Clinical trial results:
A Phase 3b, Multi-center, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease

Summary

EudraCT number	2014-000226-38
Trial protocol	GB IT SE HU DK NL BE ES CZ PL FR
Global end of trial date	14 April 2017

Results information

Result version number	v1 (current)
This version publication date	13 May 2018
First version publication date	13 May 2018

Trial information

Trial identification

Sponsor protocol code	156-13-210

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02160145
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, MD 20850
Public contact	Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp
Scientific contact	Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp

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	14 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2017
Global end of trial reached?	Yes
Global end of trial date	14 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of tolvaptan treatment in reducing the change in estimated glomerular filtration rate (eGFR) from pretreatment baseline to post-treatment follow-up, as compared with placebo, in subjects with late-stage chronic kidney disease (CKD) due to ADPKD who tolerate tolvaptan during an initial run-in period.

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the Institutional Review Board or Independent Ethics Committee at each respective trial center.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 May 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	Hungary: 15
Country: Number of subjects enrolled	Italy: 82
Country: Number of subjects enrolled	Argentina: 24
Country: Number of subjects enrolled	Australia: 44
Country: Number of subjects enrolled	Canada: 49
Country: Number of subjects enrolled	Israel: 41
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	South Africa: 25
Country: Number of subjects enrolled	United States: 637
Country: Number of subjects enrolled	Netherlands: 25
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	Spain: 61
Country: Number of subjects enrolled	Sweden: 26
Country: Number of subjects enrolled	United Kingdom: 100
Country: Number of subjects enrolled	Belgium: 73

Country: Number of subjects enrolled	Czech Republic: 34
Country: Number of subjects enrolled	Denmark: 28
Country: Number of subjects enrolled	France: 72
Country: Number of subjects enrolled	Germany: 113
Worldwide total number of subjects	1519
EEA total number of subjects	695

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)	1504
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial included subjects randomized at 213 sites (screened subjects from 225 sites) in the following 21 countries: Argentina, Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Netherlands, Norway, Poland, Romania, Russia, South Africa, Spain, Sweden, United Kingdom, and United States.

Pre-assignment

Screening details:

Subjects who provided informed consent and for whom preliminary eligibility was established entered an 8-week prerandomization period (screening + 3 single-blind periods: placebo run-in, tolvaptan titration and tolvaptan run-in). The screening period (up to Day -43) was typically 1 to 2 weeks.

Period 1

Period 1 title	Placebo Run-in Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

The subject remained blinded to treatment (matching placebo of tolvaptan).

Arms

Arm title	Placebo Run-in Period - All subjects

Arm description:

Placebo Run-in Period was from Day -42 to Day -36. In the first week after the screening period, all subjects began the single-blind, placebo run-in period with placebo in a daily split-dose in a form identical to tolvaptan tablets. Subjects unable to tolerate the placebo dose regimen were considered "run-in failures".

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:

The subjects received placebo orally in a daily split-dose of 0 mg (abbreviated 0/0 mg), in a form identical to tolvaptan tablets at the 15/15 mg dose.

Number of subjects in period 1	Placebo Run-in Period - All subjects
Started	1519
Completed	1496
Not completed	23
Subject Decision	15
Physician Decision	5
Other Reasons	2
Lost to follow-up	1

Period 2

Period 2 title	Tolvaptan titration and Run-in Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Subjects were blinded to treatment.

Arms

Arm title	Tolvaptan titration and Run-in Period: All Subjects

Arm description:

Tolvaptan Titration Period was from Day -35 to Day -22. During the single-blind, 2-week, tolvaptan titration period, all subjects received 2 boxes of tolvaptan, 1 box containing 2 bottles of 15-mg tablets and the other box containing 2 bottles of 30-mg tablets. Titration was accomplished by increasing the number of tablets/dose and/or switching from 15 mg tablets to 30 mg tablets. Those subjects unable to tolerate at least a 60/30 mg tolvaptan dose regimen were considered "run-in failures". Subjects who tolerated at least 60/30 mg tolvaptan, entered the single-blind, tolvaptan run-in period (3-week duration; Tolvaptan Run-in Period was from Day -21 to Day -1) and continued on a stable 60/30 mg or 90/30 mg tolvaptan dose to confirm tolerability over a longer period and to establish a tolvaptan pre-randomization baseline.

