Clinical trial results:
A Phase 3b, Two-part, Multicenter, One Year Randomized, Double-blind, Placebo-controlled Trial of the Safety, Pharmacokinetics, Tolerability, and Efficacy of Tolvaptan followed by a Two Year Open-label Extension in Children and Adolescent Subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Summary

EudraCT number	2016-000187-42
Trial protocol	GB DE IT BE
Global end of trial date	17 November 2021

Results information

Result version number	v1 (current)
This version publication date	29 May 2022
First version publication date	29 May 2022

Trial information

Trial identification

Sponsor protocol code	156-12-298

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02964273
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, 20850
Public contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., clinicaltransparency@otsuka-us.com
Scientific contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., clinicaltransparency@otsuka-us.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001231-PIP02-13
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long term safety of treatment with tolvaptan in a pediatric and adolescent ADPKD population.

Protection of trial subjects:

All study subjects were required to read and sign an Assent Form and subject legal guardians read and signed Informed Consent Form. Written informed consent was freely obtained from all subject's guardian(s) or legally acceptable representative(s), as applicable for local laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 September 2016
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	United Kingdom: 32
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 29
Worldwide total number of subjects	91
EEA total number of subjects	91

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)	25

Adolescents (12-17 years)	66
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 18 sites in Belgium, Germany, Italy, and the United Kingdom from 23 September 2016 to 17 November 2021.

Pre-assignment

Screening details:

A total of 91 subjects with autosomal dominant polycystic kidney disease (ADPKD) were randomised into 2 groups in a 1:1 ratio to receive tolvaptan or a matching placebo.

Period 1

Period 1 title	Phase A: Double-blind Period (12 Months)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase A: Tolvaptan

Arm description:

Subjects received tolvaptan tablets, orally as a split dose (with the first dose taken upon awakening and the second dose taken approximately 8 hours later), and starting doses based on their weight as per the following specifications: ≥20 to 45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 12 months. Doses may be titrated down dependent upon subject tolerability.

Arm type	Experimental
Investigational medicinal product name	Tolvaptan
Investigational medicinal product code	OPC-41061
Other name	JINARC®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tolvaptan spray-dried, immediate release tablets

Arm title	Phase A: Placebo

Arm description:

Subjects received matching-placebo tablets, orally as a split-dose (with the first dose taken upon awakening and second dose taken approximately 8 hours later), and starting dose based on their weight as per the following specifications: ≥20 to <45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 12 months. Doses may be titrated down dependent upon subject tolerability.

Arm type	Placebo
Investigational medicinal product name	Tolvaptan Matching-placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tolvaptan matching-placebo tablets

Number of subjects in period 1	Phase A: Tolvaptan	Phase A: Placebo
Started	48	43
Dense Pharmacokinetic/dynamic(PK/PD) Set	12 [1]	8 [2]
Completed	44	40
Not completed	4	3
Consent withdrawn by subject	3	1
Physician decision	-	2
Adverse event	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The Dense PK/PD Population included a subset of subjects half on tolvaptan and half on placebo, in the 12 to 17 year old age group who had dense PK sampling after at least 1 month on IMP.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The Dense PK/PD Population included a subset of subjects half on tolvaptan and half on placebo, in the 12 to 17 year old age group who had dense PK sampling after at least 1 month on IMP.

Period 2

Period 2 title	Phase B: Open-label Period (24 Months)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase B: Prior Tolvaptan

Arm description:

Qualified subjects (defined as those who were willing to continue in the trial and who did not have any adverse events [AEs] that would require investigational medicinal product [IMP] discontinuation) who received tolvaptan and completed Phase A were enrolled in Phase B and received tolvaptan tablets, orally as a split dose (with the first dose taken upon awakening and the second dose taken approximately 8 hours later), and starting dose based on their body weight as per following specifications: ≥20 to <45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 24 months. Doses may be titrated down dependent upon subject tolerability.

Arm type	Experimental
Investigational medicinal product name	Tolvaptan
Investigational medicinal product code	OPC-41061
Other name	JINARC®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tolvaptan spray-dried, immediate release tablets

Arm title	Phase B: Prior Placebo

Arm description:

Qualified subjects (defined as those who were willing to continue in the trial and who did not have any

AEs that would require IMP discontinuation) who received matching-placebo and completed Phase A, were enrolled in Phase B and received tolvaptan tablets, orally as a split dose (with the first dose taken upon awakening and the second dose taken approximately 8 hours later), based on their current body weight as per following specifications: ≥20 to <45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 24 months. Doses may be titrated down dependent upon subject tolerability.

Arm type	Experimental
Investigational medicinal product name	Tolvaptan
Investigational medicinal product code	OPC-41061
Other name	JINARC®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tolvaptan spray-dried, immediate release tablets

Number of subjects in period 2[3]	Phase B: Prior Tolvaptan	Phase B: Prior Placebo
Started	42	39
Completed	36	33
Not completed	6	6
Consent withdrawn by subject	4	3
Reason Not Specified	2	1
Adverse event	-	2

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 2 Phase A: Tolvaptan completers did not enter Phase B. 1 Phase A: Placebo completer did not enter Phase B.

Baseline characteristics

Reporting groups	
Reporting group title	Phase A: Tolvaptan
Reporting group description:	
Subjects received tolvaptan tablets, orally as a split dose (with the first dose taken upon awakening and the second dose taken approximately 8 hours later), and starting doses based on their weight as per the following specifications: ≥20 to 45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 12 months. Doses may be titrated down dependent upon subject tolerability.	
Reporting group title	Phase A: Placebo
Reporting group description:	
Subjects received matching-placebo tablets, orally as a split-dose (with the first dose taken upon awakening and second dose taken approximately 8 hours later), and starting dose based on their weight as per the following specifications: ≥20 to <45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 12 months. Doses may be titrated down dependent upon subject tolerability.	

Reporting group values	Phase A: Tolvaptan	Phase A: Placebo	Total
Number of subjects	48	43	91
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	12.9	12.8	
standard deviation	± 3.2	± 2.8	-
Gender categorical Units: Subjects			
Female	21	23	44
Male	27	20	47
Race Units: Subjects			
White	46	42	88
Black or African American	0	1	1
Asian	2	0	2
EthnicityHispanic or Latino Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	47	42	89

End points

End points reporting groups

Reporting group title	Phase A: Tolvaptan

Reporting group description:

Subjects received tolvaptan tablets, orally as a split dose (with the first dose taken upon awakening and the second dose taken approximately 8 hours later), and starting doses based on their weight as per the following specifications: ≥20 to 45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 12 months. Doses may be titrated down dependent upon subject tolerability.

Reporting group title	Phase A: Placebo

Reporting group description:

Subjects received matching-placebo tablets, orally as a split-dose (with the first dose taken upon awakening and second dose taken approximately 8 hours later), and starting dose based on their weight as per the following specifications: ≥20 to <45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 12 months. Doses may be titrated down dependent upon subject tolerability.

Reporting group title	Phase B: Prior Tolvaptan

Reporting group description:

Qualified subjects (defined as those who were willing to continue in the trial and who did not have any adverse events [AEs] that would require investigational medicinal product [IMP] discontinuation) who received tolvaptan and completed Phase A were enrolled in Phase B and received tolvaptan tablets, orally as a split dose (with the first dose taken upon awakening and the second dose taken approximately 8 hours later), and starting dose based on their body weight as per following specifications: ≥20 to <45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 24 months. Doses may be titrated down dependent upon subject tolerability.

Reporting group title	Phase B: Prior Placebo

Reporting group description:

Qualified subjects (defined as those who were willing to continue in the trial and who did not have any AEs that would require IMP discontinuation) who received matching-placebo and completed Phase A, were enrolled in Phase B and received tolvaptan tablets, orally as a split dose (with the first dose taken upon awakening and the second dose taken approximately 8 hours later), based on their current body weight as per following specifications: ≥20 to <45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 24 months. Doses may be titrated down dependent upon subject tolerability.

Primary: Phase A: Change From Baseline in Spot Urine Osmolality (Pre-morning Dose)

End point title	Phase A: Change From Baseline in Spot Urine Osmolality (Pre-morning Dose)[1]

End point description:

Urine osmolality is a measure of urine concentration, measured by osmometer, which evaluates the freezing point depression of a solution and supplies results as milliosmoles per kilogram of water. Spot urine osmolality was determined for urine samples collected immediately prior to morning dosing for Day 1 (Baseline), and Week 1 for all subjects. Sample was taken after the first morning's void and was provided as a mid-stream, clean catch sample. All subjects were fasting. The Full Analysis Set (FAS) included all subjects who were randomised to a treatment group, received at least 1 dose of the investigational medicinal product (IMP), and had both a Phase A baseline and at least 1 postbaseline efficacy evaluation. n = Number analysed is the number of subjects with data available for analysis at the given time point.

