



Clinical trial results:

A Phase 3b, Multicenter, Extension Follow-up Trial to Evaluate the Long-term Safety of Children and Adolescent Subjects With Euvolemic or Hypervolemic Hyponatremia Who Have Previously Participated in a Trial of Titrated Oral SAMSCA® (Tolvaptan)

Summary

EudraCT number	2013-002810-11
Trial protocol	DE GB BE IT CZ RO ES
Global end of trial date	23 October 2017

Results information

Result version number	v1 (current)
This version publication date	17 September 2021
First version publication date	17 September 2021

Trial information

Trial identification

Sponsor protocol code	156-11-294
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02020278
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc
Sponsor organisation address	2440 Research Boulevard, Rockville, MD, United States, 20850
Public contact	Otsuka Pharmaceutical Development & Commercialization, Inc., Global Clinical Development, +1 844-687-8522, OtsukaRMReconciliation@rmpdc.org
Scientific contact	Otsuka Pharmaceutical Development & Commercialization, Inc., Global Clinical Development, +1 844-687-8522, OtsukaRMReconciliation@rmpdc.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 October 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to provide 6 months of safety follow-up for children and adolescents with dilutional (euvolemic or hypervolemic) hyponatremia who had previously participated in a tolvaptan hyponatremia trial and to assess the efficacy of tolvaptan in increasing serum sodium for those participants who received optional continuing tolvaptan treatment of variable duration (up to 6 months).

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 April 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 States: 3
Worldwide total number of subjects	3
EEA total number of subjects	0

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)	1
Children (2-11 years)	1
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:

Eligible participants included those enrolled in a previous tolvaptan pediatric trial for hyponatremia (NCT02012959); who provided written informed consent at baseline and were able to understand that he/she could withdraw at any time; with the ability to comply with all requirements of the trial; ready to be followed up for 6 months.

Pre-assignment

Screening details:

There was no screening phase. Approximately 100 male or female participants were planned to be enrolled in this trial. A total of 3 participants were enrolled in this trial, but no participant received optional investigational medicinal product during this trial.

Period 1

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

Arms

Arm title	Tolvaptan
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Arm description:

All participants enrolled first entered a 6-month follow-up trial that evaluated post-treatment safety after participation in a tolvaptan hyponatremia trial. Participants were then eligible to receive open-label tolvaptan if they had a clinical need as determined by the investigator and met the eligibility criteria for optional tolvaptan treatment during the 6-month follow-up period. In this trial, no participants qualified for treatment during the 6-month follow-up period. Daily dose levels would have included 3.75 milligrams (mg), 7.5 mg, 15 mg, 30 mg, and 60 mg. However, no subjects received IMP during this trial.

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

Dosage and administration details:

Tolvaptan was planned to be supplied as 3.75-, 7.5-, 15-, and 30 mg spray-dried tablets and administered orally once daily (QD), preferably in the morning hours, with a dose-proportional amount of water. However, no subjects received IMP during this trial.

Number of subjects in period 1	Tolvaptan
Started	3
Completed	3

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	3	3	
Age categorical			
Due to the low number of participants enrolled, 0 participants are reported due to the risk of re-identification.			
Units: Subjects			
Not recorded	3	3	
Gender categorical			
Due to the low number of participants enrolled, 0 participants are reported due to the risk of re-identification.			
Units: Subjects			
Not recorded	3	3	

End points

End points reporting groups

Reporting group title	Tolvaptan
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Reporting group description:

All participants enrolled first entered a 6-month follow-up trial that evaluated post-treatment safety after participation in a tolvaptan hyponatremia trial. Participants were then eligible to receive open-label tolvaptan if they had a clinical need as determined by the investigator and met the eligibility criteria for optional tolvaptan treatment during the 6-month follow-up period. In this trial, no participants qualified for treatment during the 6-month follow-up period. Daily dose levels would have included 3.75 milligrams (mg), 7.5 mg, 15 mg, 30 mg, and 60 mg. However, no subjects received IMP during this trial.

Primary: Change From Baseline At Month 6 In Serum Sodium While Tolvaptan Was Being Administered

End point title	Change From Baseline At Month 6 In Serum Sodium While Tolvaptan Was Being Administered ^[1]
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End point description:

No enrolled participant received any investigational medicinal product during the study. Due to early study termination, efficacy data were not collected for this outcome measure.

End point type	Primary
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End point timeframe:

Baseline, Month 6

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to early study termination, efficacy data were not collected.

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[2]			
Units: number				
number (not applicable)				

Notes:

[2] - Due to early study termination, efficacy data were not collected for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Who Required Rescue Therapy While On Tolvaptan Treatment

End point title	Percentage Of Participants Who Required Rescue Therapy While On Tolvaptan Treatment
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End point description:

No enrolled participant received any investigational medicinal product during the study. Due to early study termination, efficacy data were not collected for this outcome measure.

End point type	Secondary
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End point timeframe:

Month 6

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[3]			
Units: number				
number (not applicable)				

Notes:

[3] - Due to early study termination, efficacy data were not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Who Had Recurrence Of Hyponatremia While On Tolvaptan

End point title	Percentage Of Participants Who Had Recurrence Of Hyponatremia While On Tolvaptan
End point description: No enrolled participant received any investigational medicinal product during the study. Due to early study termination, efficacy data were not collected for this outcome measure.	
End point type	Secondary
End point timeframe: Month 6	

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[4]			
Units: number				
number (not applicable)				

Notes:

[4] - Due to early study termination, efficacy data were not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Requiring Continuation Of Tolvaptan Following 30 Days Of Treatment

End point title	Percentage Of Participants Requiring Continuation Of Tolvaptan Following 30 Days Of Treatment
End point description: No enrolled participant received any investigational medicinal product during the study. Due to early study termination, efficacy data were not collected for this outcome measure.	
End point type	Secondary

End point timeframe:

Month 6

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[5]			
Units: number				
number (not applicable)				

Notes:

[5] - Due to early study termination, efficacy data were not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Pediatric Quality of Life Inventory (PedsQL) Generic Core Scale (GCS) Total Score At Month 6

End point title	Change From Baseline In Pediatric Quality of Life Inventory (PedsQL) Generic Core Scale (GCS) Total Score At Month 6
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End point description:

The PedsQL GCS was used for quality of life assessment. It is appropriate for at least 2 years of age, however availability may be limited for certain ages and languages. It encompasses 4 dimensions of functioning (physical, emotional, social, school). The age groups covered are: Toddler (2-4 years), Young child (5-7 years), Child (8-12 years), and Adolescent (13-18 years). Depending on the participant's age, the questionnaire may be completed by either the participant or the parent/caregiver, as appropriate. For the Toddler group, the PedsQL GCS consists of 21 items, using a 5-point Likert scale (0 to 4); for all other groups, the PedsQL GCS consists of 23 items, with a 3-point Likert scale (0, 2, 4) for the Young Child, and a 5-point Likert scale for the Child and Adolescent groups. Scores are transformed on a scale from 0 to 100 and averaged. Higher scores indicate improved quality of life. The change from baseline in the GCS total score is presented.

End point type	Secondary
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End point timeframe:

Baseline, Month 6

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	1 ^[6]			
Units: units on a scale				
arithmetic mean (full range (min-max))	-3.5 (-3.5 to -3.5)			

Notes:

[6] - All enrolled participants with analyzable data at specified timepoint.

Statistical analyses

Secondary: Change From Baseline In PedsQL GCS Physical Health Summary Score At Month 6

End point title	Change From Baseline In PedsQL GCS Physical Health Summary Score At Month 6
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End point description:

The PedsQL GCS was used for quality of life assessment. It is appropriate for at least 2 years of age, however availability may be limited for certain ages and languages. It encompasses 4 dimensions of functioning (physical, emotional, social, school). The age groups covered are: Toddler (2-4 years), Young child (5-7 years), Child (8-12 years), and Adolescent (13-18 years). Depending on the participant's age, the questionnaire may be completed by either the participant or the parent/caregiver, as appropriate. For the Toddler group, the PedsQL GCS consists of 21 items, using a 5-point Likert scale (0 to 4); for all other groups, the PedsQL GCS consists of 23 items, with a 3-point Likert scale (0, 2, 4) for the Young Child, and a 5-point Likert scale for the Child and Adolescent groups. Scores are transformed on a scale from 0 to 100 and averaged. Higher scores indicate improved quality of life. The change from baseline in the physical health dimension is presented.

End point type	Secondary
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End point timeframe:

Baseline, Month 6

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	1 ^[7]			
Units: units on a scale				
arithmetic mean (full range (min-max))	12.5 (12.5 to 12.5)			

Notes:

[7] - All enrolled participants with analyzable data at specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In PedsQL GCS Psychosocial Health Summary Score At Month 6

End point title	Change From Baseline In PedsQL GCS Psychosocial Health Summary Score At Month 6
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End point description:

The PedsQL GCS was used for quality of life assessment. It is appropriate for at least 2 years of age, however availability may be limited for certain ages and languages. It encompasses 4 dimensions of functioning (physical, emotional, social, school). The age groups covered are: Toddler (2-4 years), Young child (5-7 years), Child (8-12 years), and Adolescent (13-18 years). Depending on the participant's age, the questionnaire may be completed by either the participant or the parent/caregiver, as appropriate. For the Toddler group, the PedsQL GCS consists of 21 items, using a 5-point Likert scale (0 to 4); for all other groups, the PedsQL GCS consists of 23 items, with a 3-point Likert scale (0, 2, 4) for the Young Child, and a 5-point Likert scale for the Child and Adolescent groups. Scores are transformed on a scale from 0 to 100 and averaged. Higher scores indicate improved quality of life. The change from baseline in summed emotional, social, and school dimensions is presented.

End point type	Secondary
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End point timeframe:

Baseline, Month 6

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	1 ^[8]			
Units: units on a scale				
arithmetic mean (full range (min-max))	-13.5 (-13.5 to -13.5)			

Notes:

[8] - All enrolled participants with analyzable data at specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In PedsQL Multidimensional Fatigue Scale (MFS) Total Score At Month 6

End point title	Change From Baseline In PedsQL Multidimensional Fatigue Scale (MFS) Total Score At Month 6
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End point description:

The PedsQL MFS was used for quality-of-life assessment. It is appropriate for at least 2 years of age; however, availability may be limited for certain ages and languages. The PedsQL MFS consists of 18 items in 3 subscales: general fatigue, sleep/rest fatigue, and cognitive fatigue. The instrument focuses on the domains of processing speed, attention/vigilance, visual and working memory. The age groups covered by these assessments are Toddler (2–4 years), Young child (5–7 years), Child (8–12 years), and Adolescent (13–18 years). Depending on the subject's age, the questionnaire may be completed by either the subject or the parent/caregiver, as appropriate. A 5-point Likert scale is used (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items are reverse-scored and transformed to a 0–100 scale so that higher PedsQL MFS scores indicate better quality of life.

End point type	Secondary
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End point timeframe:

Baseline, Month 6

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	1 ^[9]			
Units: units on a scale				
arithmetic mean (full range (min-max))	9.7 (9.7 to 9.7)			

Notes:

[9] - All enrolled participants with analyzable data at specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants With Overly Rapid Correction In Serum

Sodium 24 Hours After The First Dose At Introduction Or Reintroduction Of Tolvaptan

End point title	Percentage Of Participants With Overly Rapid Correction In Serum Sodium 24 Hours After The First Dose At Introduction Or Reintroduction Of Tolvaptan
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End point description:

End point type	Secondary
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End point timeframe:

Month 6

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[10]			
Units: number				
number (not applicable)				

Notes:

[10] - Due to early study termination, efficacy data were not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations Of Tolvaptan And Metabolites In Participants Who Had Continued Tolvaptan Therapy For Eight Consecutive Weeks

End point title	Plasma Concentrations Of Tolvaptan And Metabolites In Participants Who Had Continued Tolvaptan Therapy For Eight Consecutive Weeks
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End point description:

End point type	Secondary
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End point timeframe:

8 Weeks

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[11]			
Units: number				
number (not applicable)				

Notes:

[11] - Due to early study termination, no pharmacokinetic analyses were performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With A Tanner Staging Score Of 1 At Month 6

End point title	Participants With A Tanner Staging Score Of 1 At Month 6
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End point description:

Tanner Staging assessment consists of 2 domains (pubic hair and breast development) for girls and 3 domains (pubic hair, penis development, and testes development) for boys. Staging was based on a single score summarizing the domains (not individual domain scores). Stages range from 1-5, with 1 indicating preadolescent and 5 adult. Participants with a Tanner staging score of 1 (preadolescent) at Month 6 are reported.

