Clinical trial results:
A Phase 3b, Multicenter, Open-label, Randomized Withdrawal Trial of the Effects of Titrated Oral SAMSCA® (Tolvaptan) on Serum Sodium, Pharmacokinetics, and Safety in Children and Adolescent Subjects Hospitalized With Euvolemic or Hypervolemic Hyponatremia

Summary

EudraCT number	2013-002005-59
Trial protocol	DE GB ES IT CZ BE
Global end of trial date	24 July 2017

Results information

Result version number	v1 (current)
This version publication date	25 April 2018
First version publication date	25 April 2018

Trial information

Trial identification

Sponsor protocol code	156-08-276

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02012959
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 Pharmaceutical Development & Commercialization, Inc., Otsuka Transparency Department, DT-inquiry@otsuka.jp
Scientific contact	Otsuka Pharmaceutical Development & Commercialization, Inc., Otsuka Transparency Department, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2017
Global end of trial reached?	Yes
Global end of trial date	24 July 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that tolvaptan effectively and safely increases and maintains serum sodium concentrations in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.

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 had been obtained from them. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the institutional review board or ethics committee at each respective trial center.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2015
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: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	9
EEA total number of subjects	2

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)	8
Adolescents (12-17 years)	1
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 42 sites were activated, 18 in the European Union and 24 in North America. After approximately 32 months of open enrollment, only 14 subjects were screened and 9 subjects were enrolled. The trial was terminated due to low subject enrollment which made the trial highly impracticable to conduct. The trial was not terminated due to safety.

Pre-assignment

Screening details:

The trial consisted of a screening phase, two treatment phases (Phases A and B), and follow-up Phase C. Overall, in this trial, subjects underwent treatment (2 to 5 days of tolvaptan among 2 treatment phases) and a post-last dose follow-up phase of 14 days.

Period 1

Period 1 title	Treatment Phase A
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Phase A: All participants

Arm description:

During Treatment Phase A, subjects received tolvaptan once daily on Days 1 and 2. If the serum sodium level did not increase at least 4 mEq/L by Day 2, treatment was extended one additional day (to Day 2a). On Day 2a, subjects achieving an increase in serum sodium of ≥ 4 mEq/L were defined as responders, and subjects not achieving a ≥ 4 mEq/L increase in serum sodium were defined as nonresponders.

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

Dosage and administration details:

Subjects received tolvaptan once daily on Days 1 and 2. If the serum sodium level did not increase at least 4 mEq/L by Day 2, treatment was extended one additional day (to Day 2a).

Number of subjects in period 1	Phase A: All participants
Started	9
Completed	7
Not completed	2
Adverse Events	2

Period 2

Period 2 title	Treatment Phase B: Responder
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Late Withdrawal

Arm description:

Subjects who were responders (serum sodium increased by ≥ 4 mEq/L) from Phase A continued to Treatment Phase B (Randomization Phase) on Day 3, and were randomized to the Late Withdrawal group (continuing tolvaptan treatment for Days 3 and 4).

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

Dosage and administration details:

Subjects continued tolvaptan treatment on Days 3 and 4.

Arm title	Early Withdrawal

Arm description:

Subjects who were responders (serum sodium increased by ≥ 4 mEq/L) from Phase A continued to Treatment Phase B (Randomization Phase) on Day 3, and were randomized to the Early Withdrawal group (not receiving additional tolvaptan on Days 3 or 4). Subjects randomized to Early Withdrawal were monitored for any interventions needed to maintain appropriate serum sodium levels. Where sodium levels declined by ≥ 4 mEq/L, or where the overall clinical condition warranted further intervention to increase serum sodium levels, subjects were treated per the investigator's preferred standard of care. Any intervention, including fluid restriction, during the first 48 hours of the Early Withdrawal phase was defined as rescue therapy, and subject data was censored thereafter.

Arm type	Any interventions

No investigational medicinal product assigned in this arm

Arm title	Treatment Phase B: Responder (Overall)

Arm description:

Subjects who were responders (serum sodium increased by ≥ 4 mEq/L) continued to Treatment Phase B (Randomization Phase) on Day 3, and were randomized to either the Early Withdrawal group (not receiving additional tolvaptan on Days 3 or 4) or the Late Withdrawal group (continuing tolvaptan treatment for Days 3 and 4).

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

Dosage and administration details:

Subjects continued tolvaptan treatment on Days 3 and 4.

Number of subjects in period 2	Late Withdrawal	Early Withdrawal	Treatment Phase B: Responder (Overall)
Started	2	3	5
Completed	2	3	5

Period 3

Period 3 title	Treatment Phase B: Non-responder
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Study Drug

Arm description:

Subjects who were nonresponders during Phase A were not randomized in Phase B but were treated per the investigator's discretion, and continued tolvaptan for Days 3 and 4.

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

Dosage and administration details:

Subjects continued tolvaptan treatment on Days 3 and 4.

Arm title	Standard of Care

Arm description:

Subjects who were nonresponders during Phase A were not randomized in Phase B but were treated per the investigator's discretion. The subjects in this arm discontinued tolvaptan and received the investigator's preferred standard of care for Days 3 and 4.

Arm type	Standard care

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Study Drug	Standard of Care
Started	1	1
Completed	1	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment Phase A

Reporting group description: -

Reporting group values	Treatment Phase A	Total	
Number of subjects	9	9	
Age categorical			
During Treatment Phase A, subjects received tolvaptan once daily on Days 1 and 2. If the serum sodium level did not increase at least 4 mEq/L by Day 2, treatment was extended one additional day (to Day 2a). On Day 2a, subjects achieving an increase in serum sodium of ≥ 4 mEq/L were defined as responders, and subjects not achieving a ≥ 4 mEq/L increase in serum sodium were defined as nonresponders. Subjects who were responders (serum sodium increased by ≥ 4 mEq/L) continued to Treatment Phase B (Randomization Phase) on Day 3.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	1	1	
Children (2-11 years)	6	6	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	6.1		
standard deviation	± 5.1	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	6	6	

End points

End points reporting groups

Reporting group title	Phase A: All participants

Reporting group description:

During Treatment Phase A, subjects received tolvaptan once daily on Days 1 and 2. If the serum sodium level did not increase at least 4 mEq/L by Day 2, treatment was extended one additional day (to Day 2a). On Day 2a, subjects achieving an increase in serum sodium of ≥ 4 mEq/L were defined as responders, and subjects not achieving a ≥ 4 mEq/L increase in serum sodium were defined as nonresponders.

Reporting group title	Late Withdrawal

Reporting group description:

Subjects who were responders (serum sodium increased by ≥ 4 mEq/L) from Phase A continued to Treatment Phase B (Randomization Phase) on Day 3, and were randomized to the Late Withdrawal group (continuing tolvaptan treatment for Days 3 and 4).

Reporting group title	Early Withdrawal

Reporting group description:

Subjects who were responders (serum sodium increased by ≥ 4 mEq/L) from Phase A continued to Treatment Phase B (Randomization Phase) on Day 3, and were randomized to the Early Withdrawal group (not receiving additional tolvaptan on Days 3 or 4). Subjects randomized to Early Withdrawal were monitored for any interventions needed to maintain appropriate serum sodium levels. Where sodium levels declined by ≥ 4 mEq/L, or where the overall clinical condition warranted further intervention to increase serum sodium levels, subjects were treated per the investigator's preferred standard of care. Any intervention, including fluid restriction, during the first 48 hours of the Early Withdrawal phase was defined as rescue therapy, and subject data was censored thereafter.

Reporting group title	Treatment Phase B: Responder (Overall)

Reporting group description:

Subjects who were responders (serum sodium increased by ≥ 4 mEq/L) continued to Treatment Phase B (Randomization Phase) on Day 3, and were randomized to either the Early Withdrawal group (not receiving additional tolvaptan on Days 3 or 4) or the Late Withdrawal group (continuing tolvaptan treatment for Days 3 and 4).

Reporting group title	Study Drug

Reporting group description:

Subjects who were nonresponders during Phase A were not randomized in Phase B but were treated per the investigator's discretion, and continued tolvaptan for Days 3 and 4.

Reporting group title	Standard of Care

Reporting group description:

Subjects who were nonresponders during Phase A were not randomized in Phase B but were treated per the investigator's discretion. The subjects in this arm discontinued tolvaptan and received the investigator's preferred standard of care for Days 3 and 4.