End point type	Primary

End point timeframe:

Baseline, and Week 1 of Phase A

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	43		
Units: milliosmoles per kilogram (mOsm/kg)				
arithmetic mean (standard deviation)				
Baseline (n=48, 43)	635 (± 252)	646 (± 250)		
Change From Baseline at Week 1, Phase A (n =48,42)	-386 (± 284)	-93 (± 332)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase A: Change From Baseline in Specific Gravity (Pre-morning Dose)

End point title	Phase A: Change From Baseline in Specific Gravity (Pre-morning Dose)[2]

End point description:

Urine specific gravity is a measure of the concentration of solutes in the urine and provides information on the kidney's ability to concentrate urine. Spot urine sample for determination of specific gravity was collected immediately prior to morning dosing for Day 1 (Baseline), and Week 1 for all subjects. Sample was taken after the first morning's void and was provided as a mid-stream, clean catch sample. All subjects were fasting. The FAS included all subjects who were randomised to a treatment group, received at least 1 dose of the IMP, and had both a Phase A baseline and at least 1 postbaseline efficacy evaluation. n=Number analysed is the number of subjects with data available for analysis at the given time point.

End point type	Primary

End point timeframe:

Baseline, and Week 1 of Phase A

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	43		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n=48, 43)	1.017 (± 0.006)	1.017 (± 0.006)		
Change From Baseline at Week 1, Phase A (n =48,41)	-0.009 (± 0.007)	-0.002 (± 0.008)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A: Percent Change From Phase A Baseline in Height-Adjusted Total Kidney Volume (htTKV) as Measured by Magnetic Resonance Imaging (MRI)

End point title	Phase A: Percent Change From Phase A Baseline in Height-Adjusted Total Kidney Volume (htTKV) as Measured by Magnetic Resonance Imaging (MRI)

End point description:

htTKV is used in subjects with autosomal dominant polycystic kidney disease to predict the onset of renal insufficiency. The FAS included all subjects who were randomised to a treatment group, received at least 1 dose of the IMP, and had both a Phase A baseline and at least 1 postbaseline efficacy evaluation. Overall number analysed are the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline, and Month 12 of Phase A

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	27		
Units: percent change				
arithmetic mean (standard deviation)	2.28 (± 8.75)	6.11 (± 7.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A and B: Mean 24-hour Fluid Balance Prior to Week 1

End point title	Phase A and B: Mean 24-hour Fluid Balance Prior to Week 1

End point description:

Subjects were instructed to record all fluid taken and all urine output for the 24-hour period. The FAS for Phase A included all subjects who were randomised to a treatment group, received at least 1 dose of the IMP, and had both a Phase A Baseline and at least 1 postbaseline efficacy evaluation. The FAS for Phase B included all subjects who enrolled to Phase B, received at least 1 dose of the IMP, and had both a baseline and at least 1 postbaseline efficacy evaluation in Phase B. Overall number analysed are the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Prior to Week 1 in Phase A and B

End point values	Phase A: Tolvaptan	Phase A: Placebo	Phase B: Prior Tolvaptan	Phase B: Prior Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	41	37	37
Units: milliliter (mL)				
arithmetic mean (standard deviation)	31 (± 1978)	241 (± 867)	138 (± 1382)	207 (± 1355)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A: Change From Baseline in Renal Function (Estimated Glomerular Filtration Rate [eGFR] by Schwartz Formula) at Each Clinic Visit in Phase A

End point title	Phase A: Change From Baseline in Renal Function (Estimated Glomerular Filtration Rate [eGFR] by Schwartz Formula) at Each Clinic Visit in Phase A

End point description:

Renal function was assessed by estimated eGFR calculated by the Schwartz formula (eGFR = 0.413 × height [cm] /serum creatinine mg/dL), expressed as mean change in eGFR at the specified time points. The units for the data reported are milliliter per minute per 1.73 meter square (mL/min/1.73 m^2). The FAS included all subjects who were randomised to a treatment group, received at least 1 dose of the IMP, and had both a Phase A baseline and at least 1 postbaseline efficacy evaluation. n=Number analysed is the number of subjects with data available for analysis at the given time point.

End point type	Secondary

End point timeframe:

Phase A Baseline, Week 1, Months 1, 6, and 12

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	43		
Units: mL/min/1.73 m^2				
arithmetic mean (standard deviation)				
Baseline (n=48,43)	98.8 (± 19.4)	99.9 (± 15.0)		
Change From Baseline at Week 1, Phase A (n=44,42)	-4.9 (± 10.3)	1.5 (± 9.2)		
Change From Baseline at Month 1, Phase A (n=45,43)	-2.3 (± 12.2)	-0.3 (± 9.2)		
Change From Baseline at Month 6, Phase A (n=44,41)	-0.2 (± 13.6)	-0.9 (± 9.2)		
Change From Baseline at Month 12, Phase A(n=43,40)	-1.4 (± 14.9)	-0.9 (± 8.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase B: Change From Phase B Baseline in Renal Function (eGFR by

Schwartz Formula) at Each Clinic Visit in Phase B

End point title	Phase B: Change From Phase B Baseline in Renal Function (eGFR by Schwartz Formula) at Each Clinic Visit in Phase B

End point description:

Renal function was assessed by estimated eGFR calculated by the Schwartz formula (eGFR = 0.413 × height [cm] /serum creatinine mg/dL), expressed as mean change in eGFR at the specified time points. The FAS for Phase B included all subjects who enrolled to Phase B, received at least 1 dose of the IMP, and had both a baseline and at least 1 postbaseline efficacy evaluation in Phase B. n=Number analysed is the number of subjects with data available for analysis at the given time point.

End point type	Secondary

End point timeframe:

Phase B Baseline, Week 1, Months 1, 6, 12, 18, and 24

End point values	Phase B: Prior Tolvaptan	Phase B: Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: mL/min/1.73 m^2				
arithmetic mean (standard deviation)				
Phase B Baseline (n=42,39)	97.0 (± 17.1)	98.5 (± 14.1)		
Change From Baseline (CFB) at Week 1 (n=40,37)	-1.7 (± 10.4)	-6.7 (± 8.0)		
CFB at Month 1, Phase B (n=41,38)	-0.9 (± 10.2)	-4.8 (± 9.0)		
CFB at Month 6, Phase B (n=38,33)	-4.2 (± 9.6)	-6.4 (± 7.9)		
CFB at Month 12, Phase B (n=36,36)	-5.6 (± 11.1)	-7.2 (± 9.3)		
CFB at Month 18, Phase B (n=29,27)	-3.5 (± 9.8)	-9.0 (± 10.9)		
CFB at Month 24, Phase B (n=34,31)	-5.2 (± 9.4)	-10.3 (± 11.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase B: Percent Change From Phase B Baseline in htTKV as Measured by MRI at Month 12 and Month 24

End point title	Phase B: Percent Change From Phase B Baseline in htTKV as Measured by MRI at Month 12 and Month 24

End point description:

htTKV is used in subjects with autosomal dominant polycystic kidney disease to predict the onset of renal insufficiency. The FAS for Phase B included all subjects who enrolled to Phase B, received at least 1 dose of the IMP, and had both a baseline and at least 1 postbaseline efficacy evaluation in Phase B. n = Number analysed is the number of subjects with data available for analysis at the given time point.

End point type	Secondary

End point timeframe:

Phase B Baseline, Months 12, and 24

End point values	Phase B: Prior Tolvaptan	Phase B: Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: percent change				
arithmetic mean (standard deviation)				
Percent Change From Baseline at Month 12 (n=26,23)	7.68 (± 9.67)	3.09 (± 8.97)		
Percent Change From Baseline at Month 24 (n=24,21)	13.55 (± 12.88)	7.35 (± 9.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A: 24-hour Urine Volume

End point title	Phase A: 24-hour Urine Volume

End point description:

Urine volume refers to the quantity of urine produced per unit of time. The Dense PK/PD Population included a subset of subjects half on tolvaptan and half on placebo, in the 12 to 17 year old age group who had dense PK sampling after at least 1 month on IMP. Overall number analysed are the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

24 hours post dose after Month 1 on study medication in Phase A

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: milliliter				
arithmetic mean (standard deviation)	7171 (± 2810)	2529 (± 2164)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A: 24-hour Fluid Intake

End point title	Phase A: 24-hour Fluid Intake

End point description:

Daily fluid intake (total water) is defined as the amount of water consumed from foods, plain drinking water, and other beverages. The Dense PK/PD Population included a subset of subjects half on tolvaptan and half on placebo, in the 12 to 17 year old age group who had dense PK sampling after at least 1 month on IMP. Overall number analysed are the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

24 hours post dose after Month 1 on study medication in Phase A

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	5		
Units: milliliter				
arithmetic mean (standard deviation)	7486 (± 2350)	3156 (± 1775)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A: 24-hour Fluid Balance

End point title	Phase A: 24-hour Fluid Balance

End point description:

Fluid balance is a term used to describe the balance of the input and output of fluids in the body to allow metabolic processes to function correctly. The Dense PK/PD Population included a subset of subjects half on tolvaptan and half on placebo, in the 12 to 17 year old age group who had dense PK sampling after at least 1 month on IMP. Overall number analysed are the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

24 hours post dose after Month 1 on study medication in Phase A

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	5		
Units: milliliter				
arithmetic mean (standard deviation)	53 (± 1894)	230 (± 1254)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A: 24-hour Sodium Clearance

End point title	Phase A: 24-hour Sodium Clearance

End point description:

Data was categorised and reported based on the total daily dose for the given time point of 0-24 hours. The Dense PK/PD Population included a subset of subjects half on tolvaptan and half on placebo, in the 12 to 17 year old age group who had dense PK sampling after at least 1 month on IMP. Overall number analysed are the number of subjects with data available for analyses. n = Number analysed is the number of subjects with data available for analysis at the given time point. 9999 = The mean or standard deviation was not estimable due to lower number of subjects with event.

End point type	Secondary

End point timeframe:

24 hours post dose after Month 1 on study medication in Phase A

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	7		
Units: milliliter per minute (mL/min)				
arithmetic mean (standard deviation)				
Total Daily Dose: 37.5 mg (n=3,0)	0.8 (± 0.3)	9999 (± 9999)		
Total Daily Dose: 45 mg (n=3,0)	0.7 (± 0.3)	9999 (± 9999)		
Total Daily Dose: 60 mg (n=4,0)	0.9 (± 0.3)	9999 (± 9999)		
Total Daily Dose: Placebo (n=0,7)	9999 (± 9999)	0.7 (± 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A: 24-hour Creatinine Clearance

End point title	Phase A: 24-hour Creatinine Clearance

End point description:

Creatinine is produced from the metabolism of protein, when muscles burn energy. Most creatinine is filtered out of the blood by the kidneys and excreted in urine. The creatinine clearance value is determined by measuring the concentration of endogenous creatinine (that which is produced by the body) in both plasma and urine. Data was categorised and reported based on the total daily dose for the given time point of 0-24 hours. The Dense PK/PD Population included a subset of subjects half on tolvaptan and half on placebo, in the 12 to 17 year old age group who had dense PK sampling after at least 1 month on IMP. Overall number analysed are the number of subjects with data available for analyses. n = Number analysed is the number of subjects with data available for analysis for the specified category. 9999 = The mean or standard deviation was not estimable due to lower number of subjects with event.

End point type	Secondary

End point timeframe:

24 hours post dose after Month 1 on study medication in Phase A

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: mL/min				
arithmetic mean (standard deviation)				
Total Daily Dose: 22.5 mg (n=1,0)	124.6 (± 9999)	9999 (± 9999)		
Total Daily Dose: 37.5 mg (n=3,0)	148.5 (± 23.4)	9999 (± 9999)		
Total Daily Dose: 45 mg (n=3,0)	95.0 (± 10.1)	9999 (± 9999)		
Total Daily Dose: 60 mg (n=4,0)	123.7 (± 23.2)	9999 (± 9999)		
Total Daily Dose: Placebo (n=0,8)	9999 (± 9999)	105.1 (± 51.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A: 24-hour Free Water Clearance

End point title	Phase A: 24-hour Free Water Clearance

End point description:

Data was categorised and reported based on the total daily dose for the given time point of 0-24 hours. The Dense PK/PD Population included a subset of subjects half on tolvaptan and half on placebo, in the 12 to 17 year old age group who had dense PK sampling after at least 1 month on IMP. Overall number analysed are the number of subjects with data available for analyses. n = Number analysed is the number of subjects with data available for analysis for the specified category. 9999 = The mean or standard deviation was not estimable due to lower number of subjects with event.

End point type	Secondary

End point timeframe:

24 hours post dose after Month 1 on study medication in Phase A

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: mL/min				
arithmetic mean (standard deviation)				
Total Daily Dose: 37.5 mg (n=3,0)	2.3 (± 0.9)	9999 (± 9999)		
Total Daily Dose: 45 mg (n=3,0)	2.6 (± 0.9)	9999 (± 9999)		
Total Daily Dose: 60 mg (n=5,0)	3.0 (± 1.2)	9999 (± 9999)		
Total Daily Dose: Placebo (n=0,8)	9999 (± 9999)	0.1 (± 1.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A: Percentage of Each Tanner Stage by Gender and Age Compared to Normative Populations

End point title	Phase A: Percentage of Each Tanner Stage by Gender and Age Compared to Normative Populations

End point description:

Tanner stages is a scale that defines physical measurements of development based on external primary and secondary sex characteristics. It was used in this study to assess pubertal development with values ranging from Stage 1 (pre-pubertal characteristics) to Stage 5 (adult or mature characteristics). Only those categories with at least one subject with event are reported. The Phase A Safety Set included all subjects who were randomised and received at least 1 dose of IMP in Phase A.

End point type	Secondary

End point timeframe:
At Baseline, Months 6 and 12 of Phase A

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	43		
Units: percentage of subjects				
number (not applicable)				
Female (>=4 to <12 Years): Baseline-Stage 1	6.3	11.6		
Female (>=4 to <12 Years): Baseline-Stage 3	0.0	2.3		
Female (>=4 to <12 Years): Month 6, Phase A-Stage1	6.3	9.3		
Female (>=4 to <12 Years): Month 6, Phase A-Stage2	0.0	2.3		
Female (>=4 to <12 Years): Month 6, Phase A-Stage4	0.0	2.3		
Female (>=4 to <12 Years): Month 12,Phase A-Stage1	4.2	7.0		
Female (>=4 to <12 Years): Month 12,Phase A-Stage2	0.0	2.3		
Female (>=4 to <12 Years): Month 12,Phase A-Stage4	0.0	2.3		
Male (>=4 to <12 Years): Baseline-Stage 1	16.7	4.7		
Male (>=4 to <12 Years): Baseline-Stage 2	0.0	4.7		
Male (>=4 to <12 Years): Baseline-Stage 3	2.1	0.0		
Male (>=4 to <12 Years): Month 6, Phase A- Stage 1	16.7	7.0		
Male (>=4 to <12 Years): Month 6, Phase A- Stage 2	2.1	0.0		
Male (>=4 to <12 Years): Month 6, Phase A- Stage 3	2.1	4.7		
Male (>=4 to <12 Years): Month 12, Phase A- Stage1	14.6	4.7		
Male (>=4 to <12 Years): Month 12, Phase A- Stage2	4.2	2.3		
Male (>=4 to <12 Years): Month 12, Phase A- Stage3	0.0	4.7		
Male (>=4 to <12 Years): Month 12, Phase A- Stage4	2.1	0.0		
Female (>=12 to <15 Years): Baseline-Stage 1	2.1	0.0		
Female (>=12 to <15 Years): Baseline-Stage 2	0.0	4.7		
Female (>=12 to <15 Years): Baseline-Stage 3	2.1	2.3		
Female (>=12 to <15 Years): Baseline-Stage 4	4.2	0.0		
Female (>=12 to <15 Years): Baseline-Stage 5	10.4	7.0		
Female (>=12 to <15 Years): Month 6,Phase A-Stage2	0.0	2.3		

Female (>=12 to <15 Years): Month 6,Phase A-Stage3	0.0	2.3		
Female (>=12 to <15 Years): Month 6,Phase A-Stage4	2.1	0.0		
Female (>=12 to <15 Years): Month 6,Phase A-Stage5	12.5	7.0		
Female (>=12 to <15 Years):Month 12,Phase A-Stage2	0.0	2.3		
Female (>=12 to <15 Years):Month 12,Phase A-Stage3	0.0	2.3		
Female (>=12 to <15 Years):Month 12,Phase A-Stage4	0.0	4.7		
Female (>=12 to <15 Years):Month 12,Phase A-Stage5	14.6	9.3		
Male (>=12 to <15 Years): Baseline-Stage 2	6.3	4.7		
Male (>=12 to <15 Years): Baseline-Stage 3	4.2	4.7		
Male (>=12 to <15 Years): Baseline-Stage 4	2.1	4.7		
Male (>=12 to <15 Years): Baseline-Stage 5	2.1	2.3		
Male (>=12 to <15 Years): Month 6, Phase A-Stage2	4.2	2.3		
Male (>=12 to <15 Years): Month 6, Phase A- Stage3	4.2	2.3		
Male (>=12 to <15 Years): Month 6, Phase A- Stage4	4.2	4.7		
Male (>=12 to <15 Years): Month 6, Phase A- Stage5	2.1	2.3		
Male (>=12 to <15 Years): Month 12,Phase A- Stage2	0.0	2.3		
Male (>=12 to <15 Years): Month 12,Phase A- Stage3	2.1	0.0		
Male (>=12 to <15 Years): Month 12,Phase A- Stage4	8.3	7.0		
Male (>=12 to <15 Years): Month 12,Phase A- Stage5	4.2	2.3		
Male (>=12 to <15 Years): End of Treatment- Stage5	2.1	2.3		
Female (>=15 to <18 Years): Baseline-Stage 4	2.1	0.0		
Female (>=15 to <18 Years): Baseline-Stage 5	12.5	18.6		
Female (>=15 to <18 Years): Month 6,Phase A-Stage4	2.1	0.0		
Female (>=15 to <18 Years): Month 6,Phase A-Stage5	12.5	16.3		
Female (>=15 to <18 Years):Month 12,Phase A-Stage4	2.1	0.0		
Female (>=15 to <18 Years):Month 12,Phase A-Stage5	14.6	16.3		
Female (>=15 to <18 Years):End of Treatment-Stage5	0.0	2.3		
Male (>=15 to <18 Years): Baseline-Stage 4	2.1	4.7		
Male (>=15 to <18 Years): Baseline-Stage 5	16.7	14.0		
Male (>=15 to <18 Years): Month 6, Phase A- Stage4	2.1	2.3		
Male (>=15 to <18 Years): Month 6, Phase A- Stage5	14.6	16.3		

Male (>=15 to <18 Years): Month 12, Phase A-Stage4	2.1	0.0		
Male (>=15 to <18 Years): Month 12, Phase A-Stage5	14.6	18.6		
Male (>=15 to <18 Years): End of Treatment- Stage5	2.1	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase B: Percentage of Each Tanner Stage by Gender and Age Compared to Normative Populations

End point title	Phase B: Percentage of Each Tanner Stage by Gender and Age Compared to Normative Populations

End point description:

Tanner stages is a scale that defines physical measurements of development based on external primary and secondary sex characteristics. It was used in this study to assess pubertal development with values ranging from Stage 1 (pre-pubertal characteristics) to Stage 5 (adult or mature characteristics). Only those categories with at least one subject with event are reported. The Phase B Safety Set included all subjects who were enrolled in Phase B and received at least 1 dose of IMP in Phase B. End of Treatment = EOT.

End point type	Secondary

End point timeframe:

At Baseline, Months 6, 12, 18, and 24 of Phase B

End point values	Phase B: Prior Tolvaptan	Phase B: Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: percentage of subjects				
number (not applicable)				
Female (>=4 to <12 Years): Phase B Baseline-Stage1	7.1	10.3		
Female (>=4 to <12 Years): Phase B Baseline-Stage2	0.0	2.6		
Female (>=4 to <12 Years): Phase B Baseline-Stage4	0.0	2.6		
Female (>=4 to <12 Years): Month 6, Phase B-Stage1	4.8	7.7		
Female (>=4 to <12 Years): Month 6, Phase B-Stage2	0.0	2.6		
Female (>=4 to <12 Years): Month 6, Phase B-Stage4	0.0	2.6		
Female (>=4 to <12 Years): Month 12,Phase B-Stage1	4.8	7.7		
Female (>=4 to <12 Years): Month 12,Phase B-Stage2	0.0	2.6		
Female (>=4 to <12 Years): Month 12,Phase B-Stage3	0.0	2.6		
Female (>=4 to <12 Years): Month 12,Phase B-Stage4	0.0	2.6		

Female (>=4 to <12 Years): Month 18,Phase B-Stage1	4.8	2.6		
Female (>=4 to <12 Years): Month 18,Phase B-Stage2	0.0	7.7		
Female (>=4 to <12 Years): Month 18,Phase B-Stage4	0.0	2.6		
Female (>=4 to <12 Years): Month 24,Phase B-Stage1	2.4	2.6		
Female (>=4 to <12 Years): Month 24,Phase B-Stage2	2.4	5.1		
Female (>=4 to <12 Years): Month 24,Phase B-Stage3	0.0	2.6		
Female (>=4 to <12 Years): Month 24,Phase B-Stage4	0.0	2.6		
Male (>=4 to <12 Years): Phase B Baseline- Stage 1	11.9	5.1		
Male (>=4 to <12 Years): Phase B Baseline- Stage 2	4.8	2.6		
Male (>=4 to <12 Years): Phase B Baseline- Stage 3	0.0	5.1		
Male (>=4 to <12 Years): Phase B Baseline- Stage 4	2.4	0.0		
Male (>=4 to <12 Years): Month 6, Phase B- Stage 1	9.5	2.6		
Male (>=4 to <12 Years): Month 6, Phase B- Stage 2	2.4	2.6		
Male (>=4 to <12 Years): Month 6, Phase B- Stage 3	2.4	2.6		
Male (>=4 to <12 Years): Month 6, Phase B- Stage 4	2.4	2.6		
Male (>=4 to <12 Years): Month 12, Phase B- Stage1	9.5	2.6		
Male (>=4 to <12 Years): Month 12, Phase B- Stage2	2.4	0.0		
Male (>=4 to <12 Years): Month 12, Phase B- Stage3	2.4	5.1		
Male (>=4 to <12 Years): Month 12, Phase B- Stage4	2.4	2.6		
Male (>=4 to <12 Years): Month 18, Phase B- Stage1	4.8	2.6		
Male (>=4 to <12 Years): Month 18, Phase B- Stage2	2.4	0.0		
Male (>=4 to <12 Years): Month 18, Phase B- Stage3	0.0	5.1		
Male (>=4 to <12 Years): Month 18, Phase B- Stage4	4.8	0.0		
Male (>=4 to <12 Years): Month 18, Phase B- Stage5	0.0	2.6		
Male (>=4 to <12 Years): Month 24, Phase B- Stage1	4.8	0.0		
Male (>=4 to <12 Years): Month 24, Phase B- Stage2	4.8	0.0		
Male (>=4 to <12 Years): Month 24, Phase B- Stage3	2.4	5.1		
Male (>=4 to <12 Years): Month 24, Phase B- Stage4	2.4	0.0		
Male (>=4 to <12 Years): Month 24, Phase B- Stage5	2.4	2.6		
Female (>=12 to <15 Years):Phase B Baseline-Stage2	0.0	2.6		
Female (>=12 to <15 Years):Phase B Baseline-Stage3	0.0	2.6		

Female (>=12 to <15 Years):Phase B Baseline-Stage4	0.0	5.1		
Female (>=12 to <15 Years):Phase B Baseline-Stage5	16.7	10.3		
Female (>=12 to <15 Years): Month 6,Phase B-Stage3	0.0	5.1		
Female (>=12 to <15 Years): Month 6,Phase B-Stage4	0.0	5.1		
Female (>=12 to <15 Years): Month 6,Phase B-Stage5	16.7	10.3		
Female (>=12 to <15 Years):Month 12,Phase B-Stage4	0.0	5.1		
Female (>=12 to <15 Years):Month 12,Phase B-Stage5	14.3	10.3		
Female (>=12 to <15 Years):Month 18,Phase B-Stage4	0.0	2.6		
Female (>=12 to <15 Years):Month 18,Phase B-Stage5	11.9	10.3		
Female (>=12 to <15 Years):Month 24,Phase B-Stage4	0.0	5.1		
Female (>=12 to <15 Years):Month 24,Phase B-Stage5	9.5	10.3		
Female (>=12 to <15 Years): EOT, Phase B, Stage 4	0.0	2.6		
Female (>=12 to <15 Years): EOT, Phase B, Stage 5	7.1	2.6		
Male (>=12 to <15 Years): Phase B Baseline- Stage2	0.0	2.6		
Male (>=12 to <15 Years): Phase B Baseline- Stage3	2.4	0.0		
Male (>=12 to <15 Years): Phase B Baseline- Stage4	9.5	7.7		
Male (>=12 to <15 Years): Phase B Baseline- Stage5	4.8	2.6		
Male (>=12 to <15 Years): Month 6, Phase B- Stage2	0.0	2.6		
Male (>=12 to <15 Years): Month 6, Phase B- Stage3	2.4	0.0		
Male (>=12 to <15 Years): Month 6, Phase B- Stage4	4.8	5.1		
Male (>=12 to <15 Years): Month 6, Phase B- Stage5	4.8	2.6		
Male (>=12 to <15 Years): Month 12, Phase B-Stage2	0.0	2.6		
Male (>=12 to <15 Years): Month 12, Phase B-Stage4	7.1	5.1		
Male (>=12 to <15 Years): Month 12, Phase B-Stage5	7.1	5.1		
Male (>=12 to <15 Years): Month 18, Phase B-Stage2	0.0	2.6		
Male (>=12 to <15 Years): Month 18, Phase B-Stage4	4.8	0.0		
Male (>=12 to <15 Years): Month 18, Phase B-Stage5	9.5	7.7		
Male (>=12 to <15 Years): Month 24, Phase B-Stage2	0.0	2.6		
Male (>=12 to <15 Years): Month 24, Phase B-Stage4	4.8	0.0		
Male (>=12 to <15 Years): Month 24, Phase B-Stage5	9.5	10.3		
Male (>=12 to <15 Years): EOT, Phase B- Stage 5	0.0	2.6		

Female (>=15 to <18 Years):Phase B Baseline-Stage4	2.4	0.0		
Female (>=15 to <18 Years):Phase B Baseline-Stage5	16.7	15.4		
Female (>=15 to <18 Years): Month 6,Phase B-Stage4	2.4	0.0		
Female (>=15 to <18 Years): Month 6,Phase B-Stage5	16.7	12.8		
Female(>=15 to <18 Years):Month 12,Phase B-Stage4	2.4	0.0		
Female(>=15 to <18 Years):Month 12,Phase B-Stage5	16.7	12.8		
Female(>=15 to <18 Years):Month 18,Phase B-Stage4	2.4	0.0		
Female(>=15 to <18 Years):Month 18,Phase B-Stage5	16.7	12.8		
Female(>=15 to <18 Years):Month 24,Phase B-Stage4	2.4	0.0		
Female(>=15 to <18 Years):Month 24,Phase B-Stage5	16.7	12.8		
Female (>=15 to <18 Years): EOT, Phase B- Stage 5	0.0	5.1		
Male (>=15 to <18 Years): Phase B Baseline- Stage4	2.4	0.0		
Male (>=15 to <18 Years): Phase B Baseline- Stage5	16.7	20.5		
Male (>=15 to <18 Years): Month 6, Phase B- Stage5	19.0	17.9		
Male (>=15 to <18 Years): Month 12, Phase B-Stage5	16.7	17.9		
Male (>=15 to <18 Years): Month 18, Phase B-Stage5	16.7	15.4		
Male (>=15 to <18 Years): Month 24, Phase B-Stage5	16.7	12.8		
Male (>=15 to <18 Years): EOT, Phase B- Stage 5	4.8	7.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A: Change From Baseline in Growth Percentile by Gender and Age

End point title	Phase A: Change From Baseline in Growth Percentile by Gender and Age

End point description:

The growth percentile was based on the assessment of height and weight. The Phase A Safety Set included all subjects who were randomised and received at least 1 dose of IMP in Phase A. Number analysed is the number of subjects with data available for analysis at the given time point. Change From Baseline = CFB, End of Treatment = EOT. 9999 = The mean or standard deviation was not estimable due to lower number of subjects with event. n = Number analysed is the number of subjects with data available for analysis at the given time point.

End point type	Secondary

End point timeframe:

At Baseline, Months 6 and 12 of Phase A

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	43		
Units: growth percentile				
arithmetic mean (standard deviation)				
Females: Age 15-18 Years - Baseline (n=9,8)	62 (± 28)	60 (± 34)		
CFB in Females: Age 15-18 Years - Month 6 (n=9,6)	2 (± 18)	-2 (± 12)		
CFB in Females: Age 15-18 Years - Month 12 (n=9,7)	7 (± 10)	-5 (± 11)		
Males: Age 15-18 Years - Baseline(n=9,8)	56 (± 29)	73 (± 18)		
CFB in Males: Age 15-18 Years - Month 6(n=8,8)	12 (± 16)	-1 (± 30)		
CFB in Males: Age 15-18 Years - Month 12(n=8,8)	2 (± 37)	-3 (± 25)		
Females: Age 12-15 Years - Baseline (n=9,8)	71 (± 20)	72 (± 29)		
CFB in Females: Age 12-15 Years - Month 6(n=7,8)	-2 (± 12)	-20 (± 21)		
CFB in Females: Age 12-15 Years - Month 12 (n=7,8)	-11 (± 9)	-18 (± 27)		
Males: Age 12-15 Years - Baseline(n=8,7)	70 (± 21)	76 (± 24)		
CFB in Males: Age 12-15 Years - Month 6(n=7,7)	-7 (± 13)	-13 (± 38)		
CFB in Males: Age 12-15 Years - Month 12(n=7,5)	0 (± 20)	8 (± 17)		
Females: Age 4-11 Years - Baseline(n=3,7)	71 (± 25)	57 (± 14)		
CFB in Females: Age 4-11 Years - Month 6(n=3,7)	-1 (± 3)	4 (± 16)		
CFB in Females: Age 4-11 Years - Month 12(n=3,7)	7 (± 15)	2 (± 18)		
Males: Age 4-11 Years - Baseline(n=10,5)	57 (± 31)	63 (± 19)		
CFB in Males: Age 4-11 Years - Month 6 (n=10,5)	4 (± 16)	0 (± 0)		
CFB in Males: Age 4-11 Years - Month 12 (n=10,5)	1 (± 3)	1 (± 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase B: Change From Baseline in Growth Percentile by Gender and Age

End point title	Phase B: Change From Baseline in Growth Percentile by Gender and Age

End point description:

The growth percentile was based on the assessment of height and weight. The Phase B Safety Set

included all subjects who were enrolled in Phase B and received at least 1 dose of IMP in Phase B. n = Number analysed is the number of subjects with data available for analysis at the given time point. Change from Baseline = CFB, End of Treatment = EOT. 9999 = The mean or standard deviation was not estimable due to lower number of subjects with event.

End point type	Secondary

End point timeframe:

At Baseline, Months 6, 12, 18, 24 of Phase B

End point values	Phase B: Prior Tolvaptan	Phase B: Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: growth percentile				
arithmetic mean (standard deviation)				
Females: Age 15-18 Years - Baseline(n=9,6)	69 (± 32)	46 (± 28)		
CFB in Females: Age 15-18 Years - Month 6(n=7,5)	-7 (± 17)	12 (± 21)		
CFB in Females: Age 15-18 Years - Month 12(n=8,5)	0 (± 7)	20 (± 18)		
CFB in Females: Age 15-18 Years - Month 18(n=6,3)	-2 (± 2)	10 (± 9)		
CFB in Females: Age 15-18 Years - Month 24(n=8,5)	6 (± 16)	16 (± 20)		
Males: Age 15-18 Years - Baseline(n=8,8)	60 (± 34)	69 (± 18)		
CFB in Males: Age 15-18 Years - Month 6(n=8,7)	-13 (± 53)	1 (± 2)		
CFB in Males: Age 15-18 Years - Month 12(n=6,6)	-8 (± 47)	8 (± 11)		
CFB in Males: Age 15-18 Years - Month 18(n=5,6)	16 (± 65)	-4 (± 25)		
CFB in Males: Age 15-18 Years - Month 24(n=6,5)	-2 (± 50)	-11 (± 25)		
Females: Age 12-15 Years - Baseline(n=7,8)	62 (± 24)	54 (± 34)		
CFB in Females: Age 12-15 Years - Month 6(n=7,8)	3 (± 6)	13 (± 18)		
CFB in Females: Age 12-15 Years - Month 12(n=6,8)	12 (± 20)	12 (± 23)		
CFB in Females: Age 12-15 Years - Month 18(n=5,5)	5 (± 9)	10 (± 22)		
CFB in Females: Age 12-15 Years - Month 24(n=4,7)	1 (± 3)	13 (± 18)		
Males: Age 12-15 Years - Baseline(n=7,5)	67 (± 26)	77 (± 23)		
CFB in Males: Age 12-15 Years - Month 6(n=5,5)	1 (± 10)	-15 (± 38)		
CFB in Males: Age 12-15 Years - Month 12(n=7,5)	4 (± 16)	-23 (± 37)		
CFB in Males: Age 12-15 Years - Month 18 (n=5,4)	-4 (± 14)	-22 (± 40)		
CFB in Males: Age 12-15 Years - Month 24(n=6,5)	-8 (± 15)	-18 (± 36)		
Females: Age 4-11 Years - Baseline(n=3,7)	78 (± 19)	59 (± 22)		

CFB in Females: Age 4-11 Years - Month 6(n=3,6)	-2 (± 2)	2 (± 12)		
CFB in Females: Age 4-11 Years - Month 12(n=3,7)	5 (± 8)	1 (± 12)		
CFB in Females: Age 4-11 Years - Month 18(n=3,7)	-5 (± 6)	2 (± 23)		
CFB in Females: Age 4-11 Years - Month 24(n=3,7)	-4 (± 5)	10 (± 21)		
Males: Age 4-11 Years -Baseline (n=8,5)	65 (± 30)	64 (± 21)		
CFB in Males: Age 4-11 Years - Month 6(n=8,4)	0 (± 13)	1 (± 2)		
CFB in Males: Age 4-11 Years - Month 12(n=8,5)	3 (± 20)	4 (± 8)		
CFB in Males: Age 4-11 Years - Month 18(n=5,4)	-4 (± 12)	2 (± 9)		
CFB in Males: Age 4-11 Years - Month 24(n=7,4)	0 (± 18)	21 (± 23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A: Change From Baseline in Creatinine Value

End point title	Phase A: Change From Baseline in Creatinine Value

End point description:

Phase A Baseline is the last pre-dose evaluation. The Last Visit is the last available post-baseline evaluation including early term. The Phase A Safety Set included all subjects who were randomised and received at least 1 dose of IMP in Phase A. n = Number analysed is the number of subjects with data available for analysis at the given time point. 9999 = The mean or standard deviation was not estimable due to lower number of subjects with event. As prespecified in the protocol, data for safety is reported by the treatment group (Phase A: Tolvaptan and Phase A: Placebo)

End point type	Secondary

End point timeframe:

Baseline, Week 1, Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, Follow Up Day 7, End of Treatment, and Last Visit

End point values	Phase A: Tolvaptan	Phase A: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	43		
Units: milligrams per deciliter (mg/dL)				
arithmetic mean (standard deviation)				
Baseline (n=48,43)	0.70 (± 0.16)	0.67 (± 0.12)		
Change From Baseline at Week 1(n=47,42)	0.04 (± 0.09)	-0.01 (± 0.06)		
Change From Baseline at Month 1(n=48,43)	0.01 (± 0.08)	0.01 (± 0.06)		
Change From Baseline at Month 2(n=44,42)	0.01 (± 0.09)	0.00 (± 0.07)		
Change From Baseline at Month 3(n=45,43)	0.00 (± 0.11)	0.01 (± 0.06)		

Change From Baseline at Month 4(n=45,40)	0.00 (± 0.09)	-0.01 (± 0.07)		
Change From Baseline at Month 5(n=45,39)	0.01 (± 0.09)	0.01 (± 0.06)		
Change From Baseline at Month 6(n=44,41)	0.01 (± 0.10)	0.02 (± 0.07)		
Change From Baseline at Month 7(n=44,39)	0.01 (± 0.10)	0.02 (± 0.06)		
Change From Baseline at Month 8(n=43,39)	0.01 (± 0.11)	0.02 (± 0.07)		
Change From Baseline at Month 9(n=44,39)	0.04 (± 0.11)	0.01 (± 0.07)		
Change From Baseline at Month 10(n=40,34)	0.01 (± 0.10)	0.03 (± 0.07)		
Change From Baseline at Month 11(n=41,38)	0.02 (± 0.11)	0.04 (± 0.08)		
Change From Baseline at Month 12(n=43,40)	0.02 (± 0.09)	0.02 (± 0.06)		
Change From Baseline at Follow Up Day 7(n=1,1)	0.09 (± 9999)	-0.02 (± 9999)		
Change From Baseline at End of Treatment(n=2,3)	0.03 (± 0.10)	0.03 (± 0.04)		
Change From Baseline at Last Visit(n=48,43)	0.03 (± 0.09)	0.02 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase B: Change From Baseline in Creatinine Value

End point title	Phase B: Change From Baseline in Creatinine Value

End point description:

Phase B Baseline is the last evaluation prior to the first dose in Phase B. The Last Visit is the last available post-baseline evaluation including early term. The Phase B Safety Set included all subjects who were enrolled in Phase B and received at least 1 dose of IMP in Phase B. n = Number analysed is the number of subjects with data available for analysis at the given time point. 9999 = The mean or standard deviation was not estimable due to lower number of subjects with event. As prespecified in the protocol, data for safety is reported by the treatment group (Phase A: Tolvaptan and Phase A: Placebo)

End point type	Secondary

End point timeframe:

Baseline, Week 1, Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, Follow Up Day 7, End of Treatment, and Last Visit

End point values	Phase B: Prior Tolvaptan	Phase B: Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n=42,39)	0.73 (± 0.17)	0.69 (± 0.13)		
Change From Baseline at Week 1(n=42,38)	0.01 (± 0.06)	0.04 (± 0.06)		

Change From Baseline at Month 1(n=41,38)	0.01 (± 0.07)	0.04 (± 0.06)		
Change From Baseline at Month 2(n=41,37)	0.02 (± 0.07)	0.04 (± 0.07)		
Change From Baseline at Month 3(n=41,37)	0.02 (± 0.07)	0.04 (± 0.07)		
Change From Baseline at Month 4(n=40,36)	0.04 (± 0.06)	0.05 (± 0.07)		
Change From Baseline at Month 5(n=38,30)	0.03 (± 0.06)	0.07 (± 0.07)		
Change From Baseline at Month 6(n=38,33)	0.03 (± 0.07)	0.06 (± 0.07)		
Change From Baseline at Month 7(n=38,32)	0.04 (± 0.07)	0.06 (± 0.07)		
Change From Baseline at Month 8(n=38,34)	0.05 (± 0.08)	0.07 (± 0.07)		
Change From Baseline at Month 9(n=38,35)	0.07 (± 0.11)	0.09 (± 0.13)		
Change From Baseline at Month 10(n=37,34)	0.06 (± 0.07)	0.06 (± 0.07)		
Change From Baseline at Month 11(n=38,32)	0.05 (± 0.07)	0.08 (± 0.08)		
Change From Baseline at Month 12(n=36,36)	0.06 (± 0.12)	0.07 (± 0.08)		
Change From Baseline at Month 13(n=34,34)	0.04 (± 0.08)	0.08 (± 0.08)		
Change From Baseline at Month 14(n=33,31)	0.08 (± 0.07)	0.08 (± 0.08)		
Change From Baseline at Month 15(n=37,30)	0.06 (± 0.07)	0.06 (± 0.08)		
Change From Baseline at Month 16(n=36,29)	0.05 (± 0.08)	0.08 (± 0.09)		
Change From Baseline at Month 17(n=33,27)	0.07 (± 0.08)	0.08 (± 0.09)		
Change From Baseline at Month 18(n=30,27)	0.05 (± 0.09)	0.09 (± 0.07)		
Change From Baseline at Month 19(n=29,25)	0.06 (± 0.10)	0.09 (± 0.10)		
Change From Baseline at Month 20(n=27,20)	0.04 (± 0.08)	0.11 (± 0.08)		
Change From Baseline at Month 21(n=27,23)	0.09 (± 0.12)	0.09 (± 0.10)		
Change From Baseline at Month 22(n=29,23)	0.06 (± 0.08)	0.09 (± 0.10)		
Change From Baseline at Month 23(n=25,24)	0.07 (± 0.06)	0.12 (± 0.08)		
Change From Baseline at Month 24(n=34,31)	0.07 (± 0.08)	0.12 (± 0.10)		
Change From Baseline at Follow Up Day 7(n=2,7)	-0.01 (± 0.02)	0.14 (± 0.08)		
Change From Baseline at End of Treatment(n=5,7)	-0.01 (± 0.11)	0.02 (± 0.08)		
Change From Baseline at Last Visit(n=42,39)	0.05 (± 0.09)	0.10 (± 0.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A and B: Percentage of Subjects With Potentially Clinically Significant Abnormalities in Vital Signs

End point title	Phase A and B: Percentage of Subjects With Potentially Clinically Significant Abnormalities in Vital Signs

End point description:

Vital signs=measurements of respiratory rate, blood pressure, body temperature and pulse. Any value outside the normal range was flagged for the attention of the investigator who assessed whether or not a flagged value is of clinical significance. Only those categories with at least one subject with event are reported. The Phase A Safety Set included all subjects who were randomized and received at least 1 dose of IMP in Phase A. The Phase B Safety Set included all subjects who were enrolled in Phase B and received at least 1 dose of IMP in Phase B. n=Number analysed is the number of subjects with at least one post-baseline numeric result for the given vital sign parameter. Pulse rate(PR) is measured in beats per minute(BPM), Systolic and Diastolic Blood Pressure (BP) is measured in millimetre of mercury (mmHg). As prespecified in the protocol, data for safety is reported by the treatment group (Phase A: Tolvaptan, Phase A: Placebo, Phase B: Prior Tolvaptan).

End point type	Secondary

End point timeframe:

From first dose of study drug up to 14 days post last dose (up to approximately 37 months)

End point values	Phase A: Tolvaptan	Phase A: Placebo	Phase B: Prior Tolvaptan	Phase B: Prior Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	43	42	39
Units: percentage of subjects				
number (not applicable)				
PR <=50 and Baseline Decrease >=15(n=48,43,42,38)	0.0	2.3	0.0	5.3
SystolicBP>=130&BaselineIncrease>=20;n=48,43,42,39	2.1	0.0	0.0	0.0
SystolicBP<=120&BaselineDecrease>=20;n=48,43,42,39	4.2	7.0	9.5	10.3
SystolicBP>=144&BaselineIncrease>=20;n=48,43,42,39	2.1	2.3	0.0	2.6
DiastolicBP<=50&BaselineDecrease>=15;n=48,43,42,39	4.2	7.0	9.5	0.0
DiastolicBP>=86&BaselineIncrease>=15;n=48,43,42,39	0.0	0.0	7.1	0.0
DiastolicBP<=80&BaselineDecrease>=15;n=48,43,42,39	12.5	18.6	16.7	12.8
DiastolicBP>=92&BaselineIncrease>=15;n=48,43,42,39	0.0	4.7	4.8	2.6

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A and B: Percentage of Subjects With Potentially Clinically Significant Abnormalities in Laboratory Test Results Including Liver Function Tests (LFTs)

End point title	Phase A and B: Percentage of Subjects With Potentially

	Clinically Significant Abnormalities in Laboratory Test Results Including Liver Function Tests (LFTs)

End point description:

Parameters=haematology,chemistry,urinalysis,&LFTs.Criteria=Increased(INC)creatinine level: Baseline(BSL):Grade 0,>BSL-1.5xBSL:1,>1.5-3xBSL:2,>3-6xBSL:3,>6xBSL:4.Decreased(DEC) glucose level: <30:-4,30-<40:-3, 40-<55:-2, 55-<65:-1,>=65:0; INC:<=115:0,>115-160:1,>160-250:2,>250-500:3,>500:4.DEC potassium: <2.5:-4,2.5-<3:-3,3-<lower limit of normal(LLN):-1,LLN:0; INC: upper limit of normal(ULN):0,>ULN-5.5:1,>5.5-6:2,>6-7:3,>7:4.DEC sodium: <120:-4,120-124:-3,125-129:-2,130-135:-1,>=136:0; INC:<=145:0,146-150:1,151-155:2,156-160:3,>160:4. INC triglyceride:ULN:0,>ULN-2.5xULN:1,>2.5-5xULN:2,>5-6xULN:3,>6xULN:4. DEC Neutrophils:<0.5:-4,0.5-<1:-3,1-<1.5:-2,1.5-<LLN:-1,LLN:0. Potentially clinically significant INC/DEC=BSL grade 0,1,-1 and post-BSL grade >1,<-1 or BSL grade >1,<-1 and post-BSL grade >or<BSL grade. Only those categories with atleast 1 subject with event are reported. Phase A and B Safety Set; n=number of subjects with≥1 post-baseline result. milliequivalents per deciliter=mEq/dL

End point type	Secondary

End point timeframe:

From first dose of study drug up to 14 days post last dose (up to approximately 37 months)

End point values	Phase A: Tolvaptan	Phase A: Placebo	Phase B: Prior Tolvaptan	Phase B: Prior Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	43	42	39
Units: percentage of subjects				
number (not applicable)				
Increase in Creatinine Level(mg/dL)(n=48,43,42,39)	8.3	0.0	7.1	7.7
Decrease in Glucose Level(mg/dL)(n=36,39,32,34)	0.0	2.6	0.0	2.9
Increase in Potassium Level(mEq/dL)(n=47,43,40,38)	2.1	0.0	0.0	2.6
Increase in Sodium Level (mEq/dL)(n=48,43,42,39)	0.0	0.0	0.0	2.6
Increased TriglycerideLevel(mg/dL)(n=36,39,32,3	0.0	0.0	3.1	0.0
Decrease in Neutrophils (10^9/L)(n=46,41,40,38)	0.0	4.9	5.0	2.6

Statistical analyses

No statistical analyses for this end point

Secondary: Phase A and B: Percentage of Subjects With Aquaretic Adverse Events (AEs)

End point title	Phase A and B: Percentage of Subjects With Aquaretic Adverse Events (AEs)

End point description:

An AE was defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Aquaretic AEs included Medical Dictionary for Regulatory Activities [MedDRA] preferred terms of thirst, polyuria (production of large volumes of dilute urine), nocturia (need to wake up to urinate at night), pollakiuria (abnormally frequent urination), and polydipsia (excessive thirst). The Phase A Safety Set included all subjects who were randomised and received at least 1 dose of IMP in Phase A. The Phase B Safety Set included all subjects who were enrolled in Phase B and received at least 1 dose of IMP in Phase B. As prespecified in the protocol, data for safety is reported by the treatment group (Phase A: Tolvaptan, Phase A: Placebo,

Phase B: Prior Tolvaptan and Phase B: Prior Placebo).

End point type	Secondary

End point timeframe:

From first dose of study drug up to 14 days post last dose (up to approximately 37 months)

End point values	Phase A: Tolvaptan	Phase A: Placebo	Phase B: Prior Tolvaptan	Phase B: Prior Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	43	42	39
Units: percentage of subjects				
number (not applicable)	64.6	16.3	14.3	48.7

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

From the first dose of the study drug up to 14 days post last dose (up to approximately 37 months)

Adverse event reporting additional description:

Phase A Safety Set=all subjects randomised and received atleast 1 dose of IMP in Phase A.Phase B Safety Set=all subjects enrolled in Phase B and received atleast 1 dose of IMP in Phase B. As prespecified in protocol, data for safety is reported by treatment group(PhaseA:Tolvaptan, PhaseA:Placebo, PhaseB:Prior Tolvaptan and PhaseB:Prior Placebo).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Phase A: Tolvaptan

Reporting group description:

Subjects received tolvaptan tablets, orally as a split dose (with the first dose taken upon awakening and the second dose taken approximately 8 hours later), and starting doses based on their weight as per the following specifications: ≥20 to 45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 12 months. Doses may be titrated down dependent upon subject tolerability.

Reporting group title	Phase A: Placebo

Reporting group description:

Subjects received matching-placebo tablets, orally as a split-dose (with the first dose taken upon awakening and second dose taken approximately 8 hours later), and starting dose based on their weight as per the following specifications: ≥20 to <45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 12 months. Doses may be titrated down dependent upon subject tolerability.

Reporting group title	Phase B: Prior Tolvaptan

Reporting group description:

Qualified subjects (defined as those who were willing to continue in the trial and who did not have any adverse events [AEs] that would require investigational medicinal product [IMP] discontinuation) who received tolvaptan and completed Phase A were enrolled in Phase B and received tolvaptan tablets, orally as a split dose (with the first dose taken upon awakening and the second dose taken approximately 8 hours later), and starting dose based on their body weight as per following specifications: ≥20 to <45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 24 months. Doses may be titrated down dependent upon subject tolerability.

Reporting group title	Phase B: Prior Placebo

Reporting group description:

Qualified subjects (defined as those who were willing to continue in the trial and who did not have any AEs that would require IMP discontinuation) who received matching-placebo and completed Phase A, were enrolled in Phase B and received tolvaptan tablets, orally as a split dose (with the first dose taken upon awakening and the second dose taken approximately 8 hours later), based on their current body weight as per following specifications: ≥20 to <45 kg: 15/7.5 mg; ≥45 to ≤75 kg: 30/15 mg; >75 kg: 45/15 mg, for 1 week. The starting dose was up-titrated (≥20 to <45 kg: 30/15 mg; ≥45 to ≤75 kg: 45/15 mg; >75 kg: 60/30 mg) after 1 week based upon tolerability and thereafter subjects continued the same dose for 24 months. Doses may be titrated down dependent upon subject tolerability.

Serious adverse events	Phase A: Tolvaptan	Phase A: Placebo	Phase B: Prior Tolvaptan
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 48 (2.08%)	6 / 43 (13.95%)	7 / 42 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 43 (2.33%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	0 / 48 (0.00%)	1 / 43 (2.33%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			

subjects affected / exposed	0 / 48 (0.00%)	1 / 43 (2.33%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Expired product administered			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 43 (2.33%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Petit mal epilepsy			
subjects affected / exposed	0 / 48 (0.00%)	1 / 43 (2.33%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 43 (2.33%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			

subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Intentional self-injury			
subjects affected / exposed	0 / 48 (0.00%)	1 / 43 (2.33%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eating disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 48 (0.00%)	1 / 43 (2.33%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 43 (2.33%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Viral pericarditis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arthritis bacterial			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase B: Prior Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 39 (20.51%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Heart rate increased			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hand fracture			

subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intentional overdose			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Expired product administered			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Petit mal epilepsy			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pelvic pain			

subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis ulcerative			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Intentional self-injury			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eating disorder			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal pain			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal impairment			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Viral pericarditis			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arthritis bacterial			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase A: Tolvaptan	Phase A: Placebo	Phase B: Prior Tolvaptan
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 48 (93.75%)	42 / 43 (97.67%)	38 / 42 (90.48%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 48 (8.33%)	1 / 43 (2.33%)	4 / 42 (9.52%)
occurrences (all)	4	1	5
Hypotension			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Orthostatic hypotension			
subjects affected / exposed	5 / 48 (10.42%)	0 / 43 (0.00%)	3 / 42 (7.14%)
occurrences (all)	5	0	3
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 48 (0.00%)	3 / 43 (6.98%)	3 / 42 (7.14%)
occurrences (all)	0	3	3
Fatigue			
subjects affected / exposed	4 / 48 (8.33%)	3 / 43 (6.98%)	3 / 42 (7.14%)
occurrences (all)	5	4	3
Non-cardiac chest pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Pyrexia			
subjects affected / exposed	4 / 48 (8.33%)	3 / 43 (6.98%)	8 / 42 (19.05%)
occurrences (all)	5	6	10
Thirst			
subjects affected / exposed	7 / 48 (14.58%)	2 / 43 (4.65%)	1 / 42 (2.38%)
occurrences (all)	8	2	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	4 / 48 (8.33%)	1 / 43 (2.33%)	0 / 42 (0.00%)
occurrences (all)	4	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 48 (14.58%)	5 / 43 (11.63%)	7 / 42 (16.67%)
occurrences (all)	10	8	9
Epistaxis			
subjects affected / exposed	3 / 48 (6.25%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences (all)	3	0	3
Oropharyngeal pain			
subjects affected / exposed	4 / 48 (8.33%)	6 / 43 (13.95%)	9 / 42 (21.43%)
occurrences (all)	5	6	11
Psychiatric disorders			
Enuresis			

subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	4
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	9 / 48 (18.75%)	2 / 43 (4.65%)	7 / 42 (16.67%)
occurrences (all)	12	2	9
Liver function test increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Vitamin D decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	5
Weight decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Hand fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Head injury			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 48 (6.25%)	5 / 43 (11.63%)	4 / 42 (9.52%)
occurrences (all)	3	6	5
Headache			
subjects affected / exposed	16 / 48 (33.33%)	21 / 43 (48.84%)	15 / 42 (35.71%)
occurrences (all)	23	37	22
Migraine			

subjects affected / exposed	2 / 48 (4.17%)	3 / 43 (6.98%)	1 / 42 (2.38%)
occurrences (all)	2	3	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	3 / 48 (6.25%)	2 / 43 (4.65%)	2 / 42 (4.76%)
occurrences (all)	6	4	6
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 48 (12.50%)	3 / 43 (6.98%)	4 / 42 (9.52%)
occurrences (all)	7	3	4
Abdominal pain upper			
subjects affected / exposed	5 / 48 (10.42%)	4 / 43 (9.30%)	5 / 42 (11.90%)
occurrences (all)	8	6	6
Constipation			
subjects affected / exposed	5 / 48 (10.42%)	1 / 43 (2.33%)	4 / 42 (9.52%)
occurrences (all)	5	1	4
Diarrhoea			
subjects affected / exposed	3 / 48 (6.25%)	7 / 43 (16.28%)	3 / 42 (7.14%)
occurrences (all)	3	8	3
Enteritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	3 / 48 (6.25%)	7 / 43 (16.28%)	7 / 42 (16.67%)
occurrences (all)	4	7	16
Toothache			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	7 / 48 (14.58%)	10 / 43 (23.26%)	5 / 42 (11.90%)
occurrences (all)	9	17	9
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	7 / 48 (14.58%)	3 / 43 (6.98%)	1 / 42 (2.38%)
occurrences (all)	8	3	1
Pollakiuria			

subjects affected / exposed	9 / 48 (18.75%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences (all)	9	0	2
Polyuria			
subjects affected / exposed	13 / 48 (27.08%)	2 / 43 (4.65%)	2 / 42 (4.76%)
occurrences (all)	13	2	2
Renal impairment			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Renal pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	4 / 48 (8.33%)	5 / 43 (11.63%)	5 / 42 (11.90%)
occurrences (all)	5	5	7
Flank pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Pain in extremity			
subjects affected / exposed	0 / 48 (0.00%)	6 / 43 (13.95%)	1 / 42 (2.38%)
occurrences (all)	0	6	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 48 (6.25%)	1 / 43 (2.33%)	2 / 42 (4.76%)
occurrences (all)	4	1	2
Cystitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	6
Ear infection			
subjects affected / exposed	1 / 48 (2.08%)	4 / 43 (9.30%)	3 / 42 (7.14%)
occurrences (all)	1	4	3
Gastoenteritis			

subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	5
Nasopharyngitis			
subjects affected / exposed	10 / 48 (20.83%)	14 / 43 (32.56%)	11 / 42 (26.19%)
occurrences (all)	14	24	18
Pharyngitis			
subjects affected / exposed	4 / 48 (8.33%)	0 / 43 (0.00%)	3 / 42 (7.14%)
occurrences (all)	4	0	3
Rhinitis			
subjects affected / exposed	3 / 48 (6.25%)	3 / 43 (6.98%)	11 / 42 (26.19%)
occurrences (all)	3	3	14
Sinusitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Tonsillitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	4
Upper respiratory tract infection			
subjects affected / exposed	4 / 48 (8.33%)	2 / 43 (4.65%)	2 / 42 (4.76%)
occurrences (all)	6	2	3
Urinary tract infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	3 / 48 (6.25%)	1 / 43 (2.33%)	5 / 42 (11.90%)
occurrences (all)	5	1	5
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 43 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 48 (8.33%)	2 / 43 (4.65%)	1 / 42 (2.38%)
occurrences (all)	4	2	2
Polydipsia			
subjects affected / exposed	5 / 48 (10.42%)	1 / 43 (2.33%)	1 / 42 (2.38%)
occurrences (all)	5	1	1

Non-serious adverse events	Phase B: Prior Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 39 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Orthostatic hypotension			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Non-cardiac chest pain			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	11		
Thirst			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Reproductive system and breast disorders			

Dysmenorrhoea subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 8		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 8 / 39 (20.51%) 10 7 / 39 (17.95%) 7 7 / 39 (17.95%) 8		
Psychiatric disorders Enuresis subjects affected / exposed occurrences (all)	 2 / 39 (5.13%) 3		
Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all) Liver function test increased subjects affected / exposed occurrences (all) Vitamin D decreased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all)	 2 / 39 (5.13%) 2 5 / 39 (12.82%) 11 2 / 39 (5.13%) 2 1 / 39 (2.56%) 1 5 / 39 (12.82%) 5		
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 5		
Hand fracture subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Head injury subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 6		
Headache subjects affected / exposed occurrences (all)	17 / 39 (43.59%) 66		
Migraine subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 4		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	12 / 39 (30.77%) 16		
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 8		
Constipation subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 6		
Enteritis			

subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	9		
Toothache			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	17		
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	9		
Pollakiuria			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Polyuria			
subjects affected / exposed	13 / 39 (33.33%)		
occurrences (all)	13		
Renal impairment			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	9		
Renal pain			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Flank pain			

subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Cystitis			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Gastoenteritis			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	6		
Nasopharyngitis			
subjects affected / exposed	13 / 39 (33.33%)		
occurrences (all)	19		
Pharyngitis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	5		
Sinusitis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	6		

Urinary tract infection subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 4		
Viral infection subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 5		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 5		
Polydipsia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2016	The following changes were implemented with Amendment 1: -Exclusion of subjects who had a known lactose intolerance. -Removed ADPKD Teen Scale.
29 July 2020	The following changes were implemented with Amendment 2: Added trial conduct information to introduce the Coronavirus 2019 (COVID-19) Addendum. Updated text for secondary endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported