22 June 2023
EMA/CHMP/158910/2023
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Jinarc

tolvaptan

Procedure no: EMEA/H/C/002788/P46/010

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 10 Feb 2023, the MAH submitted a completed paediatric study for paediatric heart failure patients aged from 6 months to less than 15 years with volume overload, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that *A Phase 3, multicenter, open-label, dose-defining trial to investigate the efficacy, safety, pharmacokinetics and pharmacodynamics of Tolvaptan in male and female paediatric heart failure patients aged from 6 months to less than 15 years with volume overload* (study number:156-102-00123) is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Pharmaceutical formulations used in this study included Tolvaptan 1% granules or tolvaptan 15 mg tablets not approved in EU.

2.3. Clinical aspects

2.3.1. Introduction

Jinarc (tolvaptan) has been authorised in EU since on 27/05/2015. The approved pharmaceutical forms are tablets 15, 30, 45, 60, 90 mg. The approved indication is:

Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease (see section 5.1).

Regarding the paediatric population, the safety and efficacy of tolvaptan in children and adolescents has not yet been established. No data are available. Tolvaptan is not recommended in the paediatric age group.

At the time of approval the following obligation to conduct post-authorisation measures, was issued:

Description	Due date
A non-interventional post-authorisation safety study (PASS) to investigate the risks of: • Hepatotoxicity associated with the use of Jinarc. In addition the study should also provide information on • Pregnancy outcomes, in patients treated with Jinarc • Patterns of medicinal product utilisation, especially with regards to off-label use and use in patients over 50 years old • ADRs associated with long term use of Jinarc Final study report should be submitted by:	Q1 2025

Within this procedure, the MAH submitted a final report for:

- Study 156-102-00123: a Phase 3, Multicenter, Open-label, Dose-defining Trial to Investigate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Tolvaptan in Pediatric Heart Failure Patients With Volume Overload.

2.3.2. Clinical study

Study 156-102-00123 - A Phase 3, Multicenter, Open-label, Dose-defining Trial to Investigate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Tolvaptan in Pediatric Heart Failure Patients With Volume Overload.

Description

This was a Phase 3, multicenter, open-label, uncontrolled, dose-titration trial to evaluate the safety and efficacy of tolvaptan in male and female pediatric heart failure patients with volume overload despite having received conventional diuretic therapy. Pediatric patients aged 6 months to less than 15 years were included. The target number of subjects for receiving tolvaptan was set at 60. A basic trial design schematic is shown in Figure 9.1-1.

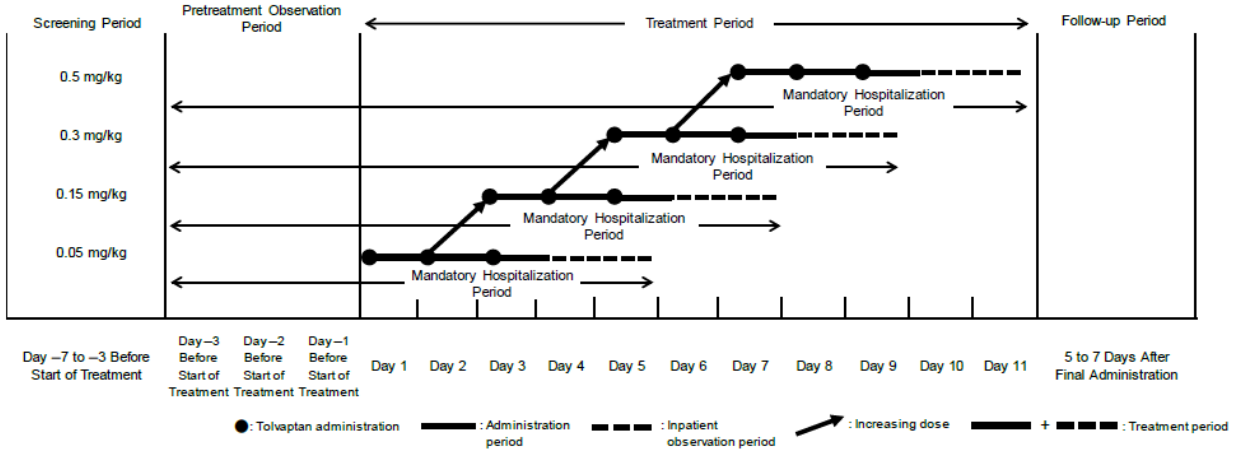


Figure 9.1-1 Basic Trial Design Schematic

After completion of a screening examination, subjects were hospitalized prior to the evening meal on 3 days before start of tolvaptan administration. Tolvaptan administration was started at 0.05 mg/kg/day, and subjects with sufficient increase in urine volume continued administration at 0.05 mg/kg/day for 3 days. For subjects whose urine volume did not sufficiently increase (see below for study rule specifications), the dose was increased to 0.15, 0.3, or 0.5 mg/kg/day according to the specification. In that case, the dose was decided for each individual subject to obtain sufficient increase in urine volume, and administration at the decided dose was continued for 3 days. When the dose was increased to 0.5 mg/kg/day, administration at 0.5 mg/kg/day was continued for 3 days. After final tolvaptan administration, subjects continued to be hospitalized for 2 days, so that their condition could be monitored. Subjects also underwent the follow-up 5 to 7 days after final tolvaptan administration.

Methods

Study participants

The target patients were divided into 3 age groups (6 months to less than 2 years, 2 years to less than 7 years, and 7 years to less than 15 years).

Table 9.3.1-1	Inclusion Criteria
1	Male or female patients age 6 months to less than 15 years at the time of informed consent by a legal representative
2	Patients with volume overload despite having received any of the following diuretic therapies in whom sufficient effects could not be expected even if the dose of the diuretics was increased or in whom the investigator or subinvestigator judged that increasing the dose of the diuretics was difficult due to concerns regarding electrolyte abnormalities or other side effects • Furosemide (oral administration) ≥0.5 mg/kg/day Azosemide 30 mg and torasemide 4 mg were to be calculated as equivalent to furosemide 20 mg. • Hydrochlorothiazide ≥2 mg/kg/day • Trichlormethiazide ≥0.05 mg/kg/day • Spironolactone ≥1 mg/kg/day
3	Patients capable of complaining of thirst. Patients unable to complain of thirst due to their young age could also be enrolled in the trial if strict management of fluid intake and excretion was conducted (frequent monitoring during the 8 hours after start of tolvaptan administration and at the time of dose-increase, and at least as frequent as every 8 hours at other times). However, even if such fluid management was possible, patients in whom the investigator or subinvestigator judged that tolvaptan could not be safely administered were to be excluded.
4	Patients who were able to be hospitalized from at least 3 days before start of tolvaptan administration until 2 days after final administration

Table 9.3.2-1	Exclusion Criteria
1	Patients whose volume overload status showed improvement during the screening period or pretreatment observation period
2	Patients who were unable to drink fluid (including patients who were unable to sense thirst)
3	Patients whose circulatory blood flow was suspected to be decreased
4	Patients with an assisted circulation apparatus
5	Patients with hypernatremia (serum or blood sodium concentration exceeding 145 mEq/L)
6	Patients with serum or blood potassium concentration exceeding the upper limit of the reference range for their age and gender
7	Patients with a history or concurrent condition of liver impairment, including those with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 times the upper limit of the reference range for their age and gender at the time of the screening examination or during the pretreatment observation period
8	Patients with serum creatinine corresponding to Stage 3 or higher in the CKD Stage Assessment Using Serum Creatinine Level (mg/dL) Chart[5] in the renal function assessment at the time of diagnosis of pediatric chronic kidney disease (pediatric CKD)
9	Patients with anuria
10	Patients with urinary excretion disorders due to urinary stenosis, urinary calculus, tumor, etc.
11	Patients who had participated in any other trials within 30 days prior to informed consent by a legal representative
12	Patients who had received tolvaptan therapy before
13	Female patients who were breastfeeding or who tested positive in pregnancy test prior to tolvaptan administration
14	Female patients who were pregnant or suspected of being pregnant, or patients who were unable to agree to remain fully abstinent during the trial and for 30 days after last dose of IMP

15	Breastfed patients (excluding those patients whose fluid intake could be measured by expressed breast milk or other ways, and whose mother did not use any of prohibited/restricted concomitant medications from 1 week before informed consent to completion of an examination 2 days after final administration)
16	Patients who were judged to be ineligible to participate in this trial by the investigator or subinvestigator.

CKD: chronic kidney disease

Treatments

Subjects took tolvaptan 1% granules or tolvaptan 15 mg tablet with water once daily after breakfast.

The dose of tolvaptan 1% granules to be administered was determined depending on the subject's body weight on the day before start of tolvaptan administration; however, the maximum dose was 15 mg/day even if the calculated dose exceeded 15 mg/day. For administration at the maximum dose of 15 mg, tolvaptan 15-mg tablet was allowed to be administered in place of tolvaptan 1% granules.

The initial dose of tolvaptan was 0.05 mg/kg/day. From the second day of the treatment period and onward, if necessary the dose could be increased to 0.15, 0.3, or 0.5 mg/kg/day according to the increase in urine volume. Decision on up-titration was based on daily urine volume. Dose increase was considered in cases of "insufficient increase in urine volume" when it was less than 150% of that for the pretreatment observation period (one day before the start of tolvaptan administration), while "sufficient increase in urine volume" was at least 150%. The dose decided for each individual subject was administered for 3 days. and then the dose decided for each individual subject was administered for 3 days.

Objective(s)

Primary: To determine the efficacy, safety, and dose and regimen of tolvaptan in pediatric heart failure patients with volume overload.

Secondary: To determine the pharmacokinetics and pharmacodynamics of tolvaptan when administered to pediatric heart failure patients with volume overload.

Outcomes/endpoints

Primary Endpoint

The percentage of subjects who satisfied the following condition:

- Body weight on the day after the third day of treatment with tolvaptan at the evaluation dose was decreased by 1.7% or more from the weight measured before breakfast on the first day of the treatment period (the initial tolvaptan administration day).

However, the mean daily urine volume for the 3 days of treatment with tolvaptan at the evaluation dose had to be higher than the daily urine volume for the pretreatment observation period. For subjects who discontinued treatment with tolvaptan, the mean daily urine volume up to the time of discontinuation had to be higher than the daily urine volume for the pretreatment observation period.

Secondary Endpoints

- Body weight

- Edematous symptoms (edema [lower limbs, eyelids, etc], dyspnea, jugular venous distension, pulmonary congestion, cardiothoracic ratio, respiration rate at rest, pulse rate, and pleural effusion),

central venous pressure (only subjects with central venous catheterization), and retention of pericardial effusion (only subjects requiring echocardiography to confirm retention of pericardial effusion prior to tolvaptan administration)

- Daily urine volume

Sample size

For the primary endpoint, the required sample size was set by first setting the threshold value for assessment of efficacy, and then using binomial distribution to determine the number of subjects required to maintain a 90% or higher probability that the lower limit of the 95% CI for the percentage of subjects achieving the primary endpoint above the threshold value.

As reference information for the threshold value and binomial distribution parameter required to set the sample size for the trial, a threshold of 0.3 and a binomial distribution parameter of 0.5 to 0.6 were used based on interviews with clinicians, since no clinical trial results for administration of tolvaptan in pediatric patients have been obtained either in Japan or other countries.

Based on the above, the required number of subjects was calculated to be a minimum of 68 for a parameter of 0.5 and a minimum of 30 for a parameter of 0.6. A sample size of 30 to 68 subjects was therefore considered to be appropriate, and in view of feasibility the number of subjects for the trial was set at 60.

Randomisation and blinding (masking)

Not applicable

Statistical Methods

The full analysis set (FAS) includes all subjects who received at least 1 dose of the IMP and have postdose data on body weight and daily urine volume.

The dose maintenance analysis set includes all subjects who received administration at same dose for at least 3 days in the full analysis set.

The safety analysis set (SAS) includes all subjects who received at least 1 dose of the IMP.

The pharmacokinetic analysis set includes all subjects who received at least 1 dose of the IMP and have postdose data on drug concentration.

The pharmacodynamic analysis set includes all subjects who received at least 1 dose of the IMP and have postdose pharmacodynamic data.

For the primary endpoint analysis, the number and percentage of subjects as well as the exact 95% CI based on binomial distribution were calculated. The same calculations were performed for body weight on the day after the final administration at the evaluation dose and the day after the final administration. The number and percentage of subjects was also calculated for each time point after the start of administration at the evaluation dose (the data to be summarized are from the first day of administration at the evaluation dose to the day after the final administration at the evaluation dose and follow-up period; the same shall apply hereinafter).

Similar calculations were performed for the percent change in body weight as secondary endpoint. For edematous signs, a shift table was prepared for changes in the degree of edema (lower limbs) from baseline to the third day of administration at the evaluation dose, the day of the final administration at the evaluation dose, and the day of the final administration. In addition, the number and percentage

of subjects as well as the exact 95% CI based on binomial distribution was calculated for the improvement rate (the percentage of subjects who had symptoms at baseline and showed remarkable improvement or improvement after the IMP administration) and the disappearance rate (the percentage of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration) on the third day of administration at the evaluation dose, the day of the final administration at the evaluation dose, and the day of the final administration. Analysis was also performed using data collected immediately before the start of administration at the evaluation dose as the baseline (the phrase "after the IMP administration" for the improvement and disappearance rates was read as that of "after the start of administration at the evaluation dose").

A shift table was prepared for changes in the degree of pulmonary congestion from baseline through the day after the final administration. The number and percentage of subjects as well as the exact 95% CI based on the binomial distribution was calculated for the improvement and disappearance rates on the day after the final administration.

Subgroup analyses and analyses by the evaluation dose of the primary endpoint, percent changes in body weight, and edematous symptoms were performed for (the day after) the third day of administration at the evaluation dose, the day of (or the day after) the final administration at the evaluation dose, and the day of (or the day after) the final administration (except for the summarization by the number of days that had elapsed since the start of administration).

Protocol Deviations

Table 10.2-1 Major Protocol Deviations (Subjects Treated with the Investigational Medicinal Product)

Deviation classification	Total (N=60) n (%)[a]
Subject with any protocol deviations	2 (3.3)
- Dosing	1 (1.7)
- Inclusion/exclusion criteria	0 (0.0)
- Met withdrawal criteria but was not withdrawn	1 (1.7)
- Prohibited concomitant medications	0 (0.0)

[a]Percentages are based on the number of IMP administered subjects.
Source: CT-2.1

Results

Participant flow

Table 10.1-1 Subject Disposition and Reasons for Discontinuation (Subjects Treated With the Investigational Medicinal Product)

Subjects:	Total n (%)[a]
Screened	67
IMP administered	60
Completed	46 (76.7)
Discontinued	14 (23.3)
Consent withdrawn	1 (1.7)
Violation of inclusion/exclusion criteria	0 (0.0)
Adverse event	0 (0.0)
Use of prohibited concomitant drug	0 (0.0)
Change of a restricted concomitant drug	0 (0.0)
Necessity of 2 step decreasing or more	0 (0.0)
AST/ALT is more than or equal to 3 times ULN	0 (0.0)
Serum or blood sodium increased by 12 mEq/L or more within 24 hr postdose	0 (0.0)
Serum or blood sodium increased by 8 mEq/L or more at 8-12 hr postdose	0 (0.0)
Serum or blood sodium exceeded 145 mEq/L	3 (5.0)
Serum or blood potassium exceeded ULN	6 (10.0)
Pregnancy	0 (0.0)
Lost to follow-up	0 (0.0)
Other[b]	4 (6.7)
Subjects with extended administration	3 (5.0)
Subjects with dose reduction	0 (0.0)

[a]Percentages are based on the number of IMP administered subjects.

[b]Discontinued reason by subject:

[redacted]; Investigator judged that it was difficult to continue the clinical trial because of the heavy mental and physical burden on patient and [redacted] parents due to frequent blood sampling.

[redacted]; It is difficult to increase the amount of investigational product because fluid retention has already improved.

[redacted]; The dose of the treatment drug could not be increased for the safety of the subjects because the weight was decreased.

[redacted]; Serum sodium concentration increased (Serum or blood sodium at 4 to 6 hours after study drug administration increased by 8 mEq/L or more from just before administration).

Source: CT-1.1, CT-2.2, 16.2.1.1

Recruitment

There was no gender difference in the 59 subjects included in the FAS (male: 28, female: 31). The mean age was 5.44 years, and the median (range) was 3.00 (0.0 to 14.0) years. By age group, young age (6 months to less than 2 years) accounted for 33.9% (20/59 subjects), middle age (2 years to less than 7 years) for 27.1% (16/59 subjects), and old age (7 years to less than 15 years) for 39.0% (23/59 subjects). The mean body weight was 18.9 kg and the median (range) was 13.1 (4.6 to 56.3) kg. The percentage of subjects with a history of surgery was 66.1% (39/59 subjects).

Table 11.2-1 Demographic and Other Baseline Characteristics (FAS)		
Baseline characteristics		**Tolvaptan (n=59)**
Sex [n(%)]	Male	28 (47.5)
	Female	31 (52.5)
	Undifferentiated	0 (0.0)
Race [n(%)]	American Indian or Alaska Native	0 (0.0)
	Asian	59 (100.0)
	Black or African American	0 (0.0)
	Native Hawaiian or other Pacific Islander	0 (0.0)
	White	0 (0.0)
	Other	0 (0.0)
Age[a] (years)	N	59
	Mean	5.44
	SD	5.03
	Min	0.0
	Median	3.00
	Max	14.0
Age[a] category [n(%)]	6 months - 1 year	20 (33.9)
	2 - 6 years	16 (27.1)
	7 - 14 years	23 (39.0)
Weight (kg)	N	59
	Mean	18.94
	SD	13.94
	Min	4.6
	Median	13.10
	Max	56.3
Height (cm)	N	59
	Mean	102.22
	SD	31.81
	Min	61.8
	Median	95.00
	Max	164.5
BMI (kg/m^2)	N	59
	Mean	15.76
	SD	3.93
	Min	11.0
	Median	14.60
	Max	39.0
Medical history [n(%)]	No	14 (23.7)
	Yes	45 (76.3)
Current symptoms [n(%)]	No	1 (1.7)
	Yes	58 (98.3)
Surgical history [n(%)]	No	20 (33.9)
	Yes	39 (66.1)

Baseline data

Table 11.2-2 Baseline Disease Evaluation (FAS)		
Baseline disease evaluation		**Tolvaptan (n=59)**
Lower limb edema [n(%)]	None	22 (37.3)
	Mild	35 (59.3)
	Moderate	1 (1.7)
	Severe	0 (0.0)
	Not done	1 (1.7)
Eyelid edema [n(%)]	Present	26 (44.1)
	Absent	33 (55.9)
Dyspnea [n(%)]	Present	7 (11.9)
	Absent	52 (88.1)
Jugular venous distension [n(%)]	Present	23 (39.0)
	Absent	36 (61.0)
Resting respiratory rate (breaths/min)	N	59
	Mean	27.6
	SD	8.1
	Min	16
	Median	26.0
	Max	48
Pulse rate (beats/min)	N	59
	Mean	104.0
	SD	24.2
	Min	56
	Median	102.0
	Max	165
Pulmonary congestion [n(%)]	None	16 (27.1)
	Mild	32 (54.2)
	Moderate	11 (18.6)
	Severe	0 (0.0)
Cardiothoracic ratio (%)	N	59
	Mean	57.54
	SD	8.09
	Min	38.0
	Median	58.00
	Max	79.0
Pleural effusion [n(%)]	Present	11 (18.6)
	Absent	48 (81.4)

Source: CT-3.2.1

Table 11.2-3 Use of Concomitant Medications on Day 1 (FAS)		
Concomitant medications		**Tolvaptan (N=59) n (%)**
Category of diuretic	Monotherapy with loop diuretic	6 (10.2)
	Loop diuretic + Thiazide diuretic	1 (1.7)
	Loop diuretic + Anti-aldosterone drug	45 (76.3)
	Loop diuretic + Thiazide diuretic + Anti-aldosterone drug	7 (11.9)
Use of thiazide diuretic	Yes	8 (13.6)
	No	51 (86.4)
Use of anti-aldosterone drug	Yes	52 (88.1)
	No	7 (11.9)
Use of drugs for heart failure other than diuretics	Yes	23 (39.0)
	No	36 (61.0)
Use of CYP3A4 inducers	Yes	0 (0.0)
	No	59 (100.0)
Use of CYP3A4 inhibitors	Yes	0 (0.0)
	No	59 (100.0)

Source: CT-4.1

Number analysed

Table 11.1-1 Disposition of Analysis Sets (Subjects Treated With the Investigational Medicinal Product)	
	Total n (%)[a]
IMP administered	60
Full analysis set[b]	59 (98.3)
Dose maintenance set[c]	47 (78.3)
Pharmacokinetics analysis set[d]	44 (73.3)
Pharmacodynamics analysis set[e]	60 (100.0)
Safety analysis set[f]	60 (100.0)

[a]Percentages are based on the number of IMP administered subjects.

[b]Subjects who received at least one dose of IMP and have at least one post-baseline measurement of both body weight and daily urine volume are included in the full analysis set.

[c]Of the subjects in full analysis set, those in whom received same dose of tolvaptan for 3 days are included in the dose maintenance set.

[d]Subjects who received at least one dose of IMP and have at least one post-baseline pharmacokinetics measurement are included in the pharmacokinetics analysis set.

[e]Subjects who received at least one dose of IMP and have at least one post-baseline pharmacodynamics measurement are included in the pharmacodynamics analysis set.

[f]Subjects who received at least one dose of IMP are included in the safety analysis.

Pharmacokinetics results

Time points of blood sampling

Blood was to be collected before administration, and at 2 to 4, 10 to 14, and approximately 24 hours after administration on the third day of treatment with tolvaptan at 0.05, 0.15, 0.3, or 0.5 mg/kg/day.

Rationale for the time points of blood sampling: To determine the pharmacokinetics of tolvaptan in pediatric heart failure patients, data on the plasma concentrations of tolvaptan (OPC-41061) and its metabolites (DM-4103 and DM-4107) were to be collected. For the time points of blood sampling, a trial in adult CHF patients (Trial 156-06-004) was referred to. As a result of consideration, a total of 4 time points (before administration, at around the peak time [2 to 4 hours after administration], and at times in an elimination phase [10 to 14 hours and 24 hours after administration]) were set, so that the pharmacokinetic parameters of tolvaptan (OPC-41061) could be determined by a population pharmacokinetic analysis, which was to be separately conducted.

In the pharmacokinetic analysis set, the plasma concentrations of tolvaptan (OPC-41061) and its metabolites (DM-4103 and DM-4107) were summarized by descriptive statistics, in the following 2 ways. The doses used for tabulation (0.05, 0.15, 0.3, and 0.5 mg/kg/day) were those on the date of blood sampling.

- Summarization for each compound, time point of blood sampling, and dose

- Summarization for each compound, time point of blood sampling, dose, and age group (young age, 6 months to less than 2 years; middle age, 2 years to less than 7 years; and old age, 7 years to less than 15 years)

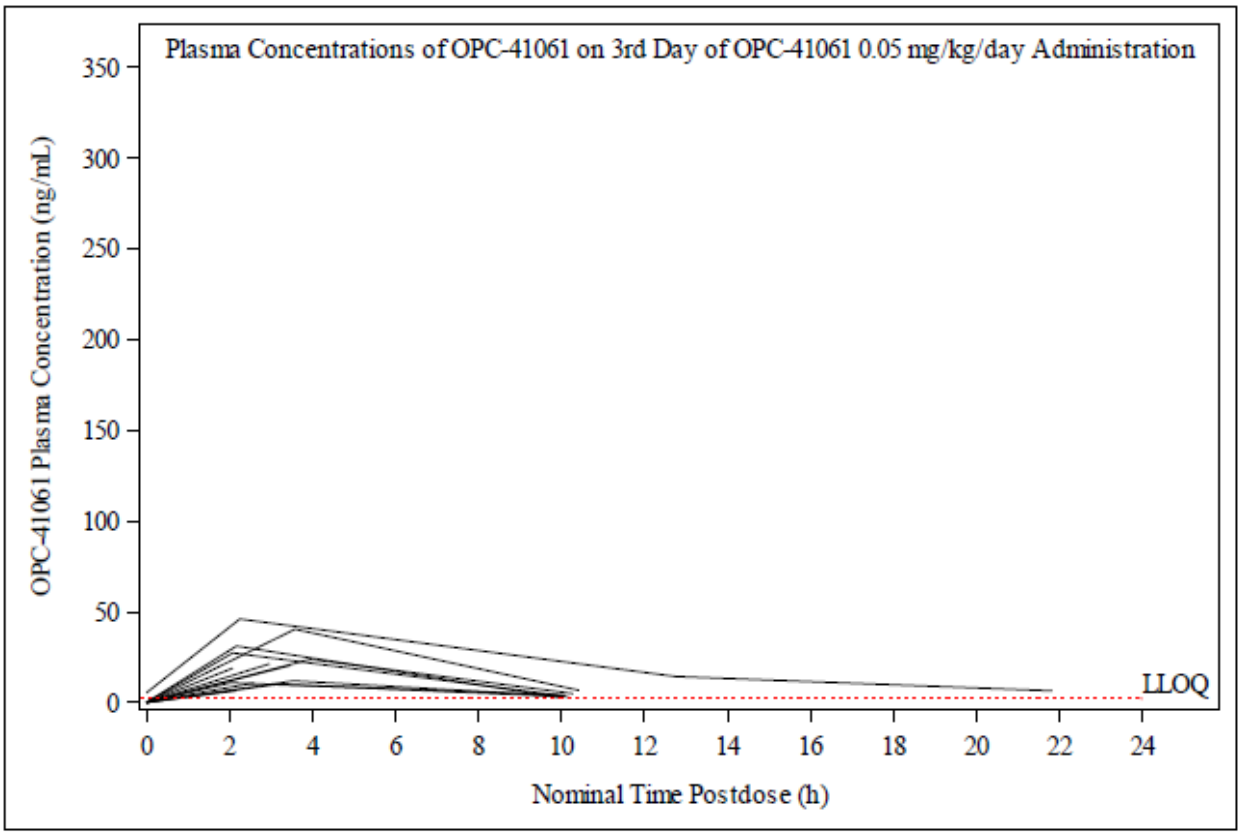
Descriptive statistics to be determined were the number of subjects, mean, SD, coefficient of variation, minimum, median, and maximum.

The population pharmacokinetic analysis of tolvaptan (OPC-41061) was to be separately performed and reported.

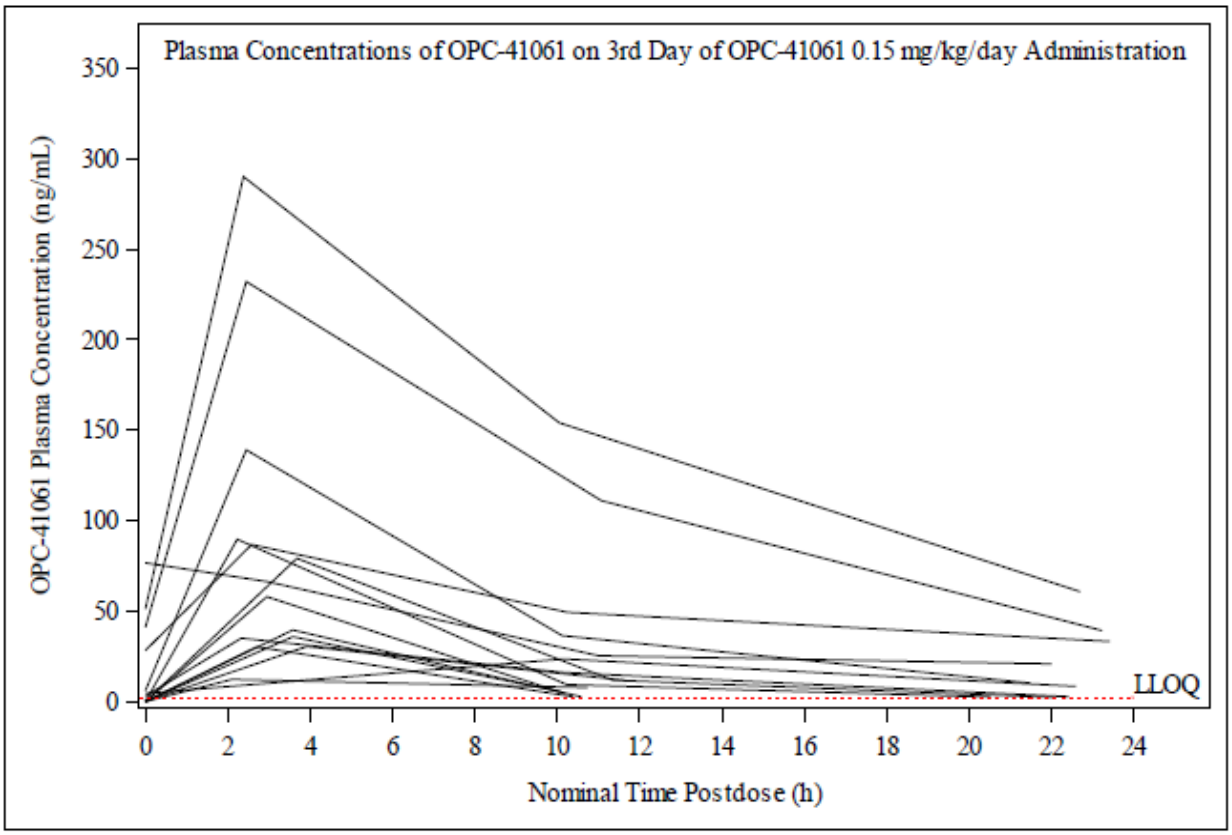
Pharmacokinetic results

For tolvaptan (OPC-41061) the changes in the plasma concentrations by subject are shown in the figures below.

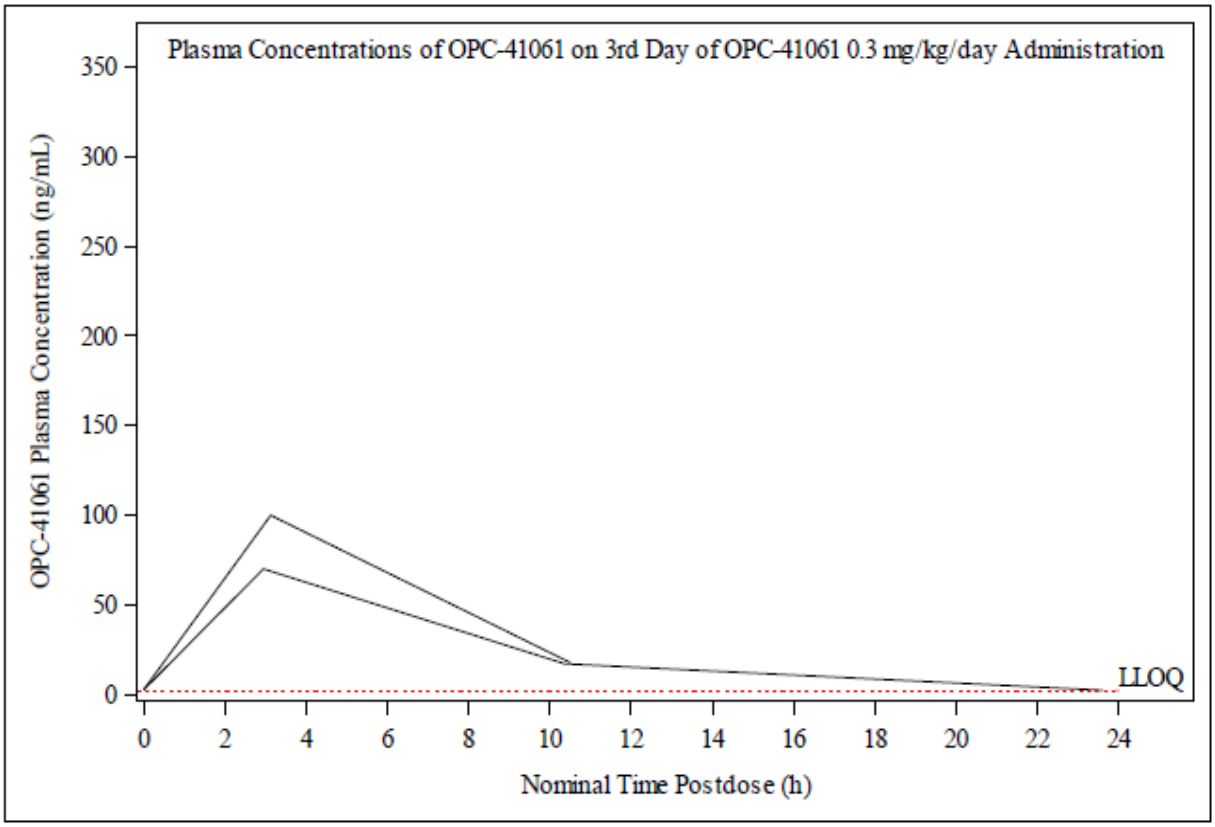
Individual OPC-41061 Plasma Concentrations on the Third Day of Administration at Each Dose
(Pharmacokinetics Analysis Set)



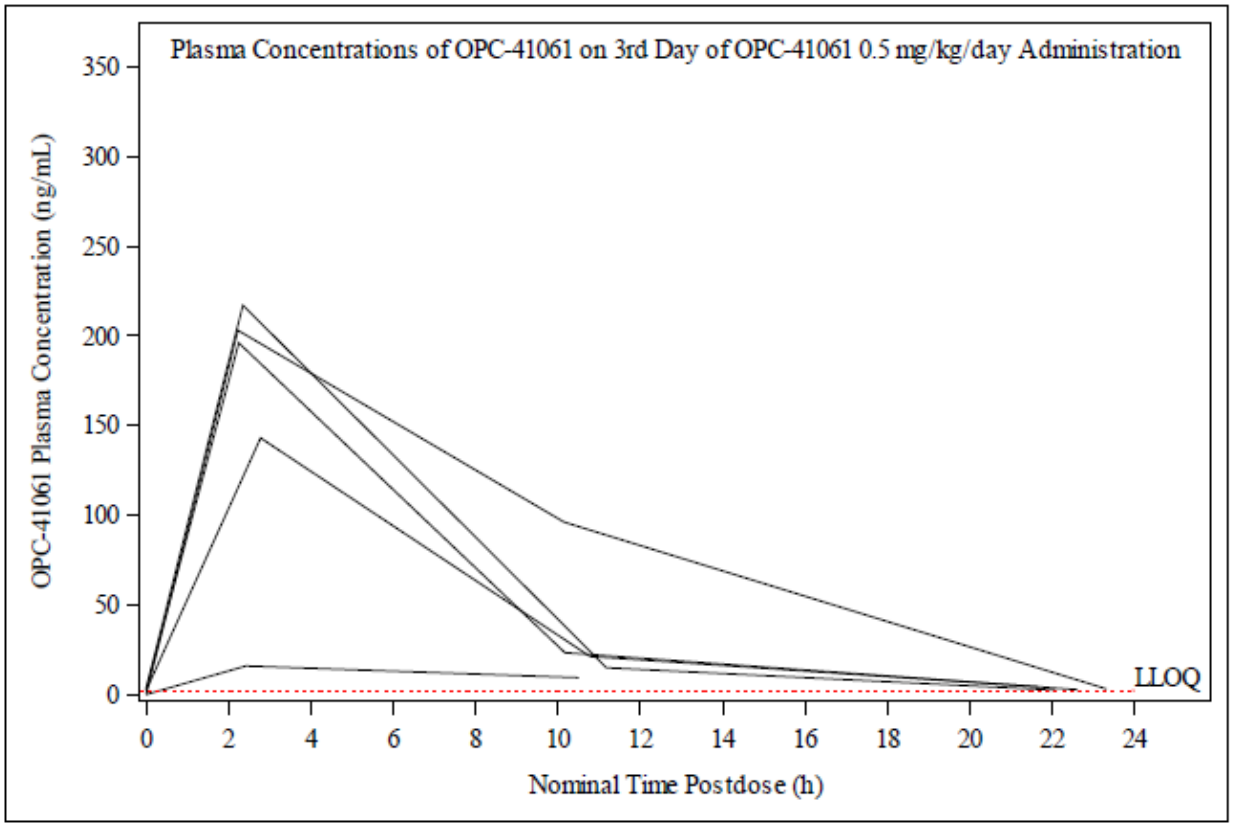
Individual OPC-41061 Plasma Concentrations on the Third Day of Administration at Each Dose
(Pharmacokinetics Analysis Set)



Individual OPC-41061 Plasma Concentrations on the Third Day of Administration at Each Dose
(Pharmacokinetics Analysis Set)



Individual OPC-41061 Plasma Concentrations on the Third Day of Administration at Each Dose
(Pharmacokinetics Analysis Set)



The plasma concentrations (mean) of tolvaptan (OPC-41061) reached the maximum values at 2 to 4 hours after administration at all of the evaluation doses of 0.05, 0.15, 0.3, and 0.5 mg/kg/day, and decreased at 10 to 14 hours after administration and at approximately 24 hours after administration. The plasma concentrations of tolvaptan (OPC-41061) at approximately 24 hours after administration were below the lower limit of quantitation (2.00 ng/mL) in 12/13 subjects at 0.05 mg/kg/day, in 5/14 subjects at 0.15 mg/kg/day, in 1/2 subject at 0.3 mg/kg/day, and in 1/5 subject at 0.5 mg/kg/day. The plasma concentrations (mean) at 2 to 4 hours after administration were comparable to those at baseline at 0.15 and 0.3 mg/kg/day, but generally increased in proportion to the evaluation dose.

The plasma concentrations (mean) of DM-4103 at each evaluation dose were highest at 10 to 14 hours after administration or at approximately 24 hours after administration. The plasma concentrations (mean) of DM-4107 at each evaluation dose reached the peak at 2 to 4 or 10 to 14 hours after administration, and decreased at approximately 24 hours after administration.

The number of subjects included in the pharmacokinetic analyses by evaluation dose and by age group, in the order of young, middle, and old age, was 3, 2, and 8 subjects at 0.05 mg/kg/day; 5, 2, and 8 subjects at 0.15 mg/kg/day; 1, 1, and 0 subjects at 0.3 mg/kg/day; and 3, 0, and 2 subjects at 0.5 mg/kg/day. It was limited to 2 or fewer subjects in 1 or more age groups, at all of the evaluation doses. The plasma concentrations (mean) of tolvaptan (OPC-41061) at 0.05 and 0.15 mg/kg/day, at which plasma drug concentration results were obtained in all age groups, showed no trends that were dependent on age-group.

Pharmacodynamic results

All 60 subjects who had received the IMP were included in the pharmacodynamics analysis set.

Daily Urine Volume

For measured values and percent changes from baseline in daily urine volume (mL) in the FAS, descriptive statistics at each time point after the start of administration at the evaluation dose are shown in Table 11.5.3.3.1.1-1.

Table 11.5.3.3.1.1-1 Measured Values and Percent Changes From Baseline in Daily Urine Volume (mL) - Time Points After the Start of Administration at the Evaluation Dose - (FAS)

Timepoint of evaluation dose	n[a]	Mean	SD	%Change from baseline			
				n[b]	Baseline mean	Mean	SD
Baseline	59	880.2	500.7				
Day 1	58	1367.2	898.6	58	883.7	53.1	52.9
Day 2	53	1321.7	810.8	53	909.4	47.8	43.3
Day 3	46	1248.9	749.1	46	859.4	45.8	29.3
Day 4	3	1767.7	570.1	3	792.0	119.2	37.5
Day 5	1	566.0		1	623.0	−9.1	

Note: Baseline is defined as 24 hours from Day −1 to Day 1 before IMP administration at treatment period.

For daily urine volume, subjects are counted on the accurately measured data of daily urine volume.

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

The percent changes (mean ± SD) from baseline in daily urine volume show increases for the 3 days after the start of administration at the evaluation dose compared to baseline.

The percent changes (mean ± SD) in daily urine volume from before the start of administration at the evaluation dose show increases for the 3 days after the start of administration at the evaluation dose compared to that before the start of administration at the evaluation dose.

Descriptive statistics of the measured values and percent changes from baseline in daily urine volume (mL) at each time point after the start of administration at the evaluation dose in the dose maintenance analysis set are shown by evaluation dose in Table 11.5.3.3.1.1-2.

The percent change (mean) was largest at the evaluation dose of 0.05 mg/kg/day and smallest at 0.5 mg/kg/day. No evaluation dose-dependent changes were observed.

Table 11.5.3.3.1.1-2 Measured Values and Percent Changes From Baseline in Daily Urine Volume (mL) - Time Points After the Start of Administration at the Evaluation Dose -: Analysis by Evaluation Dose (Dose Maintenance Analysis Set)

Evaluation dose	Timepoint of evaluation dose	n[a]	Mean	SD	%Change from baseline			
					n[b]	Baseline mean	Mean	SD
0.05 mg/kg/day	Baseline	16	929.9	462.7				
	Day 1	16	1767.9	1076.0	16	929.9	86.4	67.2
	Day 2	16	1530.6	797.4	16	929.9	70.7	44.3
	Day 3	16	1353.9	738.7	16	929.9	45.1	31.9
0.15 mg/kg/day	Baseline	19	901.9	624.9				
	Day 1	19	1358.8	887.5	19	901.9	56.5	48.9
	Day 2	18	1429.8	971.8	18	937.6	58.5	45.5
	Day 3	18	1367.6	864.3	18	896.3	58.0	28.8
	Day 4	3	1767.7	570.1	3	792.0	119.2	37.5
	Day 5	1	566.0		1	623.0	−9.1	
0.3 mg/kg/day	Baseline	4	739.5	399.5				
	Day 1	4	1168.0	642.4	4	739.5	57.5	3.3
	Day 2	4	863.3	631.2	4	739.5	10.5	28.8
	Day 3	4	1023.0	649.0	4	739.5	34.5	13.8
0.5 mg/kg/day	Baseline	8	695.4	288.4				
	Day 1	8	808.6	410.6	8	695.4	14.7	11.3
	Day 2	8	889.4	514.4	8	695.4	23.7	17.6
	Day 3	8	885.0	449.2	8	695.4	25.2	16.6

Note: Baseline is defined as 24 hours from Day −1 to Day 1 before IMP administration at treatment period.

For daily urine volume, subjects are counted on the accurately measured data of daily urine volume.

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

When analysed by age subgroups, the results showed increases compared to baseline for the 3 days after the start of administration at the evaluation dose in all age groups. The percent changes were slightly smaller in the young age group than in the middle and old age groups.

Table 11.5.3.3.5.1-1 Measured Values and Percent Changes From Baseline in Daily Urine Volume (mL) - Time Points After the Start of Administration at the Evaluation Dose -: Subgroup Analysis by Age Group (FAS)

Age category	Timepoint	n[a]	Mean	SD	%Change from baseline			
					n[b]	Baseline mean	Mean	SD
6 months - 1 year	Baseline	20	516.8	181.5				
	Day 1	20	649.9	206.0	20	516.8	28.9	25.5
	Day 2	20	642.5	180.4	20	516.8	33.4	39.4
	Day 3	17	626.2	208.4	17	482.8	32.0	27.5
	Day 4	1	1128.0		1	623.0	81.1	
	Day 5	1	566.0		1	623.0	−9.1	
2 - 6 years	Baseline	16	759.4	330.4				
	Day 1	15	1182.0	597.5	15	765.1	55.5	46.1
	Day 2	11	1325.5	391.9	11	885.5	56.5	42.3
	Day 3	10	1199.7	519.5	10	753.4	58.7	20.6
7 - 14 years	Baseline	23	1280.1	510.0				
	Day 1	23	2111.7	870.3	23	1280.1	72.7	66.4
	Day 2	22	1937.4	830.0	22	1278.3	56.4	45.7
	Day 3	19	1832.0	709.2	19	1252.2	51.3	30.9
	Day 4	2	2087.5	190.2	2	876.5	138.3	25.0

Note: Baseline is defined as 24 hours from Day −1 to Day 1 before IMP administration at treatment period.
For daily urine volume, subjects are counted on the accurately measured data of daily urine volume.
[a]Number of treated subjects with evaluation of the given parameter at each timepoint.
[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

Daily Fluid Intake

For measured values and changes from baseline in daily fluid intake (mL) in the pharmacodynamic analysis set, descriptive statistics at each time point after the start of administration at the evaluation dose are shown in Table 11.5.3.3.1.2-1.

Table 11.5.3.3.1.2-1 Measured Values and Changes From Baseline in Daily Fluid Intake (mL) - Time Points After the Start of Administration at the Evaluation Dose - (Pharmacodynamic Analysis Set)

Timepoint of evaluation dose	n[a]	Mean	SD	Change from baseline			
				n[b]	Baseline mean	Mean	SD
Baseline	59	850.1	456.1				
Day 1	58	1225.3	732.4	57	841.8	388.5	498.4
Day 2	55	1186.5	598.8	54	830.8	349.1	387.9
Day 3	46	1181.0	584.7	45	794.1	387.6	343.8
Day 4	3	1071.7	101.9	3	767.0	304.7	231.4
Day 5	1	764.0		1	781.0	−17.0	

Note: Baseline is defined as 24 hours from Day −1 to Day 1 before IMP administration at treatment period.
[a]Number of treated subjects with evaluation of the given parameter at each timepoint.
[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

The changes (mean ± SD) from baseline in daily fluid intake show increases for the 3 days after the start of administration at the evaluation dose compared to baseline.

The changes (mean ± SD) in daily fluid intake from before the start of administration at the evaluation dose show increases for the 3 days after the start of administration at the evaluation dose compared to that before the start of administration at the evaluation dose.

The change (mean) was largest at the evaluation dose of 0.05 mg/kg/day and smallest at 0.5 mg/kg/day. No evaluation dose-dependent changes were observed.

Daily Fluid Balance

For measured values and changes from baseline in daily fluid balance (mL) in the pharmacodynamic analysis set, descriptive statistics at each time point after the start of administration at the evaluation dose are shown in Table 11.5.3.3.1.3-1.

Table 11.5.3.3.1.3-1 Measured Values and Changes From Baseline in Daily Fluid Balance (mL) - Time Points After the Start of Administration at the Evaluation Dose - (Pharmacodynamic Analysis Set)

Timepoint of evaluation dose	n[a]	Mean	SD	Change from baseline			
				n[b]	Baseline mean	Mean	SD
Baseline	59	−31.1	371.1				
Day 1	58	−141.9	444.0	57	−41.6	−96.3	363.7
Day 2	53	−130.1	456.2	52	−65.4	−68.0	338.0
Day 3	46	−67.9	396.5	45	−64.4	0.6	243.3
Day 4	3	−696.0	644.9	3	−25.0	−671.0	580.8
Day 5	1	198.0		1	158.0	40.0	

Note: Baseline is defined as 24 hours from Day −1 to Day 1 before IMP administration at treatment period.
For daily fluid balance, subjects are counted on the accurately measured data of daily urine volume.
[a]Number of treated subjects with evaluation of the given parameter at each timepoint.
[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

The changes (mean ± SD) from baseline in daily fluid balance show decreases on the first and second days of administration at the evaluation dose compared to baseline, but no marked change on the third day.

The changes (mean ± SD) in daily fluid balance from before the start of administration at the evaluation dose show decreases for the 3 days after the start of administration at the evaluation dose compared to that before the start of administration at the evaluation dose.

While no decrease was observed at the evaluation dose of 0.5 mg/kg/day compared to baseline, decreases were observed at 0.05, 0.15, and 0.3 mg/kg/day. No evaluation dose-dependent changes were observed.

When analysed by age subgroups, the results showed decreases for the 3 days after the start of administration at the evaluation dose compared to the time point before the start of administration at the evaluation dose in the middle and old age groups, and decreases on the first and second days of administration at the evaluation dose in the young age group.

Urine Osmolality

For measured values and changes from baseline in urine osmolality (mOsm/L) in the pharmacodynamic analysis set, descriptive statistics at each time point after the start of administration at the evaluation dose are shown in Table 11.5.3.3.2.1-1.

Table 11.5.3.3.2.1-1 Measured Values and Changes From Baseline in Urine Osmolality (mOsm/L) - Time Points After the Start of Administration at the Evaluation Dose - (Pharmacodynamic Analysis Set)

Timepoint of evaluation dose	n[a]	Mean	SD	Change from baseline			
				n[b]	Baseline mean	Mean	SD
Baseline	27	395.5	118.9				
Day 1	24	259.5	81.9	24	426.8	−167.2	139.1
Day 2	24	279.9	72.6	24	400.0	−120.1	117.1
Day 3	19	288.3	83.0	19	406.5	−118.2	110.0
Day 4	2	355.0	113.1	2	558.5	−203.5	30.4

Note: Baseline is defined as 24 hours from Day −1 to Day 1 before IMP administration at treatment period.

For urine osmolality, subjects are counted on the measured data of whole urine collection.

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

The change (mean) from baseline in urine osmolality from the start of administration at the evaluation dose to the third day show a decrease for the 3 days after the start of administration at the evaluation dose compared to baseline.

The change (mean) in urine osmolality from before the start of administration at the evaluation dose to the third day show a decrease for the 3 days after the start of administration at the evaluation dose compared to that before the start of administration at the evaluation dose.

The extent of decrease was largest at the evaluation dose of 0.15 mg/kg/day, for the 3 days after the start of administration. No evaluation dose-dependent changes were observed.

Daily Urine Sodium Excretion

For measured values and changes from baseline in daily urine sodium excretion (mmol) in the pharmacodynamic analysis set, descriptive statistics at each time point after the start of administration at the evaluation dose are shown in Table 11.5.3.3.2.2-1.

Table 11.5.3.3.2.2-1 Measured Values and Changes From Baseline in Daily Urine Sodium Excretion (mmol) - Time Points After the Start of Administration at the Evaluation Dose - (Pharmacodynamic Analysis Set)

Timepoint of evaluation dose	n[a]	Mean	SD	Change from baseline			
				n[b]	Baseline mean	Mean	SD
Baseline	27	92.7523	36.5592				
Day 1	24	98.3555	46.8949	21	96.8092	8.1068	44.7368
Day 2	24	110.0903	78.9868	23	96.5971	15.9758	73.7022
Day 3	19	110.6545	62.5763	19	95.3741	15.2804	43.6134
Day 4	2	204.3355	81.8271	2	100.7890	103.5465	81.9699

Note: Baseline is defined as 24 hours from Day −1 to Day 1 before IMP administration at treatment period.

For daily urine excretion of sodium, subjects are counted on the measured data of whole urine collection.

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

The change (mean) from baseline in daily urine sodium excretion from the start of administration at the evaluation dose to the third day shows no substantial change in daily urine sodium excretion for the3 days after the start of administration at the evaluation dose.

The change (mean) from before the start of administration at the evaluation dose, from the start of administration at the evaluation dose to the third day shows no substantial change in daily urine sodium excretion for the 3 days after the start of administration at the evaluation dose.

Daily Urine Potassium Excretion

For measured values and changes from baseline in daily urine potassium excretion (mmol) in the pharmacodynamic analysis set, descriptive statistics at each time point after the start of administration at the evaluation dose are shown in Table 11.5.3.3.2.3-1.

Table 11.5.3.3.2.3-1 Measured Values and Changes From Baseline in Daily Urine Potassium Excretion (mmol) - Time Points After the Start of Administration at the Evaluation Dose - (Pharmacodynamic Analysis Set)

Timepoint of evaluation dose	n[a]	Mean	SD	Change from baseline			
				n[b]	Baseline mean	Mean	SD
Baseline	27	24.6624	12.8314				
Day 1	24	27.7820	14.1857	21	25.9295	2.9920	10.3541
Day 2	24	30.9433	13.6709	23	25.7177	5.9927	10.8575
Day 3	19	29.2646	10.1271	19	25.2964	3.9682	7.8508
Day 4	2	33.7730	13.5142	2	18.8535	14.9195	8.6288

Note: Baseline is defined as 24 hours from Day −1 to Day 1 before IMP administration at treatment period.

For daily urine excretion of potassium, subjects are counted on the measured data of whole urine collection.

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

The change (mean) from baseline in daily urine potassium excretion from the start of administration at the evaluation dose to the third day shows no substantial change in daily urine potassium excretion for the 3 days after the start of administration at the evaluation dose.

The change (mean) from before the start of administration at the evaluation dose, from the start of administration at the evaluation dose to the third day shows no substantial change in daily urine potassium excretion for the 3 days after the start of administration at the evaluation dose.

Serum Osmolality

For measured values and changes from baseline in serum osmolality (mOsm/L) in the pharmacodynamic analysis set, descriptive statistics at each time point after the start of administration at the evaluation dose are shown in Table 11.5.3.3.3.1-1.

Table 11.5.3.3.3.1-1 Measured Values and Changes From Baseline in Serum Osmolality (mOsm/L) - Time Points After the Start of Administration at the Evaluation Dose - (Pharmacodynamic Analysis Set)

Timepoint of evaluation dose	n[a]	Mean	SD	Change from baseline			
				n[b]	Baseline mean	Mean	SD
Baseline	46	274.8	7.2				
Day 2	42	277.9	5.7	42	275.3	2.6	4.8
Day 4	34	276.5	6.3	34	275.1	1.4	4.6
Follow-up	43	277.1	6.3	43	275.4	1.7	4.7

Note: Baseline is defined as one day before start of IMP administration at treatment period.

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

The changes (mean) from baseline show mild increases for the 3 days after the start of administration at the evaluation dose compared to baseline.

Serum or Blood Sodium Concentration

For measured values and changes from baseline in serum or blood sodium concentration (mEq/L) in the pharmacodynamic analysis set, descriptive statistics at each time point after the start of administration at the evaluation dose are shown in Table 11.5.3.3.3.2-1.

Table 11.5.3.3.3.2-1 Measured Values and Changes From Baseline in Serum or Blood Sodium Concentration (mEq/L) - Time Points After the Start of Administration at the Evaluation Dose - (Pharmacodynamic Analysis Set)

Timepoint of evaluation dose		n[a]	Mean	SD	Change from baseline			
					n[b]	Baseline mean	Mean	SD
Baseline	Pre-breakfast	60	136.65	3.81				
Day 1	4-6h	60	138.00	3.67	60	136.65	1.35	3.43
	8-12h	58	138.03	3.48	58	136.78	1.25	2.87
Day 2	Pre-breakfast	59	137.36	3.23	59	136.72	0.64	3.04
Day 3	Pre-breakfast	55	137.42	3.98	55	136.61	0.81	2.64
Day 4	Pre-breakfast	46	137.06	3.81	46	136.48	0.58	2.98
Day 5	Pre-breakfast	3	138.70	3.73	3	136.50	2.20	4.86
Day 6	Pre-breakfast	1	134.90		1	130.90	4.00	
Follow-up		60	137.96	4.53	60	136.65	1.31	4.03

Note: Baseline is defined as Day 1 before IMP administration at treatment period.
For sodium, when the value measured as the withdrawal examination was used, the timepoint was treated as pre-breakfast.

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

The change (mean) from baseline shows a mild increase for the 3 days after the start of administration at the evaluation dose compared to baseline.

Serum or Blood Potassium Concentration

For measured values and changes from baseline in serum or blood potassium concentration (mEq/L) in the pharmacodynamic analysis set, descriptive statistics at each time point after the start of administration at the evaluation dose are shown in Table 11.5.3.3.3.3-1.

Table 11.5.3.3.3.3-1 Measured Values and Changes From Baseline in Serum or Blood Potassium Concentration (mEq/L) - Time Points After the Start of Administration at the Evaluation Dose - (Pharmacodynamic Analysis Set)

Timepoint of evaluation dose	n[a]	Mean	SD	Change from baseline			
				n[b]	Baseline mean	Mean	SD
Baseline	60	4.237	0.399				
Day 2	59	4.197	0.473	59	4.239	−0.042	0.477
Day 3	55	4.336	0.439	55	4.215	0.121	0.372
Day 4	46	4.249	0.423	46	4.190	0.059	0.406
Day 5	3	4.157	0.348	3	4.267	−0.110	0.531
Day 6	1	4.300		1	4.770	−0.470	
Follow-up	60	4.181	0.440	60	4.237	−0.056	0.477

Note: Baseline is defined as Day 1 before IMP administration at treatment period.

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

The change (mean) from baseline in serum or blood potassium concentration (4.237 mEq/L) from the start of administration at the evaluation dose, to the predose on the fourth day shows no substantial change for the 3 days after the start of administration.

Plasma Arginine Vasopressin Concentration

Descriptive statistics of measured values and changes from baseline in plasma AVP concentration (ng/L) on the day after the final administration in the pharmacodynamics analysis set are shown in Table 11.5.3.3.4-1.

Table 11.5.3.3.4-1 Measured Values and Changes From Baseline in Plasma Arginine Vasopressin Concentration (ng/L) (Pharmacodynamic Analysis Set)

				Change from baseline			
Timepoint	n[a]	Mean	SD	n[b]	Baseline mean	Mean	SD
Baseline	39	2.55	2.94				
Day after final administration	27	6.07	7.87	27	2.56	3.51	8.61

Note: Baseline is defined as one day before start of IMP administration at treatment period.

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

The change (mean ± SD) from baseline in plasma AVP concentration (2.55 ng/L) on the day after the final administration shows an increase compared to baseline.

The changes (mean ± SD) from baseline in plasma AVP concentration on the day after the final administration, by age group show a greater increase in the young age group than in the middle and old age groups.

Pharmacodynamic conclusions

Data by the number of days that had elapsed since the start of the tolvaptan administration showed that the percent change (mean) from baseline in daily urine volume was from 18.9% to 46.4%, and that the changes (mean) in daily fluid intake and daily fluid balance were from 164.5 to 365.5 mL and −98.9 to 18.4 mL, respectively. The daily urine volume and daily fluid intake increased compared to baseline for the 3 days after the start of administration at the evaluation dose. The daily fluid balance decreased compared to baseline on the first and second days of administration at the evaluation dose, but did not change markedly on the third day.

Urine osmolality decreased compared to baseline for the 3 days after the start of administration at the evaluation dose. No significant changes were observed in daily urine sodium excretion or daily urine potassium excretion.

Serum osmolality and serum or blood sodium concentration increased slightly compared to baseline, for the 3 days after the start of administration at the evaluation dose. There were no marked changes in serum or blood potassium concentration.

Plasma AVP concentration on the day after the final administration increased compared to baseline.

Efficacy results

Primary endpoint

Table 11.4.1.1-1 Percentages of Subjects Whose Body Weight Was Decreased by 1.7% or More From Baseline (Under the Condition of Increased Daily Urine Volume) - Time Points After the Start of Administration at the Evaluation Dose - (FAS)

Timepoint of evaluation dose	N[a]	n[b]	(%)	Lower 95%CI	Upper 95%CI
Day 2	57	12	(21.1)		
Day 3	55	14	(25.5)		
Day 4	45	11	(24.4)		
Day 5	3	1	(33.3)		
Day 6	1	0	(0.0)		
Day after Day 3 at evaluation dose (A)	57	13	(22.8)	12.7	35.8
Day after final day at evaluation dose (A)	57	13	(22.8)	12.7	35.8
Day after final administration (A)	59	13	(22.0)	12.3	34.7
Follow-up	59	16	(27.1)		

Note: Baseline is defined as Day 1 before IMP administration at treatment period.
CI = confidence interval (exact).

[a]Number of treated subjects with evaluated at each timepoint.

[b]Number of treated subjects who decreased their body weights by 1.7% or more from baseline under the condition of increased daily urine volume.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-5.1.1

Table 11.4.1.1-2 Percentages of Subjects Whose Body Weight Was Decreased by 1.7% or More From Baseline (Under the Condition of Increased Daily Urine Volume) - Time Points After the Start of Administration at the Evaluation Dose -: Analysis by Evaluation Dose (Dose Maintenance Analysis Set)

Evaluation dose	Timepoint of evaluation dose	N[a]	n[b]	(%)	Lower 95%CI	Upper 95%CI
0.05 mg/kg/day	Day after Day 3 at evaluation dose (A)	16	4	(25.0)	7.3	52.4
	Day after final day at evaluation dose (A)	16	4	(25.0)	7.3	52.4
	Day after final administration (A)	16	4	(25.0)	7.3	52.4
0.15 mg/kg/day	Day after Day 3 at evaluation dose (A)	19	5	(26.3)	9.1	51.2
	Day after final day at evaluation dose (A)	19	5	(26.3)	9.1	51.2
	Day after final administration (A)	19	5	(26.3)	9.1	51.2
0.3 mg/kg/day	Day after Day 3 at evaluation dose (A)	4	1	(25.0)	0.6	80.6
	Day after final day at evaluation dose (A)	4	1	(25.0)	0.6	80.6
	Day after final administration (A)	4	1	(25.0)	0.6	80.6
0.5 mg/kg/day	Day after Day 3 at evaluation dose (A)	8	1	(12.5)	0.3	52.7
	Day after final day at evaluation dose (A)	8	1	(12.5)	0.3	52.7
	Day after final administration (A)	8	1	(12.5)	0.3	52.7

Note: Baseline is defined as Day 1 before IMP administration at treatment period.
CI = confidence interval (exact).

[a]Number of treated subjects with evaluated at each timepoint.

[b]Number of treated subjects who decreased their body weights by 1.7% or more from baseline under the condition of increased daily urine volume.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-5.1.6

Secondary endpoint

Body weight changes

Table 11.4.1.2.1-1 Measured Values and Percent Changes From Baseline in Body Weight (kg) - Time Points After the Start of Administration at the Evaluation Dose - (FAS)

Timepoint of evaluation dose	n[a]	Mean	SD	%Change from baseline					
				n[b]	Baseline mean	Mean	SD	Lower 95%CI	Upper 95%CI
Baseline	59	18.722	13.755						
Day 2	57	18.908	13.800	57	19.001	−0.327	1.952		
Day 3	55	18.947	13.916	55	19.119	−0.626	1.891		
Day 4	45	19.536	14.323	45	19.653	−0.267	2.478		
Day 5	3	25.603	13.323	3	26.120	−0.936	3.468		
Day 6	1	10.520		1	10.010	5.095			
Day after Day 3 at evaluation dose (A)	57	18.871	13.773	57	19.001	−0.371	2.470	−1.026	0.285
Day after final day at evaluation dose (A)	57	18.860	13.755	57	19.001	−0.381	2.558	−1.060	0.298
Day after final administration (A)	59	18.602	13.588	59	18.722	−0.218	2.666	−0.913	0.477
Follow-up	59	18.770	13.783	59	18.722	0.498	3.796		

Note: Baseline is defined as Day 1 before IMP administration at treatment period.
CI = confidence interval (exact).

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.1.1.1

Table 11.4.1.2.1-3 Measured Values and Percent Changes From Baseline in Body Weight (kg) - Time Points After the Start of Administration at the Evaluation Dose -: Analysis by Evaluation Dose (Dose Maintenance Analysis Set)

Evaluation dose	Timepoint of evaluation dose	n[a]	Mean	SD	%Change from baseline					
					n[b]	Baseline mean	Mean	SD	Lower 95%CI	Upper 95%CI
0.05 mg/kg/day	Baseline	16	24.484	15.531						
	Day after Day 3 at evaluation dose (A)	16	24.374	15.569	16	24.484	−0.755	1.541	−1.576	0.067
	Day after final day at evaluation dose (A)	16	24.374	15.569	16	24.484	−0.755	1.541	−1.576	0.067
	Day after final administration (A)	16	24.374	15.569	16	24.484	−0.755	1.541	−1.576	0.067
0.15 mg/kg/day	Baseline	19	20.604	14.199						
	Day after Day 3 at evaluation dose (A)	19	20.402	13.939	19	20.604	−0.200	3.210	−1.747	1.347
	Day after final day at evaluation dose (A)	19	20.367	13.886	19	20.604	−0.231	3.420	−1.880	1.418
	Day after final administration (A)	19	20.367	13.886	19	20.604	−0.231	3.420	−1.880	1.418
0.3 mg/kg/day	Baseline	4	9.273	3.155						
	Day after Day 3 at evaluation dose (A)	4	9.158	3.265	4	9.273	−1.578	2.213	−5.099	1.943
	Day after final day at evaluation dose (A)	4	9.158	3.265	4	9.273	−1.578	2.213	−5.099	1.943
	Day after final administration (A)	4	9.158	3.265	4	9.273	−1.578	2.213	−5.099	1.943
0.5 mg/kg/day	Baseline	8	10.758	9.335						
	Day after Day 3 at evaluation dose (A)	8	10.803	9.348	8	10.758	0.595	2.524	−1.515	2.705
	Day after final day at evaluation dose (A)	8	10.803	9.348	8	10.758	0.595	2.524	−1.515	2.705
	Day after final administration (A)	8	10.803	9.348	8	10.758	0.595	2.524	−1.515	2.705

Note: Baseline is defined as Day 1 before IMP administration at treatment period.
CI = confidence interval (exact).

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.1.1.6

Edema

Table 11.4.1.2.2.1-1 Improvement and Disappearance Rates of Lower Limb Edema - Time Points After the Start of Administration at the Evaluation Dose - (FAS)

Timepoint of evaluation dose	N[a]	Improved				Disappeared			
		n[b]	(%)	Lower 95%CI	Upper 95%CI	n[c]	(%)	Lower 95%CI	Upper 95%CI
Day 3 at evaluation dose (A)	35	24	(68.6)	50.7	83.1	23	(65.7)	47.8	80.9
Final day at evaluation dose (A)	35	25	(71.4)	53.7	85.4	24	(68.6)	50.7	83.1
Day of final administration (A)	35	25	(71.4)	53.7	85.4	24	(68.6)	50.7	83.1

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and showed remarkable improvement or improvement after the IMP administration.

[c]Number of subjects with who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.2.4.1

Table 11.4.1.2.2.1-2 Improvement and Disappearance Rates of Lower Limb Edema - Time Points After the Start of Administration at the Evaluation Dose -: Analysis by Evaluation Dose (Dose Maintenance Analysis Set)

Evaluation dose	Timepoint of evaluation dose	N[a]	Improved				Disappeared			
			n[b]	(%)	Lower 95%CI	Upper 95%CI	n[c]	(%)	Lower 95%CI	Upper 95%CI
0.05 mg/kg/day	Day 3 at evaluation dose (A)	11	9	(81.8)	48.2	97.7	8	(72.7)	39.0	94.0
	Final day at evaluation dose (A)	11	9	(81.8)	48.2	97.7	8	(72.7)	39.0	94.0
	Day of final administration (A)	11	9	(81.8)	48.2	97.7	8	(72.7)	39.0	94.0
0.15 mg/kg/day	Day 3 at evaluation dose (A)	11	8	(72.7)	39.0	94.0	8	(72.7)	39.0	94.0
	Final day at evaluation dose (A)	11	9	(81.8)	48.2	97.7	9	(81.8)	48.2	97.7
	Day of final administration (A)	11	9	(81.8)	48.2	97.7	9	(81.8)	48.2	97.7
0.3 mg/kg/day	Day 3 at evaluation dose (A)	3	3	(100.0)	29.2	100.0	3	(100.0)	29.2	100.0
	Final day at evaluation dose (A)	3	3	(100.0)	29.2	100.0	3	(100.0)	29.2	100.0
	Day of final administration (A)	3	3	(100.0)	29.2	100.0	3	(100.0)	29.2	100.0
0.5 mg/kg/day	Day 3 at evaluation dose (A)	5	2	(40.0)	5.3	85.3	2	(40.0)	5.3	85.3
	Final day at evaluation dose (A)	5	2	(40.0)	5.3	85.3	2	(40.0)	5.3	85.3
	Day of final administration (A)	5	2	(40.0)	5.3	85.3	2	(40.0)	5.3	85.3

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and showed remarkable improvement or improvement after the IMP administration.

[c]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.2.4.6

Eyelid Edema

Table 11.4.1.2.2.1-3 Disappearance Rates of Eyelid Edema - Time Points After the Start of Administration at the Evaluation Dose - (FAS)

Timepoint of evaluation dose	N[a]	Disappeared			
		n[b]	(%)	Lower 95%CI	Upper 95%CI
Day 3 at evaluation dose (A)	26	18	(69.2)	48.2	85.7
Final day at evaluation dose (A)	26	18	(69.2)	48.2	85.7
Day of final administration (A)	26	18	(69.2)	48.2	85.7

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.3.4.1

Table 11.4.1.2.2.1-4 Disappearance Rates of Eyelid Edema - Time Points After the Start of Administration at the Evaluation Dose -: Analysis by Evaluation Dose (Dose Maintenance Analysis Set)

Evaluation dose	Timepoint of evaluation dose	N[a]	Disappeared			
			n[b]	(%)	Lower 95%CI	Upper 95%CI
0.05 mg/kg/day	Day 3 at evaluation dose (A)	7	4	(57.1)	18.4	90.1
	Final day at evaluation dose (A)	7	4	(57.1)	18.4	90.1
	Day of final administration (A)	7	4	(57.1)	18.4	90.1
0.15 mg/kg/day	Day 3 at evaluation dose (A)	9	7	(77.8)	40.0	97.2
	Final day at evaluation dose (A)	9	7	(77.8)	40.0	97.2
	Day of final administration (A)	9	7	(77.8)	40.0	97.2
0.3 mg/kg/day	Day 3 at evaluation dose (A)	1	1	(100.0)	2.5	100.0
	Final day at evaluation dose (A)	1	1	(100.0)	2.5	100.0
	Day of final administration (A)	1	1	(100.0)	2.5	100.0
0.5 mg/kg/day	Day 3 at evaluation dose (A)	4	4	(100.0)	39.8	100.0
	Final day at evaluation dose (A)	4	4	(100.0)	39.8	100.0
	Day of final administration (A)	4	4	(100.0)	39.8	100.0

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.3.4.6

Venous Distension

Table 11.4.1.2.2.2-1 Disappearance Rates of Jugular Venous Distension - Time Points After the Start of Administration at the Evaluation Dose - (FAS)

Timepoint of evaluation dose	N[a]	Disappeared			
		n[b]	(%)	Lower 95%CI	Upper 95%CI
Day 3 at evaluation dose (A)	22	10	(45.5)	24.4	67.8
Final day at evaluation dose (A)	22	10	(45.5)	24.4	67.8
Day of final administration (A)	22	10	(45.5)	24.4	67.8

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.3.4.1

Table 11.4.1.2.2.2-2 Disappearance Rates of Jugular Venous Distension - Time Points After the Start of Administration at the Evaluation Dose -: Analysis by Evaluation Dose (Dose Maintenance Analysis Set)

Evaluation dose	Timepoint of evaluation dose	N[a]	Disappeared			
			n[b]	(%)	Lower 95%CI	Upper 95%CI
0.05 mg/kg/day	Day 3 at evaluation dose (A)	8	4	(50.0)	15.7	84.3
	Final day at evaluation dose (A)	8	4	(50.0)	15.7	84.3
	Day of final administration (A)	8	4	(50.0)	15.7	84.3
0.15 mg/kg/day	Day 3 at evaluation dose (A)	6	3	(50.0)	11.8	88.2
	Final day at evaluation dose (A)	6	3	(50.0)	11.8	88.2
	Day of final administration (A)	6	3	(50.0)	11.8	88.2
0.3 mg/kg/day	Day 3 at evaluation dose (A)	-	-	-	-	-
	Final day at evaluation dose (A)	-	-	-	-	-
	Day of final administration (A)	-	-	-	-	-
0.5 mg/kg/day	Day 3 at evaluation dose (A)	4	1	(25.0)	0.6	80.6
	Final day at evaluation dose (A)	4	1	(25.0)	0.6	80.6
	Day of final administration (A)	4	1	(25.0)	0.6	80.6

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.3.4.6

Pulmonary Congestion

Table 11.4.1.2.2.3-1 Improvement and Disappearance Rates of Pulmonary Congestion on the Day After the Final Administration (FAS)

Timepoint of evaluation dose	N[a]	Improved				Disappeared			
		n[b]	(%)	Lower 95%CI	Upper 95%CI	n[c]	(%)	Lower 95%CI	Upper 95%CI
Day after final administration (A)	31	16	(51.6)	33.1	69.8	13	(41.9)	24.5	60.9

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and showed remarkable improvement or improvement after the IMP administration.

[c]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.2.4.1

Table 11.4.1.2.2.3-2 Improvement and Disappearance Rates of Pulmonary Congestion on the Day after the Final Administration: Analysis by Evaluation Dose (Dose Maintenance Analysis Set)

Evaluation dose	Timepoint of evaluation dose	N[a]	Improved				Disappeared			
			n[b]	(%)	Lower 95%CI	Upper 95%CI	n[c]	(%)	Lower 95%CI	Upper 95%CI
0.05 mg/kg/day	Day after final administration (A)	12	7	(58.3)	27.7	84.8	7	(58.3)	27.7	84.8
0.15 mg/kg/day	Day after final administration (A)	11	7	(63.6)	30.8	89.1	4	(36.4)	10.9	69.2
0.3 mg/kg/day	Day after final administration (A)	2	1	(50.0)	1.3	98.7	1	(50.0)	1.3	98.7
0.5 mg/kg/day	Day after final administration (A)	6	1	(16.7)	0.4	64.1	1	(16.7)	0.4	64.1

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and showed remarkable improvement or improvement after the IMP administration.

[c]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.2.4.6

Pleural Effusion

Table 11.4.1.2.2.4-1 Disappearance Rate of Pleural Effusion on the Day After the Final Administration (FAS)

Timepoint of evaluation dose	N[a]	Disappeared			
		n[b]	(%)	Lower 95%CI	Upper 95%CI
Day after final administration (A)	10	8	(80.0)	44.4	97.5

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.3.4.1

Table 11.4.1.2.2.4-2 Disappearance Rates of Pleural Effusion on the Day After the Final Administration: Analysis by Evaluation Dose (Dose Maintenance Analysis Set)

Evaluation dose	Timepoint of evaluation dose	N[a]	Disappeared			
			n[b]	(%)	Lower 95%CI	Upper 95%CI
0.05 mg/kg/day	Day after final administration (A)	4	2	(50.0)	6.8	93.2
0.15 mg/kg/day	Day after final administration (A)	3	3	(100.0)	29.2	100.0
0.3 mg/kg/day	Day after final administration (A)	2	2	(100.0)	15.8	100.0
0.5 mg/kg/day	Day after final administration (A)	1	1	(100.0)	2.5	100.0

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.3.4.6

Daily Urine Volume

The percent changes (mean ± SD) from baseline in daily urine volume in the full analysis set were 53.1 ± 52.9% on the first day of administration at the evaluation dose, 47.8 ± 43.3% on the second day, and 45.8 ± 29.3% on the third day, showing similar increases for the 3 days after the start of administration at the evaluation dose. The percent changes (mean) from baseline in daily urine volume increased throughout the IMP treatment period.

The percent changes (mean ± SD) from baseline by evaluation dose on the first day of administration at the evaluation dose in the dose maintenance analysis set were 86.4 ± 67.2% at 0.05 mg/kg/day, 56.5 ± 48.9% at 0.15 mg/kg/day, 57.5 ± 3.3% at 0.3 mg/kg/day, and 14.7 ± 11.3% at 0.5 mg/kg/day, showing increases on the first day of administration at the evaluation dose compared to baseline at all evaluation doses.

Subgroup analyses

Primary Endpoint

Table 11.4.2.8.1-1 Percentages of Subjects Whose Body Weight (kg) Was Decreased by 1.7% or More From Baseline (Under the Condition of Increased Daily Urine Volume) - Time Points After the Start of Administration at the Evaluation Dose -: Subgroup Analysis by Age Group (FAS)

Age category	Timepoint of evaluation dose	N[a]	n[b]	(%)	Lower 95%CI	Upper 95%CI
6 months - 1 year	Day after Day 3 at evaluation dose (A)	20	6	(30.0)	11.9	54.3
	Day after final day at evaluation dose (A)	20	6	(30.0)	11.9	54.3
	Day after final administration (A)	20	6	(30.0)	11.9	54.3
2 - 6 years	Day after Day 3 at evaluation dose (A)	14	2	(14.3)	1.8	42.8
	Day after final day at evaluation dose (A)	14	2	(14.3)	1.8	42.8
	Day after final administration (A)	16	2	(12.5)	1.6	38.3
7 - 14 years	Day after Day 3 at evaluation dose (A)	23	5	(21.7)	7.5	43.7
	Day after final day at evaluation dose (A)	23	5	(21.7)	7.5	43.7
	Day after final administration (A)	23	5	(21.7)	7.5	43.7

Note: Baseline is defined as Day 1 before IMP administration at treatment period.
CI = confidence interval (exact).

[a]Number of treated subjects with evaluated at each timepoint.

[b]Number of treated subjects who decreased their body weights by 1.7% or more from baseline under the condition of increased daily urine volume.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-5.1.3

Secondary Endpoint

Body weight

Table 11.4.2.8.2.1-2 Measured Values and Percent Changes From Baseline in Body Weight (kg) - Number of Days Elapsed Since the Start of Administration -: Subgroup Analysis by Age Group (FAS)

					%Change from baseline			
Age category	Timepoint	n[a]	Mean	SD	n[b]	Baseline mean	Mean	SD
6 months - 1 year	Baseline	20	7.092	1.478				
	Day 2	20	7.049	1.423	20	7.092	−0.486	1.520
	Day 3	20	7.070	1.425	20	7.092	−0.164	2.043
	Day 4	19	7.038	1.495	19	7.081	−0.525	2.259
	Day 5	16	6.958	1.460	16	6.983	−0.310	2.402
	Day 6	15	6.965	1.491	15	6.946	0.383	3.055
	Day 7	10	7.010	1.497	10	7.064	−0.888	1.639
	Day 8	9	7.078	1.640	9	7.073	−0.122	2.953
	Day 9	6	6.598	1.164	6	6.590	0.249	1.795
	Day 10	6	6.643	1.228	6	6.590	0.815	2.937
2 - 6 years	Baseline	16	12.054	2.177				
	Day 2	16	12.046	2.196	16	12.054	−0.084	1.557
	Day 3	16	12.110	2.163	16	12.054	0.508	1.739
	Day 4	11	12.502	2.098	11	12.431	0.756	2.025
	Day 5	6	11.992	1.943	6	11.858	1.497	2.640
	Day 6	5	12.286	1.967	5	12.262	0.472	2.555
	Day 7	2	11.630	2.927	2	11.490	1.327	0.837
	Day 8	2	11.490	3.055	2	11.490	−0.083	0.637
7 - 14 years	Baseline	23	33.475	10.530				
	Day 2	23	33.333	10.451	23	33.475	−0.359	1.191
	Day 3	23	33.368	10.518	23	33.475	−0.318	1.111
	Day 4	22	33.762	10.435	22	33.955	−0.457	1.780
	Day 5	13	32.301	9.533	13	32.817	−1.341	1.514
	Day 6	11	31.267	9.997	11	31.688	−1.306	0.987
	Day 7	4	28.218	10.030	4	28.718	−1.909	2.226
	Day 8	2	23.030	13.817	2	23.260	−1.474	1.654
	Day 9	2	23.130	13.675	2	23.260	−0.739	0.616
	Day 10	2	23.280	13.746	2	23.260	−0.068	0.526

Note: Baseline is defined as Day 1 before IMP administration at treatment period.
Timepoints include the day from the start day of administration to the day after final administration date.

[a]Number of treated subjects with evaluation of the given parameter at each timepoint.

[b]Number of treated subjects with both baseline and evaluation of the given parameter at each timepoint.

Source: CT-6.1.3.3

Edema

Table 11.4.2.8.2.2-1 Improvement and Disappearance Rates of Lower Limb Edema - Time Points After the Start of Administration at the Evaluation Dose -: Subgroup Analysis by Age Group (FAS)

Age category	Timepoint of evaluation dose	N[a]	Improved				Disappeared			
			n[b]	(%)	Lower 95%CI	Upper 95%CI	n[c]	(%)	Lower 95%CI	Upper 95%CI
6 months - 1 year	Day 3 at evaluation dose (A)	12	7	(58.3)	27.7	84.8	6	(50.0)	21.1	78.9
	Final day at evaluation dose (A)	12	8	(66.7)	34.9	90.1	7	(58.3)	27.7	84.8
	Day of final administration (A)	12	8	(66.7)	34.9	90.1	7	(58.3)	27.7	84.8
2 - 6 years	Day 3 at evaluation dose (A)	8	7	(87.5)	47.3	99.7	7	(87.5)	47.3	99.7
	Final day at evaluation dose (A)	8	7	(87.5)	47.3	99.7	7	(87.5)	47.3	99.7
	Day of final administration (A)	8	7	(87.5)	47.3	99.7	7	(87.5)	47.3	99.7
7 - 14 years	Day 3 at evaluation dose (A)	15	10	(66.7)	38.4	88.2	10	(66.7)	38.4	88.2
	Final day at evaluation dose (A)	15	10	(66.7)	38.4	88.2	10	(66.7)	38.4	88.2
	Day of final administration (A)	15	10	(66.7)	38.4	88.2	10	(66.7)	38.4	88.2

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and showed remarkable improvement or improvement after the IMP administration.

[c]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.2.4.3

Table 11.4.2.8.2.2-2 Disappearance Rates of Eyelid Edema - Time Points After the Start of Administration at the Evaluation Dose -: Subgroup Analysis by Age Group (FAS)

Age category	Timepoint of evaluation dose	Disappeared				
		N[a]	n[b]	(%)	Lower 95%CI	Upper 95%CI
6 months - 1 year	Day 3 at evaluation dose (A)	12	9	(75.0)	42.8	94.5
	Final day at evaluation dose (A)	12	9	(75.0)	42.8	94.5
	Day of final administration (A)	12	9	(75.0)	42.8	94.5
2 - 6 years	Day 3 at evaluation dose (A)	9	5	(55.6)	21.2	86.3
	Final day at evaluation dose (A)	9	5	(55.6)	21.2	86.3
	Day of final administration (A)	9	5	(55.6)	21.2	86.3
7 - 14 years	Day 3 at evaluation dose (A)	5	4	(80.0)	28.4	99.5
	Final day at evaluation dose (A)	5	4	(80.0)	28.4	99.5
	Day of final administration (A)	5	4	(80.0)	28.4	99.5

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.3.4.3

Venous Distension

Table 11.4.2.8.2.2-3 Disappearance Rates of Jugular Venous Distension - Time Points After the Start of Administration at the Evaluation Dose -: Subgroup Analysis by Age Group (FAS)

Age category	Timepoint of evaluation dose	N[a]	Disappeared			
			n[b]	(%)	Lower 95%CI	Upper 95%CI
6 months - 1 year	Day 3 at evaluation dose (A)	4	2	(50.0)	6.8	93.2
	Final day at evaluation dose (A)	4	2	(50.0)	6.8	93.2
	Day of final administration (A)	4	2	(50.0)	6.8	93.2
2 - 6 years	Day 3 at evaluation dose (A)	6	3	(50.0)	11.8	88.2
	Final day at evaluation dose (A)	6	3	(50.0)	11.8	88.2
	Day of final administration (A)	6	3	(50.0)	11.8	88.2
7 - 14 years	Day 3 at evaluation dose (A)	12	5	(41.7)	15.2	72.3
	Final day at evaluation dose (A)	12	5	(41.7)	15.2	72.3
	Day of final administration (A)	12	5	(41.7)	15.2	72.3

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.3.4.3

Pleural Effusion

Table 11.4.2.8.2.2-5 Disappearance Rates of Pleural Effusion on the Day After the Final Administration: Subgroup Analysis by Age Group (FAS)

Age category	Timepoint of evaluation dose	N[a]	Disappeared			
			n[b]	(%)	Lower 95%CI	Upper 95%CI
6 months - 1 year	Day after final administration (A)	6	6	(100.0)	54.1	100.0
2 - 6 years	Day after final administration (A)	1	0	(0.0)	0.0	97.5
7 - 14 years	Day after final administration (A)	3	2	(66.7)	9.4	99.2

Note: Baseline is defined as last measurement at pre-observational period.
CI = confidence interval (exact).

[a]Number of subjects who had symptoms at baseline.

[b]Number of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration.

(A): Derived analysis visit. Missing data on the derived analysis visit was imputed using the last available post-dose data obtained by the timepoint.

Source: CT-6.3.4.3

Safety results

Table 12.1-1 Extent of Exposure to the Investigational Medicinal Product (Safety Analysis Set)

Extent of exposure		Evaluation dose				Total (N=60)
		0.05 mg/kg/day (N=22)	0.15 mg/kg/day (N=24)	0.3 mg/kg/day (N=6)	0.5 mg/kg/day (N=8)	
Duration of exposure [n(%)] [a]	1 - 3 days	22 (100.0)	2 (8.3)	0 (0.0)	0 (0.0)	24 (40.0)
	4 - 5 days	0 (0.0)	19 (79.2)	1 (16.7)	0 (0.0)	20 (33.3)
	6 - 7 days	0 (0.0)	3 (12.5)	5 (83.3)	0 (0.0)	8 (13.3)
	8 - 9 days	0 (0.0)	0 (0.0)	0 (0.0)	8 (100.0)	8 (13.3)
	10 -13 days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Duration of exposure (Days) [a]	N	22	24	6	8	60
	Mean	2.7	4.9	6.5	9.0	4.8
	SD	0.6	0.9	0.8	0.0	2.2
	Min	1	3	5	9	1
	Median	3.0	5.0	7.0	9.0	5.0
	Max	3	7	7	9	9
Evaluation dose [n(%)]	0.05 mg/kg/day					22 (36.7)
	0.15 mg/kg/day					24 (40.0)
	0.3 mg/kg/day					6 (10.0)
	0.5 mg/kg/day					8 (13.3)

[a]End date of IMP administration − Start date of IMP administration + 1.

Source: CT-7.1

Summary of AEs

Table 12.2.1-1 Summary of Adverse Events (Safety Analysis Set)	
Number of:	**Tolvaptan n (%)[a]**
Subjects treated	60
Subjects with AEs	30 (50.0)
Adverse events (number of events)	54
Subjects with TEAEs	26 (43.3)
TEAEs (number of events)	41
Subjects with IMP-related TEAEs	10 (16.7)
Deaths	0 (0.0)
Subjects with serious TEAEs	1 (1.7)
Subjects with IMP-related serious TEAEs	0 (0.0)
Subjects with severe TEAEs	1 (1.7)
Subjects with IMP-related severe TEAEs	0 (0.0)
Subjects with discontinuation of IMP due to AE	2 (3.3)
Subjects with IMP-related discontinuation of IMP due to AE	0 (0.0)

TEAE (treatment-emergent adverse event): adverse event which started after start of IMP treatment.

[a]Percentages are based on the number of treated subjects.

Source: CT-8.1.1

Treatment-emergent AEs

Table 12.2.2.1-1 Adverse Events (Safety Analysis Set)	
System organ class Preferred term	**Tolvaptan (N=60) n (%)**
Subject with any treatment-emergent adverse events[a]	26 (43.3)
Blood and lymphatic system disorders	3 (5.0)
Anaemia	2 (3.3)
Neutropenia	1 (1.7)
Cardiac disorders	2 (3.3)
Cardiac failure chronic	1 (1.7)
Cardiovascular insufficiency	1 (1.7)
Eye disorders	1 (1.7)
Erythema of eyelid	1 (1.7)
Gastrointestinal disorders	8 (13.3)
Abdominal pain	1 (1.7)
Constipation	2 (3.3)
Dry mouth	2 (3.3)
Nausea	1 (1.7)
Vomiting	2 (3.3)
Gastrointestinal hypomotility	1 (1.7)
Anal erythema	1 (1.7)
General disorders and administration site conditions	6 (10.0)
Pyrexia	2 (3.3)
Thirst	4 (6.7)
Infections and infestations	3 (5.0)
Nasopharyngitis	1 (1.7)
Urinary tract infection	1 (1.7)
Bacterial infection	1 (1.7)
Investigations	2 (3.3)
Blood pressure increased	1 (1.7)
Blood pressure systolic decreased	1 (1.7)
Hepatic enzyme increased	1 (1.7)
Metabolism and nutrition disorders	5 (8.3)
Dehydration	1 (1.7)
Hyperkalaemia	2 (3.3)
Hypokalaemia	1 (1.7)
Polydipsia	1 (1.7)
Nervous system disorders	2 (3.3)
Dizziness	1 (1.7)
Headache	1 (1.7)
Renal and urinary disorders	1 (1.7)
Renal impairment	1 (1.7)
Skin and subcutaneous tissue disorders	3 (5.0)
Pruritus	1 (1.7)
Rash	1 (1.7)
Skin exfoliation	1 (1.7)

Note: Adverse events are coded in MedDRA v24.0.
Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

[a]Subjects with adverse event in multiple system organ classes were counted only once towards the total.

Source: CT-8.1.2.1

Confidential - Proprietary Information

IMP-related AEs

Table 12.2.2.2-1 Adverse Events Related to the Investigational Medicinal Product (Adverse Reactions) (Safety Analysis Set)	
System organ class Preferred term	**Tolvaptan (N=60) n (%)**
Subject with any treatment-emergent adverse events[a]	10 (16.7)
Blood and lymphatic system disorders	1 (1.7)
Neutropenia	1 (1.7)
Gastrointestinal disorders	3 (5.0)
Constipation	1 (1.7)
Dry mouth	2 (3.3)
General disorders and administration site conditions	5 (8.3)
Pyrexia	1 (1.7)
Thirst	4 (6.7)
Investigations	1 (1.7)
Blood pressure systolic decreased	1 (1.7)
Metabolism and nutrition disorders	1 (1.7)
Polydipsia	1 (1.7)
Nervous system disorders	1 (1.7)
Dizziness	1 (1.7)

Note: Adverse events are coded in MedDRA v24.0.
Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

[a]Subjects with adverse event in multiple system organ classes were counted only once towards the total.
Source: CT-8.1.3

AEs by evaluation dose

Table 12.2.3.1-1 All Adverse Events by Evaluation Dose (Safety Analysis Set)

System organ class Preferred term	Evaluation dose 0.05 mg/kg/day (N=22) n (%)	0.15 mg/kg/day (N=24) (%)	0.3 mg/kg/day (N=6) n (%)	0.5 mg/kg/day (N=8) n (%)	Total (N=60) n (%)
Subject with any treatment-emergent adverse events[a]	7 (31.8)	13 (54.2)	2 (33.3)	4 (50.0)	26 (43.3)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (16.7)	2 (25.0)	3 (5.0)
Anaemia	0 (0.0)	0 (0.0)	1 (16.7)	1 (12.5)	2 (3.3)
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (1.7)
Cardiac disorders	1 (4.5)	1 (4.2)	0 (0.0)	0 (0.0)	2 (3.3)
Cardiac failure chronic	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Cardiovascular insufficiency	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Eye disorders	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Erythema of eyelid	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Gastrointestinal disorders	2 (9.1)	4 (16.7)	0 (0.0)	2 (25.0)	8 (13.3)
Abdominal pain	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Constipation	0 (0.0)	1 (4.2)	0 (0.0)	1 (12.5)	2 (3.3)
Dry mouth	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	2 (3.3)
Nausea	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Vomiting	1 (4.5)	1 (4.2)	0 (0.0)	0 (0.0)	2 (3.3)
Gastrointestinal hypomotility	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Anal erythema	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (1.7)
General disorders and administration site conditions	1 (4.5)	3 (12.5)	1 (16.7)	1 (12.5)	6 (10.0)
Pyrexia	0 (0.0)	1 (4.2)	0 (0.0)	1 (12.5)	2 (3.3)
Thirst	1 (4.5)	2 (8.3)	1 (16.7)	0 (0.0)	4 (6.7)
Infections and infestations	1 (4.5)	2 (8.3)	0 (0.0)	0 (0.0)	3 (5.0)
Nasopharyngitis	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Urinary tract infection	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Bacterial infection	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Investigations	1 (4.5)	1 (4.2)	0 (0.0)	0 (0.0)	2 (3.3)
Blood pressure increased	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Blood pressure systolic decreased	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Hepatic enzyme increased	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Metabolism and nutrition disorders	3 (13.6)	1 (4.2)	1 (16.7)	0 (0.0)	5 (8.3)
Dehydration	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Hyperkalaemia	1 (4.5)	1 (4.2)	0 (0.0)	0 (0.0)	2 (3.3)
Hypokalaemia	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (1.7)
Polydipsia	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Nervous system disorders	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	2 (3.3)
Dizziness	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Headache	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Renal and urinary disorders	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Renal impairment	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Skin and subcutaneous tissue disorders	2 (9.1)	1 (4.2)	0 (0.0)	0 (0.0)	3 (5.0)
Pruritus	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Rash	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Skin exfoliation	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)

Note: Adverse events are coded in MedDRA v24.0.
Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

[a]Subjects with adverse event in multiple system organ classes were counted only once towards the total.
Source: CT-8.3.2

Table 12.2.3.1-2 All Adverse Events by Evaluation Dose After the Start of Administration at the Evaluation Dose (Safety Analysis Set)

System organ class Preferred term	Evaluation dose 0.05 mg/kg/day (N=22) n (%)	 0.15 mg/kg/day (N=24) (%)	 0.3 mg/kg/day (N=6) n (%)	 0.5 mg/kg/day (N=8) n (%)	Total (N=60) n (%)
Subject with any treatment-emergent adverse events[a]	7 (31.8)	12 (50.0)	1 (16.7)	2 (25.0)	22 (36.7)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (1.7)
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (1.7)
Cardiac disorders	1 (4.5)	1 (4.2)	0 (0.0)	0 (0.0)	2 (3.3)
Cardiac failure chronic	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Cardiovascular insufficiency	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Eye disorders	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Erythema of eyelid	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Gastrointestinal disorders	2 (9.1)	3 (12.5)	0 (0.0)	1 (12.5)	6 (10.0)
Abdominal pain	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Constipation	0 (0.0)	1 (4.2)	0 (0.0)	1 (12.5)	2 (3.3)
Nausea	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Vomiting	1 (4.5)	1 (4.2)	0 (0.0)	0 (0.0)	2 (3.3)
Gastrointestinal hypomotility	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
General disorders and administration site conditions	1 (4.5)	3 (12.5)	1 (16.7)	1 (12.5)	6 (10.0)
Pyrexia	0 (0.0)	1 (4.2)	0 (0.0)	1 (12.5)	2 (3.3)
Thirst	1 (4.5)	2 (8.3)	1 (16.7)	0 (0.0)	4 (6.7)
Infections and infestations	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Bacterial infection	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Investigations	1 (4.5)	1 (4.2)	0 (0.0)	0 (0.0)	2 (3.3)
Blood pressure increased	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Blood pressure systolic decreased	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Hepatic enzyme increased	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Metabolism and nutrition disorders	3 (13.6)	1 (4.2)	0 (0.0)	0 (0.0)	4 (6.7)
Dehydration	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Hyperkalaemia	1 (4.5)	1 (4.2)	0 (0.0)	0 (0.0)	2 (3.3)
Polydipsia	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Nervous system disorders	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	2 (3.3)
Dizziness	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Headache	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Renal and urinary disorders	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Renal impairment	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Skin and subcutaneous tissue disorders	2 (9.1)	1 (4.2)	0 (0.0)	0 (0.0)	3 (5.0)
Pruritus	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Rash	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)
Skin exfoliation	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)

Note: Adverse events are coded in MedDRA v24.0.

Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

[a]Subjects with adverse event in multiple system organ classes were counted only once towards the total.

Source: CT-8.4.2

AEs by age group

The incidence of AEs by age group was 50% (10/20 subjects) in the young age group, 37.5% (6/16 subjects) in the middle age group, and 41.7% (10/24 subjects) in the old age group. The AEs that occurred in at least 2 subjects in the young age group were pyrexia and thirst (two subjects each, 10%).

No AEs occurred in the middle age group.

The AEs occurring in at least 2 subjects in the oldest age group were vomiting, thirst, and hyperkaelimia (2 subjects each, 8.3%).

Deaths

No deaths occurred in this trial.

Other SAEs

An SAE occurred in 1/60 subjects (1.7%). The SAE that occurred was cardiac failure chronic, and was determined to be unrelated to the IMP. The subject was between 10 and 13 years old at the evaluation dose of 0.05 mg/kg/day. after the completion of the treatment with the IMP, the event occurred on Day 8 (5 days affetr the completion of treatment) and resolved on day 17 after onset (21 days after the completion of treatment).

AEs leading to discontinuation

Table 12.3.1.3-1 Adverse Events Leading to Discontinuation of the Investigational Medicinal Product (Safety Analysis Set)

System organ class Preferred term	Tolvaptan (N=60) n (%)
Subject with any treatment-emergent adverse events[a]	2 (3.3)
Metabolism and nutrition disorders	2 (3.3)
Hyperkalaemia	2 (3.3)

Note: Adverse events are coded in MedDRA v24.0.
Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.
[a]Subjects with adverse event in multiple system organ classes were counted only once towards the total.
Source: CT-9.1.5

AEs of special interest

The AEs of special interest in this trial were dehydration and renal impairment. Dehydration and renal impairment were reported in one subject each (the same subject). The subject who experienced dehydration and renal impairment was a between 11 and 14 years old; both of these two events were determined to be unrelated to the IMP. All of the events were mild in severity and occurred on Day 5 (4 days after discontinuation), and the outcome was unresolved.

Discussion on clinical aspects

According to Article 46 of Regulation (EC) No 1901/2006, the MAH has submitted the results of a paediatric clinical trial with tolvaptan in patients with heart failure. The presented data pertain a short-term administration of tolvaptan in a Phase 3, multicenter, open-label, dose-defining trial to investigate the efficacy, safety, pharmacokinetics and pharmacodynamics of the drug in male and female paediatric heart failure patients with volume overload, aged from 6 months to less than 15

years. The study design contemplated an initial 3 day-hospitalisation period before IMP administration, followed by an up-titration scheme starting at 0.05 mg/kg/day that was progressively increased to 0.15, 0.3, or 0.5 mg/kg/day according with daily urine volume. Dose augmentation was considered in cases of "insufficient increase in urine volume" when it was less than 150% of that for the pretreatment observation period (one day before the start of tolvaptan administration). Once reached the target dose (i.e. evaluation dose), treatment was maintained for 3 days, and that period was considered for efficacy evaluation. The dose range was empirically chosen, based on the adult dose finding trials and post-marketing experience in Japan.

The study was conducted in Japan, where a MA is in place for tolvaptan in the treatment of heart failure in adults. This is indication is not licensed in the EU, nor a paediatric line of extension is herein pursued.

Pharmacokinetics

The plasma concentrations (mean) of tolvaptan (OPC-41061) reached the maximum value at 2 to 4 hours after administration, and subsequently decreased. The MAH states that plasma concentrations (mean) of tolvaptan (OPC-41061) at 0.05 and 0.15 mg/kg/day, at which plasma drug concentration results were obtained in all age groups, showed no trends that were dependent on age-group. However, no clear graphical or tabular data are reported to allow drawing firm conclusions.

In addition, it is not clear why pharmacokinetic analysis set included only 44/60 participants, i.e. why post dose samples are not available for a significant number of subjects.

Subjects took tolvaptan 1% granules or tolvaptan 15 mg tablet with water once daily after breakfast. The impact of the different formulations used on pharmacokinetics cannot be excluded, since it is not clear if bioequivalence was demonstrated.

Pharmacodynamics

Pharmacodynamics parameters were well described and analysed, age subgroups analysis was performed, even though numbers are small.

Efficacy and Safety

Definition of treatment response was derived from the clinical experience with tolvaptan as accumulated in the adult heart failure setting. Specifically, based on the body weight reduction of 1.27 kg observed 3 days post-treatment initiation in adults, a cut-off of 1.5 kg in body weight decrease on Day 3 was taken for the efficacy evaluation in children. Body weight reduction was under the condition that the mean daily urine volume for the 3 days of treatment with tolvaptan at the evaluation dose was higher than the daily urine volume for the pre-treatment observation period. By acknowledging the general lack of a standardised measure of diuretic responsiveness, the primary endpoint appears quite controversial since body weight fluctuations do not represent changes in volume distribution, and poorly correlate with fluid output. This measure appears even weaker in the paediatric setting, particularly in the youngest ages. As a more solid measure of decongestion, a net fluid output would have been more informative or, alternatively and as recently suggested in a position paper from the Heart Failure Association of the European Society of Cardiology (2019), a combination of biomarkers and clinical parameters should have been considered for clinical efficacy determination.

In total, 60 patients were exposed to tolvaptan for a mean duration of 4.8 ± 2.2 days. Evaluation dose groups included 0.05 mg/kg/day (36.7%), 0.15 mg/kg/day (40%), 0.3 mg/kg/day (10%) and 0.5 mg/kg/day (13.3%). The IMP treatment periods (mean ± SD) by evaluation dose were 2.7 ± 0.6 days at 0.05 mg/kg/day, 4.9 ± 0.9 days at 0.15 mg/kg/day, 6.5 ± 0.8 days at 0.3 mg/kg/day, and 9.0 ± 0.0 days at 0.5 mg/kg/day. The sample size was calculated based on a value for assessment of

efficacy as defined by the primary endpoint, and then using binomial distribution to determine the number of subjects required to maintain a 90% or higher probability that the lower limit of the 95% CI for the percentage of subjects achieving the primary endpoint.

According with the baseline characteristics, the recruited population showed a representation of the three pre-defined age groups (6 months-1 year: 33.9%; 2-6 years: 27.1%; 7-14 years:14%) which is in line with disease epidemiology for time of diagnosis. Only Asian patients were recruited, with 47.5% and 52.5% of male and female sex, respectively. Surgical history was present in 76.3% of the population. As expected, congenital heart disease and cardiomyopathy leading to either over-circulation failure or pump failure, were among the most common causes of heart failure in the studied population. Of note, a wide variety of symptomatology was included encompassing Class II and III of the disease severity grading system adopted in children (i.e. NYHA or Ross). Indeed, the majority was symptomatic at the time of recruitment (98.3%), as per inclusion criteria requiring patients to present with volume overload and inadequate response to "conventional diuretic therapy". The definition was left to the investigator, leading to the recruitment of a heterogeneous population in terms of concomitant diuretic medications that mostly reflects clinical practice. The majority of patients were on a combination of loop diuretics and anti-aldosterone drugs (76.3%), while a minority was on monotherapy with loop diuretics (10.2%), or Loop diuretic + Thiazide diuretic + Antialdosterone drug (11.9%). According with clinical practice and as a standard-of-care, additional heart failure medications were concomitantly used with tolvaptan, including the phosphodiesterase inhibitor milrinone (administrated to 20% of participants on Day 1), and digoxin (used in 8.3% of patients on Day 1).

The percentage of subjects whose body weight was decreased by 1.7% or more from baseline on the day after the third day of administration at the evaluation dose was 22.8% (13/57 subjects; 95% CI [0.127, 0.358]). A similar percentage of "responders" was identified across all the different dose ranges (around 25%) with the exception of the highest dose group, for which a reduced response to treatment (12.5%) was registered. Lack of dose-dependency would be expected in an individualised up-titration scheme as defined in the study protocol. Of note, the highest dose of tolvaptan was most frequently employed in the youngest patients (75% of those receiving 0.5 mg/kg/day were aged between 6 month-<2 years), while the oldest patients were more prevalent in the lower dose ranges (45% and 50% of those receiving 0.05 mg/kg/day and 0.15 mg/kg/day were aged between 7-15 years, respectively). The use of concomitant medications including diuretics and anti-aldosterone drugs was almost comparable across dose groups. It could be that disease severity varied across ages, and this might justify the worse response rate observed at the highest dose. However, data on disease severity were not collected during the study; therefore, this hypothesis remains a speculative observation.

As regards the secondary endpoint, namely the percentage of body weight change from baseline, the trend was generally consistent with the primary endpoint variations, showing a dose-independent reduction by 0.7%, 0.2% and 1.5% in the 0.05, 0.15 and 0.3 mg/kg/day group respectively, while an increase in body weight from baseline was observed in the 0.5 mg/kg/day dose, which could be attributed to either a reduced individual response or increased disease severity in the group receiving the highest dose. The requested dose and age subgroup characterisation could offer insight into these data. However, the clinical meaning of this observation remains unclear taking into consideration the abovementioned poor correlation between body weight fluctuations and volume distribution. In keeping with this, the clinical response as evaluated by signs of congestion was generally better compared to the primary endpoint results, and was overall consistent across the different dose groups, although missing a clear dose-dependency. Improvement in peripheral oedema was registered in 68.6% of the population, and resolution of symptoms occurred in 65.7% of patients; the proportion of responders progressively augmented by dose increase between 0.05 and 0.3 mg/kg/day (from 81.8% to 100% for

improvement and 72.7% and 100% for disappearance), although falling in the highest dose group (0.5 mg/kg/day; 40% for improvement and disappearance, respectively). More variable trends were observed for improvement in jugular venous distension (50% in all groups with the exception of 0.5mg/kg/day registering 25% response) and pulmonary congestion (59.3%, 63.6%, 50% and 16.7% in the four dose groups); their respective disappearance rates were similar, suggesting a variable individual response. Finally, evaluation of daily urine volume as indicative of the aquaretic effect of tolvaptan, showed dose-independent percent changes (mean ± SD) from baseline and high inter-individual variability, based on the values on the first day of administration at the evaluation dose in the dose maintenance analysis (86.4 ± 67.2% at 0.05 mg/kg/day, 56.5 ± 48.9% at 0.15 mg/kg/day, 57.5 ± 3.3% at 0.3 mg/kg/day, and 14.7 ± 11.3% at 0.5 mg/kg/day) and the full analysis set (53.1 ± 52.9% on the first day of administration at the evaluation dose, 47.8 ± 43.3% on the second day, and 45.8 ± 29.3% on the third day).

At the subgroup analysis, the intermediate 2-6 year age category had the lowest percentage of responders based on the primary endpoint (14.3% compared to 30% and 21.7% of the 6 months-1 year and 7-14 year group, respectively), while achieving the best clinical response when evaluating oedema improvement (47.3% compared to 27.7% and 38.4% of the 6 months-1 year and 7-14 year group, respectively) and disappearance rates (87.5% compared to 50% and 66.7% of the 6 months-1 year and 7-14 year group, respectively).

From a safety perspective, the incidence of AEs was 43.3% in the total population, with AEs related to the IMP occurring in 16.7% of patients. A consistent rate of events was observed across age groups and dose ranges. No deaths were reported, nor cases of acute liver toxicity were registered in this trial. The majority of AEs by SOC categories included gastrointestinal disorders (13.3%), general disorders and administration site conditions (10.0%), and metabolism and nutrition disorders (8.3%). AEs occurring with common frequency were thirst (6.7%) and anaemia, constipation, dry mouth, vomiting, pyrexia, and hyperkalaemia (3.3% for all of them). AEs were more often mild in severity (35.0%), with only a minority reporting moderate AEs (6.7%) and one patient (1.7%) developing a serious event, namely cardiac failure that was judged unrelated to the IMP. This was about a 13-old boy with dilated cardiomyopathy receiving tolvaptan 0.05 mg/kg/day for 3 days who suffered acute cardiac decompensation 5 days post-last dose administration. On revision of this case, no concerns arise. Among IMP-related AEs, General disorders and administration site conditions (i.e. pyrexia 1.7%; and thirst 6.7%) were the most frequent (8.3%), followed by gastrointestinal disorders (5.5%; dry mouth 3.3% and constipation 1.7%); polydipsia, dizziness and neutropenia occurred with a frequency of 1.7%.

3. CHMP overall conclusion and recommendation

In conclusion, based on the primary and secondary efficacy endpoints, the MAH claims treatment efficacy for Jinarc (tolvaptan) in children aged from 6 months to less than 15 years with heart failure and signs of congestions not controlled by conventional diuretic therapy. However, the benefit of treatment in the short-term remains undefined due to the abovementioned study limitations, and information on the long-term effect are currently unavailable. No new safety signals emerged in this paediatric investigation. The safety profile for this short-term course of tolvaptan administration appears manageable and in line with the adult clinical experience accumulated so far. Considering that the MAH is not pursuing a paediatric indication in the EU, the presented data have only a limited clinical and regulatory impact.

☒ **Fulfilled:**

No regulatory action required.