End point type	Secondary
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End point timeframe:
Month 6

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[12]			
Units: Count of Participants				
number (not applicable)	2			

Notes:

[12] - All enrolled participants with analyzable data at specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Growth Percentiles For Body Height And Weight At Month 6

End point title	Change From Baseline In Growth Percentiles For Body Height And Weight At Month 6
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End point description:

Changes from baseline in growth percentiles for body height and weight were calculated and are reported.

End point type	Secondary
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End point timeframe:
Baseline, Month 6

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[13]			
Units: percentile				
arithmetic mean (standard deviation)				
Height Percentile	19.0 (± 40.0)			

Weight Percentile	0.7 ($\pm$ 8.0)			
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Notes:

[13] - All enrolled participants with analyzable data at specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Alanine Aminotransferase (ALT) And Aspartate Aminotransferase (AST) For Participants On Tolvaptan At Month 2

End point title	Change From Baseline In Alanine Aminotransferase (ALT) And Aspartate Aminotransferase (AST) For Participants On Tolvaptan At Month 2
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End point description:

No enrolled participant received any investigational medicinal product during the study. Due to early study termination, efficacy data were not collected. Data reported only include assessments made for ALT and AST during the Core Safety Follow-up Component of the trial. Results are reported in units/liter (U/L).

End point type	Secondary
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End point timeframe:

Baseline, Month 2

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	2 ^[14]			
Units: U/L				
arithmetic mean (standard deviation)				
ALT	-10.00 ($\pm$ 45.25)			
AST	-7.50 ($\pm$ 0.71)			

Notes:

[14] - All enrolled participants with analyzable data at specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Bilirubin For Participants On Tolvaptan At Month 2

End point title	Change From Baseline In Bilirubin For Participants On Tolvaptan At Month 2
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End point description:

No enrolled participant received any investigational medicinal product during the study. Due to early study termination, efficacy data were not collected. Data reported only include assessments made for bilirubin during the Core Safety Follow-up Component of the trial. Results are reported in micromoles (umol)/L.

End point type	Secondary
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End point timeframe:

Baseline, Month 2

End point values	Tolvaptan			
Subject group type	Reporting group			
Number of subjects analysed	2 ^[15]			
Units: umol/L				
arithmetic mean (standard deviation)	2.57 (± 3.63)			

Notes:

[15] - All enrolled participants with analyzable data at specified timepoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Month 6

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Tolvaptan
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Reporting group description:

All participants enrolled first entered a 6-month follow-up trial that evaluated post-treatment safety after participation in a tolvaptan hyponatremia trial. Participants were then eligible to receive open-label tolvaptan if they had a clinical need as determined by the investigator and met the eligibility criteria for optional tolvaptan treatment during the 6-month follow-up period. In this trial, no participants qualified for treatment during the 6-month follow-up period. Daily dose levels would have included 3.75 milligrams (mg), 7.5 mg, 15 mg, 30 mg, and 60 mg.

Serious adverse events	Tolvaptan		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Enterovirus Infection			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhinovirus Infection			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			

subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tolvaptan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Enterovirus Infection			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Rhinovirus Infection			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Urosepsis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2013	- To increase the consistency of this protocol with other tolvaptan pediatric hyponatremia protocols - To revise trial endpoints in accordance with the Pediatric Investigation Plan - To clarify study design, procedures, and assessments - To incorporate revised definitions of IMP causality
26 February 2015	- Implementation of additional serum sodium testing during drug titration to align with the current EU label (SmPC) for the adult indication of hyponatremia. We are adding safety testing for serum sodium 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. - Additional background data from non-clinical juvenile toxicity studies. - Updates to clarify prohibition of hypertonic saline. - Clarify roll-over into extension study 156-11-294. - Clarification of scheduled treatment interruption after 30 days of treatment and close clinical monitoring with the addition of visits.
09 November 2015	The main intent of the amendment is to streamline text within the protocol by providing administrative clarifications, removing duplicative language, and ensuring consistency across sections. Efficiencies have been established in the Schedule of Assessments between the core safety and optional tolvaptan treatment components. This amendment is also intended to reduce burden on the subject, including the replacement of Months 2 and 4 in-clinic visits with telephone assessments. Therefore assessments required for in clinic visits on these months have been removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 October 2017	Terminated. Issues with recruitment and enrollment made the trial impossible or highly impracticable. Termination of this trial was not due to safety reasons.	-

Notes:

Limitations and caveats

None reported