Primary: Mean Change from Baseline in Serum Sodium Concentration (mEq/L) for Responders

End point title	Mean Change from Baseline in Serum Sodium Concentration (mEq/L) for Responders[1]

End point description:

To assess the change in serum sodium level for responders from Day 2 (or 2a) at the end of Treatment Phase A (where all subjects received tolvaptan) to the end of Treatment Phase B for the Early compared to Late Withdrawal groups. Once a subject was randomized to Treatment Phase B, any additional therapies for the purpose of raising serum sodium, including fluid restriction, was considered rescue therapy. Upon receipt of rescue therapy, a subject's endpoint data was collected and then censored from the efficacy analysis thereafter unless specified.

End point type	Primary

End point timeframe:

Day 2/2a/3, Day 4/5

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: The trial was terminated due to low subject recruitment and enrollment which made the trial highly impracticable or impossible to conduct. No statistical analysis was done for the primary endpoint.

End point values	Late Withdrawal	Early Withdrawal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	3		
Units: mEq/L				
arithmetic mean (standard deviation)	-4.0 (± 4.2)	-1.0 (± 1.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs)

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

End point description:

An AE was defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which did not necessarily have a causal relationship with this treatment. AEs would not include information recorded as medical history at screening for pre planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction was any untoward and unintended response to an investigational medicinal product (IMP) related to any dose administered.

End point type	Secondary

End point timeframe:

Adverse events were recorded from the time of the informed consent was signed until the follow-up visit 14 (+ 2) days post-last dose.

End point values	Phase A: All participants	Late Withdrawal	Early Withdrawal	Study Drug
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	2	3	1
Units: Subjects				
number (not applicable)				
Subjects with Adverse Events	5	2	2	1
Subjects with Treatment-Emergent Adverse Events	4	2	2	1
Subjects with Serious Treatment-Emergent AEs	2	1	0	1
Subjects with Severe Treatment-Emergent AEs	0	0	0	1
Subjects Discontinued Due to AEs	2	0	0	0

End point values	Standard of			

	Care			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Subjects				
number (not applicable)				
Subjects with Adverse Events	1			
Subjects with Treatment-Emergent Adverse Events	1			
Subjects with Serious Treatment-Emergent AEs	0			
Subjects with Severe Treatment-Emergent AEs	0			
Subjects Discontinued Due to AEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in serum sodium concentration (mEq/L) in Treatment Phase A

End point title	Mean change from baseline in serum sodium concentration (mEq/L) in Treatment Phase A

End point description:

To assess the change from baseline in serum sodium concentration at the end of Day 2 (or 2a) at the end of Treatment Phase A. A hierarchical testing procedure was used to maintain the overall experiment-wise type I error rate at 0.05. Thus, if the primary efficacy analysis yielded a statistically significant result at an alpha level of 0.05 (2-sided), then the paired t-test was performed at an alpha level of 0.05 for the key secondary endpoint.

End point type	Secondary

End point timeframe:

Day 2/2a

End point values	Phase A: All participants			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: mEq/L				
arithmetic mean (standard deviation)				
Phase A Day 1 : 24 hour Post-Dose (N = 8)	1 (± 3)			
Phase A Day 2 : 24 hour Post-Dose (N = 7)	3.4 (± 4.8)			
Phase A Day 2a : 24 hour Post-Dose (N = 3)	2.3 (± 2.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in serum sodium from 24 hours post-last dose to 7 days post-last dose in Phase B for Responders

End point title	Mean change in serum sodium from 24 hours post-last dose to 7 days post-last dose in Phase B for Responders

End point description:

To assess the change in serum sodium concentration from 24 hours post-last dose to 7 days post-last dose. This analysis used a paired Student's t-test, descriptive statistics, and/or 2-sided 95% Confidence Intervels (CIs).

End point type	Secondary

End point timeframe:

7 Days

End point values	Treatment Phase B: Responder (Overall)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: mEq/L				
arithmetic mean (standard deviation)				
72h Post-last Dose	-0.8 (± 0.8)			
7 Days Post-last Dose	3.6 (± 3.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fluid intake in Treatment Phase A

End point title	Fluid intake in Treatment Phase A

End point description:

To assess the fluid intake (both oral and intravenous [IV]) every 6 hours on Days 1 and 2 in Treatment Phase A. Fluid intake is one of the pharmacodynamic [PD] endpoints. The fluid content of foods with significant water content (eg, soup) was added to the total fluid intake. Fluid intake was monitored per institutional guidelines.

End point type	Secondary

End point timeframe:

Every 6 hours on Days 1 and 2

End point values	Phase A: All participants			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: mL				
arithmetic mean (standard deviation)				
Day 1: 0-6 hours	555 (± 402)			
Day 1 : 6-12 hours	396 (± 282)			
Day 1 : 12-18 hours	435 (± 496)			
Day 1 : 18-24 hours	387 (± 308)			
Day 1 : 0-24 hours	1774 (± 1242)			
Day 2 : 0-6 hours (N=8)	411 (± 134)			
Day 2 : 6-12 hours (N=8)	461 (± 522)			
Day 2 : 12-18 hours (N=8)	307 (± 221)			
Day 2 : 18-24 hours (N=8)	424 (± 299)			
Day 2 : 0-24 hours (N=8)	1603 (± 1099)			

Statistical analyses

No statistical analyses for this end point

Secondary: Urine output in Treatment Phase A

End point title	Urine output in Treatment Phase A

End point description:

To assess the urine output 6 hours on Days 1 and 2 in Treatment Phase A. Urine output is one of the PD endpoints.

End point type	Secondary

End point timeframe:

Every 6 hours on Days 1 and 2

End point values	Phase A: All participants			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: mL				
arithmetic mean (standard deviation)				
Day 1 : 0-6 hours	557 (± 293)			
Day 1 : 6-12 hours	658 (± 595)			
Day 1 : 12-18 hours	472 (± 498)			
Day 1 : 18-24 hours	355 (± 329)			
Day 1 : 0-24 hours	2041 (± 1127)			
Day 2 : 0-6 hours (N=8)	512 (± 398)			
Day 2 : 6-12 hours (N=8)	455 (± 485)			
Day 2 : 12-18 hours (N=8)	352 (± 482)			
Day 2 : 18-24 hours (N=8)	444 (± 442)			
Day 2 : 0-24 hours (N=8)	1763 (± 1358)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fluid balance (intake minus output) in Treatment Phase A

End point title	Fluid balance (intake minus output) in Treatment Phase A

End point description:

To assess the fluid balance every 6 hours and for the 24-hour daily interval on Days 1 and 2 in Treatment Phase A. Fluid balance is one of the PD endpoints. Fluid balance was monitored per institutional guidelines.

End point type	Secondary

End point timeframe:

Every 6 hours on Days 1 and 2

End point values	Phase A: All participants			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: mL				
arithmetic mean (standard deviation)				
Day 1 : 0-6 hours	-1 (± 505)			
Day 1 : 6-12 hours	-261 (± 533)			
Day 1 : 12-18 hours	-36 (± 253)			
Day 1 : 18-24 hours	31 (± 344)			
Day 1 : 0-24 hours	-268 (± 849)			
Day 2 : 0-6 hours (N=8)	-101 (± 376)			
Day 2 : 6-12 hours (N=8)	6 (± 513)			
Day 2 : 12-18 hours (N=8)	-45 (± 400)			
Day 2 : 18-24 hours (N=8)	-21 (± 191)			
Day 2 : 0-24 hours (N=8)	-160 (± 733)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Laboratory Values of Potential Clinical Relevance

End point title	Incidence of Laboratory Values of Potential Clinical Relevance

End point description:

The laboratory values were one of the variables to measure the safety of individual participants. Incidence of treatment emergent adverse events (TEAEs) of potential clinical relevance include abnormal

values in hematology, coagulation, chemistry and urinalysis that were identified based on pre-defined criteria. Abnormal laboratory values in participants were reported as serious adverse event/adverse events (SAE/AEs) and are reported in the SAE/other AE section of this report.

End point type	Secondary

End point timeframe:

From baseline to end of study

End point values	Phase A: All participants	Late Withdrawal	Early Withdrawal	Study Drug
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	2	3	1
Units: Participants				
number (not applicable)				
Chemistry- Potassium	1	0	0	0
Hematology - Hemoglobin	0	0	1	0
Hematology - Lymphocytes	0	1	0	0

End point values	Standard of Care			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Participants				
number (not applicable)				
Chemistry- Potassium	0			
Hematology - Hemoglobin	0			
Hematology - Lymphocytes	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Vital sign (blood pressure) of potential clinical relevance - mean change from baseline to study for Phase B (Responders)

End point title	Vital sign (blood pressure) of potential clinical relevance - mean change from baseline to study for Phase B (Responders)

End point description:

Vital sign (blood pressure) was assessed after the subject had been supine for greater than or equal to 3 minutes. Vital signs were assessed prior to any blood draws.

End point type	Secondary

End point timeframe:

7 days post last dose

End point values	Late Withdrawal	Early Withdrawal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	3		
Units: mmHg				
arithmetic mean (standard deviation)				
Supine systolic blood pressure	6.0 (± 2.8)	1.3 (± 20.3)		
Supine diastolic blood pressure	8.0 (± 0)	3.0 (± 8.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vital sign (supine heart rate) of potential clinical relevance - mean change from baseline to study for Phase B (Responders)

End point title	Vital sign (supine heart rate) of potential clinical relevance - mean change from baseline to study for Phase B (Responders)

End point description:

Vital sign (supine heart rate) was assessed after the subject had been supine for greater than or equal to 3 minutes. Vital signs were assessed prior to any blood draws.

End point type	Secondary

End point timeframe:

7 days post last dose

End point values	Late Withdrawal	Early Withdrawal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	3		
Units: beats/min				
arithmetic mean (standard deviation)	10.5 (± 2.1)	-2.3 (± 4.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vital sign (supine respiratory rate) of potential clinical relevance - mean change from baseline to study for Phase B (Responders)

End point title	Vital sign (supine respiratory rate) of potential clinical relevance - mean change from baseline to study for Phase B (Responders)

End point description:

Vital sign (supine respiratory rate) was assessed after the subject had been supine for greater than or equal to 3 minutes. Vital signs were assessed prior to any blood draws.

End point type	Secondary

End point timeframe:

7 days post last dose

End point values	Late Withdrawal	Early Withdrawal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	2		
Units: breaths/min				
arithmetic mean (standard deviation)	4.5 (± 3.5)	-6.0 (± 9.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vital sign (supine temperature) of potential clinical relevance - mean change from baseline to study for Phase B (Responders)

End point title	Vital sign (supine temperature) of potential clinical relevance - mean change from baseline to study for Phase B (Responders)

End point description:

Vital sign (blood pressure) was assessed after the subject had been supine for greater than or equal to 3 minutes. Vital signs were assessed prior to any blood draws.

End point type	Secondary

End point timeframe:

7 days post last dose

End point values	Late Withdrawal	Early Withdrawal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	2		
Units: Degree Centigrade				
arithmetic mean (standard deviation)	0.5 (± 0.1)	0.2 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Body weight of potential clinical relevance - mean change from baseline to study for Phase B (Responders)

End point title	Body weight of potential clinical relevance - mean change from baseline to study for Phase B (Responders)

End point description:

Body weight was measured predose each day throughout Treatment Phase B. Effort was made to ensure that body weight measurements were performed in a

reproducible and consistent manner. Body weight measurements were performed using the same scale.

End point type	Secondary

End point timeframe:

7 days post last dose

End point values	Late Withdrawal	Early Withdrawal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	3		
Units: kg				
arithmetic mean (standard deviation)	-0.4 (± 0.8)	1.1 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening till follow-up Phase C/early termination (ET)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Treatment Phase A

Reporting group description:

During Treatment Phase A, subjects received tolvaptan once daily on Days 1 and 2. If the serum sodium level did not increase at least 4 mEq/L by Day 2, treatment was extended one additional day (to Day 2a). On Day 2a, subjects achieving an increase in serum sodium of ≥ 4 mEq/L were defined as responders, and subjects not achieving a ≥ 4 mEq/L increase in serum sodium were defined as nonresponders.

Reporting group title	Treatment Phase B: Responder - Late Withdrawal

Reporting group description:

Subjects who were responders (serum sodium increased by ≥ 4 mEq/L) from Phase A continued to Treatment Phase B (Randomization Phase) on Day 3, and were randomized to the Late Withdrawal group (continuing tolvaptan treatment for Days 3 and 4).

Reporting group title	Treatment Phase B: Responder - Early Withdrawal

Reporting group description:

Subjects who were responders (serum sodium increased by ≥ 4 mEq/L) from Phase A continued to Treatment Phase B (Randomization Phase) on Day 3, and were randomized to the Early Withdrawal group (not receiving additional tolvaptan on Days 3 or 4). Subjects randomized to Early Withdrawal were monitored for any interventions needed to maintain appropriate serum sodium levels. Where sodium levels declined by ≥ 4 mEq/L, or where the overall clinical condition warranted further intervention to increase serum sodium levels, subjects were treated per the investigator's preferred standard of care. Any intervention, including fluid restriction, during the first 48 hours of the Early Withdrawal phase was defined as rescue therapy, and subject data was censored thereafter.

Reporting group title	Treatment Phase B: Non-responder - Study Drug

Reporting group description:

Subjects who were nonresponders during Phase A were not randomized in Phase B but were treated per the investigator's discretion, and continued tolvaptan for Days 3 and 4.

Reporting group title	Treatment Phase B: Non-responder - Standard of Care

Reporting group description:

Subjects who were nonresponders during Phase A were not randomized in Phase B but were treated per the investigator's discretion. The subjects in this arm discontinued tolvaptan and received the investigator's preferred standard of care for Days 3 and 4.

Serious adverse events	Treatment Phase A	Treatment Phase B: Responder - Late Withdrawal	Treatment Phase B: Responder - Early Withdrawal
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)	1 / 2 (50.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			

Catheter site extravasation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	0 / 3 (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
Medical device site haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	0 / 3 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecal volume increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treatment Phase B: Non-responder - Study Drug	Treatment Phase B: Non-responder - Standard of Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Catheter site extravasation			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecal volume increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	Treatment Phase A	Treatment Phase B: Responder - Late Withdrawal	Treatment Phase B: Responder - Early Withdrawal
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	1 / 2 (50.00%)	2 / 3 (66.67%)
Investigations			
Blood sodium decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 9 (33.33%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nasal inflammation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Treatment Phase B: Non-responder - Study Drug	Treatment Phase B: Non-responder - Standard of Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	
Investigations			
Blood sodium decreased			

subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Hypoxia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Nasal inflammation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Infections and infestations			
Upper respiratory tract infection			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2013	Amendment 1: To update the clinical management representative for this trial To remove the serum chemistry assessment at 7 (plus/minus 1) days post-randomization To change the sample size from 80 to 70 responders To clarify that subjects who cannot safely swallow the tablet are excluded until a liquid formulation is available To add neurological exam as an exploratory variable To update the dosing rationale based on starting doses (mg/kg) used for hyponatremia trials of tolvaptan in adults To change early termination from the 7-day Follow-up Visit to Day 5/6 To clarify that Phase B (Randomization Phase) applies to all subjects To correct the definition of a rapid correction of serum sodium To update the interim analysis To update the contact list for reporting an IRE
19 May 2014	Amendment 2: To increase the consistency of this protocol with other tolvaptan pediatric hyponatremia protocols To add neurocognitive and quality-of-life assessments as exploratory endpoints To clarify study design, procedures, and assessments To better define study phases and associated visits To provide greater detail about clinical laboratory tests To add Tanner staging to the assessments performed during the physical examination To better define completers and stopping rules To incorporate newly revised definitions of IMP causality
26 February 2015	Amendment 3: Implementation of additional serum sodium testing during drug titration to align with the current EU label (SmPC) for the adult indication of hyponatremia. Safety testing for serum sodium was added at interim time points during titration with the option of using a point of care device to minimize impact on total blood volume required for the trial. Clarification of the “baseline” assessment for trial qualification. Additional background data from non-clinical juvenile toxicity studies. Updates to clarify the titration and rescue therapy schematic. Clarify roll-over into extension study 156-11-294. Implementation of a suspension formulation for short-term use in hospitalized subjects. Implementation of an optional swallow test for the tablet formulation.
07 May 2015	Amendment 4: Correction of typographical errors in the dosing table for the suspension for subjects taking a CYP3A inhibitor. Removed the word “Tablet” from the title of Table 2.1.1-2 as the table includes dosing information for tolvaptan tablets and for the suspension formulation of tolvaptan. Updated the Clinical Management contact information on the title page and in Appendix 1. Correction of typographical error in Section 2.1.1 Dosing Rationale.
17 November 2015	Amendment 5 : The main intent was to clarify administrative sections, align with current protocol templates, and incorporate recent requests from Regulatory Authorities (Food and Drug Administration [FDA]).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
24 July 2017	The trial was terminated 24 Jul 2017 due to low subject recruitment and enrollment which made the trial highly impracticable or impossible to conduct. The trial was not terminated due to safety reasons. The Food and Drug Administration (FDA) granted Otsuka release/Pediatric Research Equity Act (PREA) waiver on 19 Jul 2017 and rescinded the pediatric written request (WR) on 19 Jul 2017.	-

Notes:

Limitations and caveats

None reported