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

Dosage and administration details:

Subjects were instructed to take tolvaptan orally at a split-dose of 30/15 mg (as two 15-mg tablets upon waking and one 15-mg tablet approximately 8 to 9 hours later) and to titrate up every 3 to 4 days; first to 45/15, then 60/30, then, up to the maximum dose of 90/30 mg. In tolvaptan run-in period, subjects who tolerated at least 60/30 mg tolvaptan, continued on a stable 60/30 mg or 90/30 mg tolvaptan dose.

Number of subjects in period 2	Tolvaptan titration and Run-in Period: All Subjects
Started	1496
Completed	1370
Not completed	126
Subject Decision	97

Physician Decision	19
Other Reasons	6
Lost to follow-up	4

Period 3

Period 3 title	Double-blind Randomized Treatment Period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Except in cases of emergency unblinding, subjects, investigational site personnel, sponsor employees, and all other trial personnel remained blinded to the identity of the treatment assignments until every subject had completed trial treatment and the database had been locked. Once the blind was broken for a given subject, that subject could not reinitiate treatment with IMP.

Arms

Are arms mutually exclusive?	Yes
Arm title	Tolvaptan

Arm description:

Treatment Period was from Day 0 to Month 12. Subjects who tolerated the 60/30- or 90/30-mg dose of tolvaptan were randomized to tolvaptan treatment period. Subjects randomized to tolvaptan continued to take the same dose that they received during the tolvaptan run-in period. The treatment duration was for 12 months from the date of randomization.

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

Dosage and administration details:

Tolvaptan was administered at 60/30 or 90/30 mg, as split-doses, with down-titrations to 45/15 and 30/15 mg as needed for tolerability. Planned down titration to 30/15 mg was approved by the medical monitor.

Arm title	Placebo

Arm description:

Subjects randomized to placebo received placebo tablets matching their tolerated tolvaptan dose during the tolvaptan run-in period. The treatment duration was for 12 months from the date of randomization.

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:

Matching placebo tablets (15 or 30 mg) were self-administered orally as split-dose regimens, once upon awakening and another approximately 8 to 9 hours later.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: This study consisted of pre-randomization period which comprised of a screening period, a placebo run-in period and a tolvaptan run-in period. Since the actual randomization of subjects occurred after this pre-randomization period, Period 3 was considered as the "Baseline period". Only the randomized subjects were taken into account for the efficacy and safety analysis

Number of subjects in period 3[2]	Tolvaptan	Placebo
Started	683	687
Completed	654	659
Not completed	29	28
Subject Decision	21	20
Physician Decision	7	5
Lost to follow-up	1	3

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In order to achieve 90% power with the assumption of 10% dropout rate in the trial, a total sample size of approximately 1300 subjects were planned. But in the trial, 1370 subjects were randomized and were considered as the baseline population count.

Baseline characteristics

Reporting groups	
Reporting group title	Tolvaptan

Reporting group description:

Treatment Period was from Day 0 to Month 12. Subjects who tolerated the 60/30- or 90/30-mg dose of tolvaptan were randomized to tolvaptan treatment period. Subjects randomized to tolvaptan continued to take the same dose that they received during the tolvaptan run-in period. The treatment duration was for 12 months from the date of randomization.

Reporting group title	Placebo

Reporting group description:

Subjects randomized to placebo received placebo tablets matching their tolerated tolvaptan dose during the tolvaptan run-in period. The treatment duration was for 12 months from the date of randomization.

Reporting group values	Tolvaptan	Placebo	Total
Number of subjects	683	687	1370
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	47.3	47.2	
standard deviation	± 8.2	± 8.2	-
Gender categorical Units: Subjects			
Female	336	354	690
Male	347	333	680

End points

End points reporting groups

Reporting group title	Placebo Run-in Period - All subjects

Reporting group description:

Placebo Run-in Period was from Day -42 to Day -36. In the first week after the screening period, all subjects began the single-blind, placebo run-in period with placebo in a daily split-dose in a form identical to tolvaptan tablets. Subjects unable to tolerate the placebo dose regimen were considered "run-in failures".

Reporting group title	Tolvaptan titration and Run-in Period: All Subjects

Reporting group description:

Tolvaptan Titration Period was from Day -35 to Day -22. During the single-blind, 2-week, tolvaptan titration period, all subjects received 2 boxes of tolvaptan, 1 box containing 2 bottles of 15-mg tablets and the other box containing 2 bottles of 30-mg tablets. Titration was accomplished by increasing the number of tablets/dose and/or switching from 15 mg tablets to 30 mg tablets. Those subjects unable to tolerate at least a 60/30 mg tolvaptan dose regimen were considered "run-in failures". Subjects who tolerated at least 60/30 mg tolvaptan, entered the single-blind, tolvaptan run-in period (3-week duration; Tolvaptan Run-in Period was from Day -21 to Day -1) and continued on a stable 60/30 mg or 90/30 mg tolvaptan dose to confirm tolerability over a longer period and to establish a tolvaptan pre-randomization baseline.

Reporting group title	Tolvaptan

Reporting group description:

Treatment Period was from Day 0 to Month 12. Subjects who tolerated the 60/30- or 90/30-mg dose of tolvaptan were randomized to tolvaptan treatment period. Subjects randomized to tolvaptan continued to take the same dose that they received during the tolvaptan run-in period. The treatment duration was for 12 months from the date of randomization.

Reporting group title	Placebo

Reporting group description:

Subjects randomized to placebo received placebo tablets matching their tolerated tolvaptan dose during the tolvaptan run-in period. The treatment duration was for 12 months from the date of randomization.

Primary: Treatment difference in the change of eGFR (Estimated glomerular filtration rate), from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subject's trial duration

End point title	Treatment difference in the change of eGFR (Estimated glomerular filtration rate), from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subject's trial duration

End point description:

Treatment difference in the change of eGFR was calculated using Chronic Kidney Disease-Epidemiology (CKD-EPI) formula. To reduce the variation in this primary endpoint, 3 observations of eGFR were obtained at baseline during a 3-week interval (screening and placebo run-in periods) and another 3 observations were obtained post-treatment during a 2-week interval that began 1 week after the end of treatment (3-week post-treatment follow-up). The average of the 3 eGFR values observed during the baseline period was set as the baseline and the average of the 3 eGFR values observed during the post-treatment follow-up period was set as the renal function measurement post-treatment.

End point type	Primary

End point timeframe:

From prior to randomization to follow-up (3 weeks post-treatment)

End point values	Tolvaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	668	663		
Units: mL/min/1.73 m2/yr				
arithmetic mean (standard deviation)	-2.961 (± 4.590)	-4.249 (± 4.009)		

Statistical analyses

Statistical analysis title	Treatment difference in Change in eGFR
Comparison groups	Placebo v Tolvaptan
Number of subjects included in analysis	1331
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.271
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.859
upper limit	1.684

Notes:

[1] - Derived from weighted ANCOVA with effects of treatment and randomization stratification factors and covariate baseline.

Secondary: Number of subjects with adverse events (AEs)

End point title	Number of subjects with adverse events (AEs)

End point description:

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE.

End point type	Secondary

End point timeframe:

From Day 0 until the follow-up visit (3 weeks post-treatment)

End point values	Tolvaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	681	685		
Units: Participants				
number (not applicable)				
Subjects with AEs	581	564		
Subjects with treatment-emergent AEs	581	564		
Subjects with serious treatment-emergent AEs	85	60		
Subjects with non-serious treatment-emergent AEs	569	556		

Subjects with severe treatment-emergent AEs	70	50		
Subjects discontinued drug due to AEs	65	15		
Number of subjects who died	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment difference in annualized slope of eGFR calculated for individual subjects using eGFR data observed in the placebo run-in, tolvaptan run-in (not including tolvaptan titration), double-blind treatment, and post-treatment follow-up periods

End point title	Treatment difference in annualized slope of eGFR calculated for individual subjects using eGFR data observed in the placebo run-in, tolvaptan run-in (not including tolvaptan titration), double-blind treatment, and post-treatment follow-up periods

End point description:

The key secondary endpoint of the trial was the annualized rate of eGFR change, which was derived from each individual subject's eGFR slope using the CKD-EPI formula. The analysis of the key secondary endpoint was formally conducted, once the primary endpoint was significant at a 2-sided alpha of 0.05. Then a 2-sided alpha of 0.05 was applied to the primary analysis of the key secondary endpoint. In this analysis, all eGFR observations from placebo run-in, tolvaptan run-in (not including tolvaptan titration), double-blind treatment, and post-treatment follow-up (not including data collected in the first week after the last IMP dose) periods were included in the analysis, with the data of tolvaptan run-in and tolvaptan subjects in the double-blind treatment period were flagged (yes = 1 and no = 0) with a tolvaptan acute hemodynamic effect.

End point type	Secondary

End point timeframe:

Prior to and post 13 1/2 months of treatment

End point values	Tolvaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	680	682		
Units: mL/min/1.73 m2/yr				
arithmetic mean (standard deviation)	-2.552 (± 7.911)	-3.238 (± 5.757)		

Statistical analyses

Statistical analysis title	Treatment difference in annualized slope of eGFR
Comparison groups	Placebo v Tolvaptan

Number of subjects included in analysis	1362
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [2]
Method	Linear Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.618
upper limit	1.403

Notes:

[2] - Derived from linear mixed model with effects of treatment, time, treatment time interaction, acute hemodynamic effect, pre-treatment baseline, and randomization stratification factors.

Secondary: Pharmacodynamic endpoint: Mean change from baseline in Urinalysis - Urine osmolality (Uosm)

End point title	Pharmacodynamic endpoint: Mean change from baseline in Urinalysis - Urine osmolality (Uosm)

End point description:

Uosm was one of the pharmacodynamic endpoints. Urine osmolality was summarized by treatment (tolvaptan or placebo) and time point using descriptive statistics. Baseline values were from the sample obtained at the end of the tolvaptan run-in period.

End point type	Secondary

End point timeframe:

From Day -1 through Month 12/end of treatment (EoTx) visit, and the last follow-up visit (3 weeks post-treatment).

End point values	Tolvaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	681	685		
Units: mOsm/kg				
arithmetic mean (standard deviation)				
Month 3 (N = 655, 664)	10.2 (± 80.3)	177.7 (± 124.5)		
Month 6 (N = 637, 652)	22.9 (± 84.3)	179.1 (± 126.2)		
Month 9 (N = 625, 646)	30.4 (± 92.1)	179.9 (± 125.1)		
Month 12 (N = 629, 651)	36.9 (± 96.0)	180.3 (± 121.1)		
Follow-up Day 21 (N = 624, 650)	162.4 (± 114.0)	179.5 (± 128.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic endpoint: Mean change from baseline in Urinalysis - urine specific gravity

End point title	Pharmacodynamic endpoint: Mean change from baseline in Urinalysis - urine specific gravity

End point description:

Urine specific gravity was one of the pharmacodynamic endpoints. Urine specific gravity was summarized by treatment (tolvaptan or placebo) and time point using descriptive statistics. Baseline values were from the sample obtained at the end of the tolvaptan run-in period.

End point type	Secondary

End point timeframe:

From Day -1 through Month 12/end of treatment (EoTx) visit, and the last follow-up visit (3 weeks post-treatment).

End point values	Tolvaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	681	685		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 3 (N = 654, 662)	0.0001 (± 0.0022)	0.0041 (± 0.0033)		
Month 6 (N = 638, 649)	0.0003 (± 0.0024)	0.0042 (± 0.0033)		
Month 9 (N = 623, 641)	0.0004 (± 0.0025)	0.0040 (± 0.0032)		
Month 12 (N = 635, 648)	0.0006 (± 0.0027)	0.0040 (± 0.0033)		
Follow-up Day 21 (N = 620, 653)	0.0037 (± 0.0031)	0.0040 (± 0.0034)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening until the follow-up visit (3 weeks post-treatment)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Tolvaptan

Reporting group description:

Subjects who reached the end of the tolvaptan run-in period and who tolerated the 60/30- or 90/30-mg dose of tolvaptan were randomized to tolvaptan treatment period. Subjects randomized to tolvaptan continued to take the same dose that they received during the tolvaptan run-in period. Treatment Period was from Day 0 to Month 12.

Reporting group title	Placebo

Reporting group description:

Subjects randomized to placebo received placebo tablets matching their tolerated tolvaptan dose during the tolvaptan run-in period. The treatment duration was for 12 months from the date of randomization.

Serious adverse events	Tolvaptan	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	85 / 681 (12.48%)	60 / 685 (8.76%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 681 (0.00%)	2 / 685 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm benign			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			

subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phaeochromocytoma			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cyst rupture			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 681 (0.15%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 681 (0.15%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 681 (0.29%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	8 / 681 (1.17%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	7 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 681 (0.44%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bicarbonate decreased			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 681 (0.00%)	2 / 685 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	11 / 681 (1.62%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	10 / 12	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	3 / 681 (0.44%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			

subjects affected / exposed	4 / 681 (0.59%)	2 / 685 (0.29%)	
occurrences causally related to treatment / all	7 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic specific antigen increased			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	2 / 681 (0.29%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (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			
Fall			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural intestinal perforation			

subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 681 (0.15%)	3 / 685 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	2 / 681 (0.29%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital hepatic fibrosis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 681 (0.00%)	2 / 685 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 681 (0.15%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve prolapse			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery aneurysm			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery thrombosis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 681 (0.15%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			

subjects affected / exposed	1 / 681 (0.15%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 681 (0.29%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal incarcerated hernia			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			

subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 681 (0.15%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swollen tongue			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			

subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic hepatic cyst			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 681 (0.15%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	2 / 681 (0.29%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 681 (0.15%)	2 / 685 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst haemorrhage			
subjects affected / exposed	3 / 681 (0.44%)	2 / 685 (0.29%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haemorrhage			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 681 (0.29%)	3 / 685 (0.44%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal pain			
subjects affected / exposed	1 / 681 (0.15%)	3 / 685 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthritis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 681 (0.29%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter bacteraemia			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 681 (0.15%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst infection			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 681 (0.15%)	3 / 685 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst infection			

subjects affected / exposed	2 / 681 (0.29%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 681 (0.15%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 681 (0.44%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 681 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 681 (0.00%)	2 / 685 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitamin B complex deficiency			
subjects affected / exposed	1 / 681 (0.15%)	0 / 685 (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: 5 %

Non-serious adverse events	Tolvaptan	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	569 / 681 (83.55%)	556 / 685 (81.17%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	46 / 681 (6.75%)	44 / 685 (6.42%)	
occurrences (all)	58	54	
Vascular disorders			
Hypertension			
subjects affected / exposed	73 / 681 (10.72%)	79 / 685 (11.53%)	
occurrences (all)	88	95	
Nervous system disorders			
Headache			
subjects affected / exposed	55 / 681 (8.08%)	59 / 685 (8.61%)	
occurrences (all)	66	65	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	45 / 681 (6.61%)	24 / 685 (3.50%)	
occurrences (all)	48	26	
Oedema peripheral			
subjects affected / exposed	30 / 681 (4.41%)	45 / 685 (6.57%)	
occurrences (all)	37	50	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	47 / 681 (6.90%)	23 / 685 (3.36%)	
occurrences (all)	54	25	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	37 / 681 (5.43%)	35 / 685 (5.11%)	
occurrences (all)	51	40	
Polyuria			
subjects affected / exposed	36 / 681 (5.29%)	11 / 685 (1.61%)	
occurrences (all)	38	11	
Renal pain			
subjects affected / exposed	112 / 681 (16.45%)	127 / 685 (18.54%)	
occurrences (all)	157	171	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	33 / 681 (4.85%)	41 / 685 (5.99%)	
occurrences (all)	35	45	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	58 / 681 (8.52%)	58 / 685 (8.47%)	
occurrences (all)	69	71	
Urinary tract infection			
subjects affected / exposed	38 / 681 (5.58%)	55 / 685 (8.03%)	
occurrences (all)	44	65	
Viral upper respiratory tract infection			
subjects affected / exposed	72 / 681 (10.57%)	84 / 685 (12.26%)	
occurrences (all)	98	111	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2014	Administrative Change 1: Corrected typographical errors and added additional clarifying information to Figure 3.1-1 (Trial Design Schematic).
31 March 2014	Amendment 1: The primary purpose of this amendment was to increase the sample size and period of enrollment to increase power for the primary and secondary endpoints. In addition, information associated with a potential interim analysis was added, the number of creatinine blood draws was reduced, an inclusion criterion was added, and an exclusion criterion was modified. Minor revisions were also made to the protocol for clarity.
25 June 2014	Administrative Change 2: Aligned the Statistical Analysis Plan with the protocol. In addition, an administrative change to Home Nursing Services was made and several clarifications to the protocol were added.
26 March 2015	Amendment 2: The primary purpose of this amendment is to clarify the inclusion criterion for older subjects, and to correct a misstatement regarding SUSAR reporting for procedures. Other clarifications were added for consistency between the Schedule of Assessments table and text or to clarify sample collection process or timing. The DNA sample collection time was changed from the second screening visit only to any visit from the second screening visit onwards.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported