# 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<br>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<br>Units: years | | | |
| arithmetic mean | 47.3 | 47.2 | |
| standard deviation | ± 8.2 | ± 8.2 | - |
| Gender categorical<br>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 | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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