5-8 ng/ml if

determined with immunoassay).

Number of subjects in period 1	Study Treatment
Started	28
Completed	22
Not completed	6
Adverse event, non-fatal	6

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period
Reporting group description:	
Active Treatment Arm with Envarsus tablets administred once daily in combination with Everolimus (Certican®). Envarsus® Active ingredient: tacrolimus monohydrate Oral administration once daily Starting dose: 0.07 mg/kg/day The dose of Envarsus® was maintained constant until Day 3. Starting from Day 4, the initial tacrolimus dose was adjusted in order to maintain tacrolimus Ctrough within the following target: 4-7 ng/ml until end of Month 3, then 3-6 ng/ml. Certican® Active ingredient: everolimus Oral administration twice daily Starting dose: 2 mg/day The dose of everolimus was maintained constant until Day 3. Starting from Day 4, the initial dose was adjusted in order to maintain everolimus Ctrough within the following target: 3-8 ng/ml (5-8 ng/ml if determined with immunoassay).	

Reporting group values	Treatment period	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
Adults (18-64 years)	9	9	
From 65-84 years	19	19	
Age continuous Units: years			
arithmetic mean	66.2		
standard deviation	± 3.3	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	21	21	
Race Units: Subjects			
white	28	28	

End points

End points reporting groups

Reporting group title	Study Treatment

Reporting group description:

all the subjects receiving the study drugs (Envarsus® and everolimus)

Primary: 1_Tacrolimus AUC24

End point title	1_Tacrolimus AUC24[1]

End point description:

A 24-hour multiple blood sampling for PK assessment was performed on Visit 6 (study Day 10 to 12). Thirteen (13) samples for the determination of tacrolimus concentrations in whole blood in the 0-24 h interval were taken at the following times: 0.00 (within 5 minutes before the morning dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 20.00 and 24.00 h post-dose. Area under the whole blood drug concentration curve observed from time 0 to 24 hours post dose was computed using the linear trapezoidal rule. Overall results have been reported.

End point type	Primary

End point timeframe:

Visit 6 (Day 10 to Day 12)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the study design (only one arm, without any comparator), primary endpoint's statistical analysis is a descriptive analysis.

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	23[2]			
Units: ng.h/ml				
arithmetic mean (standard deviation)	160.20 (± 53.96)			

Notes:

[2] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: 2_Tacrolimus Cmin

End point title	2_Tacrolimus Cmin[3]

End point description:

A 24-hour multiple blood sampling for PK assessment was performed on Visit 6 (study Day 10 to 12). Thirteen (13) samples for the determination of tacrolimus concentrations in whole blood in the 0-24 h interval were taken at the following times: 0.00 (within 5 minutes before the morning dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 20.00 and 24.00 h post-dose. Minimum observed blood concentration following a single dose, obtained directly from the blood concentration versus time curves. It was obtained directly from the experimental data without interpolation. Overall results have been reported.

End point type	Primary

End point timeframe:

Visit 6 (Day 10 to Day 12)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the study design (only one arm, without any comparator), primary endpoint's statistical analysis is a descriptive analysis.

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	23[4]			
Units: ng/ml				
arithmetic mean (standard deviation)	4.26 (± 1.54)			

Notes:

[4] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 3_Tacrolimus Cmax

End point title	3_Tacrolimus Cmax

End point description:

A 24-hour multiple blood sampling for PK assessment was performed on Visit 6 (study Day 10 to 12). Thirteen (13) samples for the determination of tacrolimus concentrations in whole blood in the 0-24 h interval were taken at the following times: 0.00 (within 5 minutes before the morning dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 20.00 and 24.00 h post-dose. Maximum observed blood concentration (Cmax) following a single dose, obtained directly from the blood concentration versus time curves. It was obtained directly from the experimental data without interpolation. Overall results have been reported.

End point type	Secondary

End point timeframe:

Visit 6 (Day 10 to Day 12)

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	23[5]			
Units: ng/ml				
arithmetic mean (standard deviation)	10.50 (± 4.33)			

Notes:

[5] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 4_Tacrolimus tmax

End point title	4_Tacrolimus tmax

End point description:

A 24-hour multiple blood sampling for PK assessment was performed on Visit 6 (study Day 10 to 12). Thirteen (13) samples for the determination of tacrolimus concentrations in whole blood in the 0-24 h

interval were taken at the following times: 0.00 (within 5 minutes before the morning dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 20.00 and 24.00 h post-dose. Time from dosing to Cmax (tmax), reported using actual times. Overall results have been reported.

End point type	Secondary

End point timeframe:

Visit 6 (Day 10 to Day 12)

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	23[6]			
Units: hour				
arithmetic mean (standard deviation)	6.62 (± 3.36)			

Notes:

[6] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 5_Tacrolimus linear correlation coefficient between AUC24 and Cmin

End point title	5_Tacrolimus linear correlation coefficient between AUC24 and Cmin

End point description:

A 24-hour multiple blood sampling for PK assessment was performed on Visit 6 (study Day 10 to 12). Thirteen (13) samples for the determination of tacrolimus concentrations in whole blood in the 0-24 h interval were taken at the following times: 0.00 (within 5 minutes before the morning dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 20.00 and 24.00 h post-dose. Time from dosing to Cmax, reported using actual times.
Linear correlation refers to linear correlation coefficient (R2) between AUC24 and Cmin.
Overall results have been reported expressed as a pure number to be multiplied by 10(-4).

End point type	Secondary

End point timeframe:

Visit 6 (Day 10 to Day 12)

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	23[7]			
Units: pure number by 10(-4) [0 - 1]	7309			

Notes:

[7] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 6_Everolimus day time AUC12

End point title	6_Everolimus day time AUC12

End point description:

A 24-hour multiple blood sampling for PK assessment was performed on Visit 6 (study Day 10 to 12). Thirteen (13) samples for the determination of tacrolimus concentrations in whole blood in the 0-24 h interval were taken at the following times: 0.00 (within 5 minutes before the morning dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 20.00 and 24.00 h post-dose.
Area under the whole blood drug concentration curve observed from time 0 to 12 hours post dose (AUC12, day time) was computed using the linear trapezoidal rule. Overall results have been reported.

End point type	Secondary

End point timeframe:

Visit 6 (Day 10 to Day 12) - day time

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	23[8]			
Units: ng.h/ml				
arithmetic mean (standard deviation)	58.84 (± 16.47)			

Notes:

[8] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 7_Everolimus day time Cmin and Cmax

End point title	7_Everolimus day time Cmin and Cmax

End point description:

A 24-hour multiple blood sampling for PK assessment was performed on Visit 6 (study Day 10 to 12). Thirteen (13) samples for the determination of tacrolimus concentrations in whole blood in the 0-24 h interval were taken at the following times: 0.00 (within 5 minutes before the morning dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 20.00 and 24.00 h post-dose. Minimum (Cmin) and maximum (Cmax) observed blood concentration following a single dose, obtained directly from the blood concentration versus time curves. It was obtained directly from the experimental data without interpolation. Overall results have been reported.

End point type	Secondary

End point timeframe:

Visit 6 (Day 10 to Day 12) - day time

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	23[9]			
Units: ng/ml				
arithmetic mean (standard deviation)				
everolimus_Cmin_day time	2.81 (± 0.91)			
everolimus_Cmax_day time	10.65 (± 3.55)			

Notes:
[9] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 8_Everolimus day time tmax

End point title	8_Everolimus day time tmax

End point description:

A 24-hour multiple blood sampling for PK assessment was performed on Visit 6 (study Day 10 to 12). Thirteen (13) samples for the determination of tacrolimus concentrations in whole blood in the 0-24 h interval were taken at the following times: 0.00 (within 5 minutes before the morning dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 20.00 and 24.00 h post-dose.
Time from dosing to Cmax (tmax), reported using actual times. Overall results have been reported.

End point type	Secondary

End point timeframe:

Visit 6 (Day 10 to Day 12) - day time

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	23[10]			
Units: hour				
arithmetic mean (standard deviation)	1.34 (± 0.91)			

Notes:
[10] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 9_Everolimus day time linear correlation coefficient between AUC12 and Cmin

End point title	9_Everolimus day time linear correlation coefficient between AUC12 and Cmin

End point description:

A 24-hour multiple blood sampling for PK assessment was performed on Visit 6 (study Day 10 to 12). Thirteen (13) samples for the determination of tacrolimus concentrations in whole blood in the 0-24 h interval were taken at the following times: 0.00 (within 5 minutes before the morning dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 20.00 and 24.00 h post-dose.
Linear correlation refers to linear correlation coefficent (R2) between Cmin and AUC12.
Overall results have been reported expressed as a pure number to be multiplied by 10(-4).

End point type	Secondary

End point timeframe:

Visit 6 (Day 10 to Day 12) - day time

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	23[11]			
Units: pure number by 10(-4) [0-1]	7706			

Notes:

[11] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 10_Serum creatinine

End point title	10_Serum creatinine

End point description:

For serum creatinine, baseline was defined as Visit 1 (screening) evaluation. Change from baseline for serum creatinine results have been reported from day 1 to month 6.

End point type	Secondary

End point timeframe:

Renal function was evaluated measuring serum creatinine on blood samples taken at each visit (before transplant and on Day 1, 3, 5, 7, 10 and Month 1, 2, 3, 4, 5 and 6).

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	28[12]			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)				
change from baseline_day 1	-135.6 (± 298.2)			
change from baseline_day 3	-290.7 (± 378.6)			
change from baseline_day 5	-378.0 (± 402.5)			
change from baseline_day 7	-427.4 (± 374.2)			
change from baseline_day 10	-485.0 (± 349.3)			
change from baseline_month 1	-508.4 (± 308.8)			
change from baseline_month 2	-459.3 (± 277.7)			
change from baseline_month 3	-501.4 (± 313.9)			
change from baseline_month 4	-496.1 (± 312.5)			
change from baseline_month 5	-505.6 (± 327.1)			

change from baseline_month 6	-507.7 (± 333.8)			

Notes:

[12] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: 11_Estimated glomerular filtration rate (eGFR)

End point title	11_Estimated glomerular filtration rate (eGFR)

End point description:

The eGFR was calculated with different methods for each site, therefore at the DRM it was decided to derive the eGFR. It was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.
For eGFR, baseline was defined as Visit 1 (screening) evaluation. Actual valueas and Change from baseline for eGFR results have been reported from day 1 to month 6.

End point type	Secondary

End point timeframe:

Analised before transplant (screening) and on Day 1, 3, 5, 7, 10 and Month 1, 2, 3, 4, 5 and 6.

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	28[13]			
Units: ml/min per 1.73 m2				
arithmetic mean (standard deviation)				
change from baseline_day 1	3.0 (± 7.9)			
change from baseline_day 3	13.7 (± 22.0)			
change from baseline_day 5	20.6 (± 23.3)			
change from baseline_day 7	24.8 (± 22.5)			
change from baseline_day 10	29.5 (± 26.0)			
change from baseline_month 1	32.4 (± 19.8)			
change from baseline_month 2	29.8 (± 15.6)			
change from baseline_month 3	29.5 (± 16.9)			
change from baseline_month 4	29.0 (± 18.8)			
change from baseline_month 5	30.4 (± 16.9)			
change from baseline_month 6	31.3 (± 17.8)			
actual value_day 1	10.5 (± 7.5)			
actual value_day 3	21.4 (± 21.2)			
actual value_day 5	28.5 (± 22.5)			
actual value_day 7	32.6 (± 21.7)			
actual value_day 10	37.3 (± 25.4)			
actual value_month 1	40.0 (± 18.0)			
actual value_month 2	37.6 (± 13.8)			
actual value_month 3	37.2 (± 15.3)			
actual value_month 4	36.9 (± 17.4)			
actual value_month 5	38.2 (± 15.0)			
actual value_month 6	39.2 (± 15.8)			

Notes:
[13] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: 12_Treatment failure rate

End point title	12_Treatment failure rate

End point description:

Efficacy endpoint.
Treatment failure rate, a composite endpoint,including biopsy proven acute rejection (BPAR), graft failure, death and lost to follow up, and the rate of each component of composite endpoint. Overall results have been reported.
Note: BPAR= biopsy proven acute rejection.

End point type	Secondary

End point timeframe:

Within 6 months.

End point values	Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	28[14]			
Units: percentage of subject (0-100%)				
overall_BPAR	0			
overall_graft failure	0			
overall_death	0			
overall_treatment failure	0			
overall_lost to follow up	0			

Notes:
[14] - ITT population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE, SAE and ADR were collected throughout the study. From Visit 1 (screening) to Visit 12 (month 6).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Study Treatment

Reporting group description:

all the subjects receiving the study drugs (Envarsus® and everolimus)

Serious adverse events	Study Treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 28 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Perirenal haematoma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural urine leak			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Lymphocele			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pelvic fluid collection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			

subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ureteric stenosis				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urethral stenosis				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Urinary tract infection				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	3 / 28 (10.71%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Escherichia urinary tract infection				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Study Treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 28 (96.43%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Haematoma			

subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all) Lymphocele subjects affected / exposed occurrences (all) Lymphorrhoea subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1 1 / 28 (3.57%) 1 1 / 28 (3.57%) 1 1 / 28 (3.57%) 1		
General disorders and administration site conditions Oedema subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Catheter site pain subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Peripheral swelling subjects affected / exposed occurrences (all)	 6 / 28 (21.43%) 6 2 / 28 (7.14%) 2 2 / 28 (7.14%) 2 1 / 28 (3.57%) 1 1 / 28 (3.57%) 1 1 / 28 (3.57%) 1		
Reproductive system and breast disorders Pelvic fluid collection subjects affected / exposed occurrences (all)	 1 / 28 (3.57%) 1		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Sputum culture positive			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Procedural pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 28 (50.00%)		
occurrences (all)	14		
Leukopenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Inguinal hernia			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Proteinuria			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Anuria			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Bladder spasm			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Oliguria			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Strangury			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	7		
Cytomegalovirus infection			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		

Urinary tract infection enterococcal subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 2		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	11 / 28 (39.29%) 14		
Hypomagnesaemia subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 5		
Hyperuricaemia subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 4		
Hypocalcaemia subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 5		
Hypercholesterolaemia subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Hyperkalaemia subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 4		
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Metabolic acidosis subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 4		
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Hypernatraemia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Hypophosphataemia			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hyposideraemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported.

Notes: