CLINICAL STUDY PROTOCOL

A Multicenter, Open-label, Dose-defining Trial to Investigate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Tolvaptan in Pediatric Heart Failure Patients With Volume Overload

NCT Number: NCT03255226

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

OPC-41061 (Tolvaptan)

CLINICAL PROTOCOL
Translation

A Multicenter, Open-label, Dose-defining Trial to Investigate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Tolvaptan in Pediatric Heart Failure Patients With Volume Overload

Protocol No. 156-102-00123

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event	Office of Pharmacovigilance Operation, Department of Pharmacovigilance Otsuka Pharmaceutical Co., Ltd Email: IRE_156-102-00123@otsuka.jp Fax: +81-6-6942-3692
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd Name of Investigational Medicinal Product: tolvaptan (OPC-41061)	Protocol No.: 156-102-00123
Protocol Title:	A Multicenter, Open-label, Dose-defining Trial to Investigate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Tolvaptan in Pediatric Heart Failure Patients With Volume Overload
Clinical Phase/ Trial Type:	3 Dose-defining
Treatment Indication:	For the treatment of volume overload despite having received conventional diuretic therapy in pediatric heart failure patients age 6 months to less than 15 years
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
Trial Design:	Multicenter, open-label, uncontrolled, dose-titration trial
Subject Population:	The planned number of subjects for receiving tolvaptan is set at 60. The subject population includes male or female pediatric heart failure patients age 6 months to less than 15 years with volume overload despite having received conventional diuretic therapy.
Inclusion/Exclusion Criteria:	[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 cannot be expected even if the dose of the diuretics is increased or in whom the investigator or subinvestigator judges that increasing the dose of the diuretics is 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 will 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 can also be enrolled in the trial if strict management of fluid intake and excretion is 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 is possible, patients in whom the investigator or subinvestigator judges that tolvaptan cannot be safely administered are to be excluded.
4) Patients who can be hospitalized from at least 3 days before start of tolvaptan administration until 2 days after final administration

[Main Exclusion Criteria]

1) Patients whose volume overload status shows improvement during the screening period or pretreatment observation period
2) Patients who are unable to drink fluid (including patients who are unable to sense thirst)
3) Patients whose circulatory blood flow is 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 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 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
Trial Site(s):	Approximately 30 trial sites in Japan
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Subjects will take tolvaptan 1% granules or tolvaptan 15 mg tablet with water once daily after breakfast. The initial dose of tolvaptan will be 0.05 mg/kg/day. From the second day of the treatment period and onward, if necessary the dose may be increased to 0.15, 0.3, or 0.5 mg/kg/day according to the rules specified in Section 3.2.2, and then the dose decided for each individual subject will be administered for 3 days. The dose of tolvaptan 1% granules to be administered will be determined depending on the subject's body weight on the day before start of tolvaptan administration; however, the maximum dose is 15 mg/day even if the calculated dose exceeds 15 mg/day. For administration at the maximum dose of 15 mg, tolvaptan 15-mg tablet may be administered in place of tolvaptan 1% granules. Regarding dose reduction or extension of treatment with tolvaptan, refer to Section 3.2.3 and Section 3.2.4.
Trial Assessments:	Efficacy: Body weight, daily urine volume, edematous symptoms (edema [lower limbs, eyelids, etc], dyspnea, jugular venous distension, respiration rate at rest, and pulse rate), chest x-ray (pulmonary congestion, cardiothoracic ratio, and pleural effusion), central venous pressure (only subjects with central venous catheterization), and retention of pericardial effusion (only subjects requiring echocardiography) Pharmacodynamics: Daily fluid intake, serum osmolality, serum or blood sodium concentration, serum or blood potassium concentration, urine osmolality, urine concentrations of sodium and potassium, and plasma arginine vasopressin (AVP) concentration (only subjects from whom samples are available) Pharmacokinetics: Blood sampling for measurement of plasma drug concentration

	Safety: Adverse event (AE) reporting, clinical laboratory tests, vital signs, 12-lead electrocardiogram, and pregnancy test (only for female subjects who have begun menstruation)
Criteria for Evaluation:	**Primary Endpoint:** The percentage of subjects who satisfy the following condition: • Body weight on the day after the third day of treatment with tolvaptan at the evaluation dose (see Section 7.4) is decreased by 1.7% or more from the weight measured before breakfast on the first day of the treatment period However, mean daily urine volume for the 3 days of treatment with tolvaptan at the evaluation dose must be higher than the daily urine volume for the pretreatment observation period. For subjects who discontinued treatment with tolvaptan, mean daily urine volume up until the time of discontinuation must be higher than the daily urine volume for the pretreatment observation period. **Secondary Endpoint(s):** • 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
Statistical Methods:	[Statistical Methods for Primary Endpoint] The number and percentage of subjects whose body weight on the day after the third day of treatment with tolvaptan at the evaluation dose is decreased by 1.7% or more from the weight measured before breakfast on the first day of the treatment period will be calculated together with exact 95% confidence intervals (CI) based on binomial distribution. The same calculations will be performed regarding body weight on the day after final tolvaptan administration. The number and percentage of subjects will also be calculated for each time

	point after the start of treatment at the tolvaptan evaluation dose using body weight on the first day of administration at the evaluation dose as the baseline. [Rationale for the 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 will be 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.
Trial Duration:	Duration of the trial: May 2017 to Nov 2021 Expected duration of trial participation for individual subjects: Maximum 27 days (0 to 4 days for screening period, 3 days for pretreatment observation period, 5 to 15 days for treatment period, and 3 to 5 days for follow-up)

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AVP	Arginine vasopressin
CKD	Chronic Kidney Disease
CHF	Congestive heart failure
CRF	Case report form
CYP	Cytochrome P450
ECG	Electrocardiogram
EDC	Electronic data capture
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
IAF	Informed assent form
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational medicinal product
IRB	Institutional review board
IRE	Immediately reportable event
PQC	Product quality complaint
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event

1 Introduction

1.1 Nonclinical Data

Tolvaptan is a vasopressin V_2-receptor antagonist that specifically blocks the binding of arginine vasopressin (AVP) at the V_2 receptors of the distal portions of the nephron, thereby inducing water diuresis (aquaresis) without depletion of electrolytes.

In a beagle dog model of congestive heart failure (CHF), tolvaptan produced a significant decrease in cardiac preload without affecting cardiac afterload or renal functions. Consequently, tolvaptan can be expected to be useful for the treatment of the volume overload state of heart failure without having any undesirable effects on renal function, systemic hemodynamics, or circulating neurohormones. For detailed data, see the Investigator's Brochure (IB).

1.2 Clinical Data

1.2.1 A Dose-ranging Trial in Adult Heart Failure Patients With Volume Overload in Japan (Trial 156-03-001)

A total of 122 adult heart failure patients with volume overload whose condition had not been resolved by the use of furosemide (at 40 mg/day or more) received 7-day repeated oral administration of tolvaptan at 15 mg/day, 30 mg/day, and 45 mg/day or placebo.

As a result, a change in body weight from baseline (mean) was observed from the day after the first administration in all tolvaptan groups. Decreases in body weight following 7-day repeated administration of tolvaptan at 15 mg/day, 30 mg/day, and 45 mg/day were significantly greater than those seen in the placebo group; however, the degree of change was similar across all tolvaptan doses.

Incidence of adverse events (AEs) was 62.1% (18/29 subjects, 55 events) in the placebo group while it was 85.7% (24/28 subjects, 72 events), 97.0% (32/33 subjects, 92 events), and 82.1% (23/28 subjects, 63 events) in the tolvaptan 15 mg, 30 mg, and 45 mg groups, respectively. The most frequently reported AEs were thirst and dehydration, considered to be due to the pharmacological effects of tolvaptan, and the number of subjects who experienced these events increased dose-dependently in the tolvaptan groups. Incidence of adverse reactions was 37.9% (11/29 subjects, 22 events) in the placebo group while 60.7% (17/28 subjects, 42 events), 63.6% (21/33 subjects, 51 events), and 75.0% (21/28 subjects, 45 events) in the tolvaptan 15 mg, 30 mg, and 45 mg groups, respectively. Most

of observed adverse reactions were transient and resolved or improved through appropriate treatment.

Two subjects died (sudden death and cardio-respiratory arrest), both of whom were in the placebo group. Serious adverse events (SAEs) other than death were observed in 5 subjects: 2 (heart failure congestive andumbilical hernia) in the placebo group, 1 (epistaxis) in the 30 mg group, and 2(dyspnoea exertional and transient ischaemic attack) in the 45 mg group. For all of these events excluding those observed in 1 subject in the placebo group (cardio-respiratory arrest) and 1 subject in the tolvaptan 45 mg group (dyspnoea exertional), a causal relationship with the investigational medicinal product (IMP) was ruled out. Treatment discontinuation due to AEs occurred in 3 subjects in the placebo group (dehydration, renal impairment, and hyperkalaemia; pleural effusion and dyspnoea exertional; cardiac failure), no subjects in the tolvaptan 15 mg group, 2 subjects in the tolvaptan 30 mg group (dehydration, malaise), 5 subjects in the tolvaptan 45 mg group (dehydration and renal impairment; dyspnoea exertional; blood urea increased; blood potassium increased; blood pressure decreased). For all of these events, a causal relationship with the IMP was not ruled out. All SAEs, and AEs leading to discontinuation were resolved by treatment discontinuation or other appropriate measures. For detailed data, see the IB.

1.2.2 A Phase 3, Double-blind, Placebo-controlled Trial in Adult Heart Failure Patients With Volume Overload in Japan (Trial 156-06-002)

A total of 110 adult heart failure patients with volume overload whose condition had not been resolved by conventional diuretic therapy received 7-day administration of tolvaptan at 15 mg/day or placebo.

As a result, a change in body weight at final administration (mean ± standard deviation) was −1.54 ± 1.61 kg in the tolvaptan 15 mg group, and −0.45 ± 0.93 kg in the placebo group. Body weight in the tolvaptan 15 mg group decreased significantly in comparison with the placebo group ($p < 0.0001$ by t-test), and a difference in the mean change between the tolvaptan 15 mg group and the placebo group was −1.09 kg (95% CI: −1.58 to −0.60 kg).

Adverse events occurring in the tolvaptan 15 mg group at an incidence of 3% or higher and also at an incidence of at least 3% higher than in the placebo group were thirst (17.0% [9/53 subjects] in the tolvaptan 15 mg group, 1.8% [1/57 subjects] in the placebo group), constipation (17.0% [9/53 subjects], 5.3% [3/57 subjects]), pollakiuria (9.4% [5/53 subjects], 0.0%), nausea and malaise (5.7% [3/53 subjects], 0.0%), and dizziness

and headache (3.8% [2/53 subjects], 0.0%). All of these AEs were mild or moderate in severity. The events of thirst, constipation, and pollakiuria were probably due to the diuretic action of tolvaptan.

Serious AEs occurred in 2 subjects in the tolvaptan 15 mg group and 7 subjects in the placebo group.

Of the 2 subjects in the tolvaptan 15 mg group, one subject died, and in that subject renal failure chronic (SAE) and cardiac failure (AE resulting in death) were reported. In the other subject, atrial fibrillation was reported as a SAE. For detailed data, see the IB.

1.3 Known and Potential Risks and Benefits

In trials in adult heart failure patients with volume overload (Trials 156-03-001, 156-06-002, 156-06-004, 156-06-006, 156-10-005, 156-TWA-1101i, and 156-12-809-01), The most frequently reported AEs in 437 subjects treated with tolvaptan (with an incidence of >3% of all tolvaptan treated subjects) were as follows: Thirst, blood urea increased, blood uric acid increased, constipation, cardiac failure, blood creatinine increased, blood potassium increased, pollakiuria, dry mouth, dehydration, dizziness, nasopharyngitis, hyperuricaemia, diarrhoea, and hypokalaemia. The most frequently reported AEs with an incidence of >5% in placebo group were cardiac failure and hypokalaemia. The AEs with a higher incidence in subjects treated with oral tolvaptan at all doses than in subjects receiving placebo (with an incidence of >5% of all tolvaptan treated subjects and a higher incidence than that of subjects receiving placebo) were blood uric acid increased, constipation, blood creatinine increased, and blood potassium increased. In patients with volume overload that had not been resolved despite having received furosemide, administration of tolvaptan (15 mg, 30 mg, and 45 mg) decreased body weight significantly and increased urine volume dose-dependently. In the tolvaptan groups, edematous symptoms, such as lower limb edema and jugular venous distension, showed an improvement compared with the placebo group. For the details of AEs attributable to tolvaptan therapy in clinical trials, see the IB.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Tolvaptan is a vasopressin V_2-receptor antagonist synthesized by Otsuka Pharmaceutical Co., Ltd., which specifically blocks the binding of AVP at the V_2 receptors of the distal portions of the nephron to induce water diuresis (aquaresis) without depletion of electrolytes. Tolvaptan was approved in Japan in Oct 2010 for the indication of the treatment for adult patients with "volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics)". However, no clinical trial has been conducted to evaluate its efficacy and safety in pediatric heart failure patients with volume overload.

Volume overload in pediatric heart failure patients is caused by diverse etiologies, and diuretics are widely used to treat it. The diuretics used for pediatric patients, as in adult patients, are conventional diuretics, eg, mainly loop diuretics. Tolvaptan, which has a mechanism of action different from that of conventional diuretics, is expected to become a useful therapeutic approach to improve volume overload in pediatric heart failure patients when adequate response is not obtained with conventional diuretics.

This trial was planned in order to determine the efficacy, safety, pharmacokinetics, and pharmacokinetics of tolvaptan in pediatric heart failure patients with volume overload despite having received conventional diuretic therapy.

This protocol was prepared in accordance with the agreement reached with the Pharmaceuticals and Medical Devices Agency about the appropriateness of the trial plan at the consultation after completion of a phase 2 trial (04 Oct 2016, Application Number P4175).

In view of the above, the conduct of this trial is scientifically and ethically appropriate.

2.2 Dosing Rationale

According to the Clinical Guideline for Medical Treatment of Pediatric Heart Failure (JSPCCS 2015)[1] prepared by the Japanese Society of Pediatric Cardiology and Cardiac Surgery, tolvaptan "should be administered at 0.3 to 0.5 mg/kg/day once daily, starting at around half of this dose" for pediatric heart failure patients. On the other hand, a lower starting dose than that recommended in the guideline is often noted in literatures or case reports addressing tolvaptan therapy in pediatric heart failure patients.[2] In a retrospective

study collecting the outcomes of pediatric heart failure patients who received tolvaptan therapy in Japan,[2] a wide range of starting doses was seen (0.02-0.76 mg/kg/day). A usual dose of tolvaptan for adult heart failure patients with volume overload is 15 mg/day (0.25 mg/kg/day for adults with a body weight of 60 kg). However, the postmarketing survey results with 3000 patients showed that the proportion of patients receiving tolvaptan at 7.5 mg/day (0.125 mg/kg/day for adults with a body weight of 60 kg) was the highest at 52%, and that even the proportion of those at 3.75 mg/day (0.0625 mg/kg/day for adults with a body weight of 60 kg) was as high as 9%. Based on these findings, tolvaptan can be expected to show a certain efficacy at a starting dose of 0.05 mg/kg/day in this trial. On the other hand, the risk for excessive aquaresis should be avoided as some patients are highly responsive to tolvaptan. A dose of 0.05 mg/kg/day, which is equivalent to 3 mg/day for adults with a body weight of 60 kg, can reduce risks in such patients. Consequently, a starting dose was set at 0.05 mg/kg/day in consideration of a balance between efficacy and safety. A subsequent dose should be set for each individual subject by increasing the dose to 0.15, 0.3, or 0.5 mg/kg/day as per the guideline while monitoring each subject's response because responsiveness to tolvaptan may vary from subject to subject.

In the dose-ranging trial of tolvaptan in adult heart failure patients with volume overload (Trial 156-03-001), tolvaptan was administered at 15 mg/day, 30 mg/day, or 45 mg/day, and urine volume was increased with an increase in dose. For a decrease in body weight, on the other hand, no difference was noted between the 3 doses. This finding demonstrated that a dose of 15 mg/day was sufficient to obtain clinical effects. As a result, the approved dose of tolvaptan for adult heart failure patients with volume overload was determined to be 15 mg/day. The maximum dose in pediatric heart failure patients (0.5 mg/kg/day) is equivalent to 30 mg/day (adults with a body weight of 60 kg) in adult heart failure patients. This dose is sufficient to obtain an aquaretic effect even the effect in pediatric heart failure patients is as weak as around half of that in adults. In the dose-ranging trial (Trial 156-03-001), 7-day repeated administration of placebo or tolvaptan at 15 mg/day (0.25 mg/kg/day for adults with a body weight of 60 kg), 30 mg/day (0.5 mg/kg/day for adults with a body weight of 60 kg), or 45 mg/day (0.75 mg/kg/day for adults with a body weight of 60 kg) resulted in thirst with an incidence of 10.3% in the placebo group, 21.4% in the tolvaptan 15 mg/day group, 27.3% in the tolvaptan 30 mg/day group, and 53.6% in the tolvaptan 45 mg/day group, showing the higher incidence of AEs associated with the pharmacological action of tolvaptan in the 45 mg/day group. It is unlikely that tolvaptan therapy will pose safety issues when its maximum dose is set at 30 mg/day (equivalent to 0.5 mg/kg/day in children). The dose of

0.5 mg/kg/day is equivalent to the upper limit on the dose of tolvaptan specified in the Clinical Guideline for Medical Treatment of Pediatric Heart Failure.

Therefore, a trial of tolvaptan using an ascending dose regimen within the range of 0.05 to 0.5 mg/kg/day can provide information about its appropriate dose and regimen in pediatric heart failure patients.

2.3 Trial Objectives

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

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, open-label, uncontrolled, dose-titration trial. In this trial, an ascending dose regimen where administration is started at a low dose is employed to ensure the safety of subjects. A basic trial design schematic is shown in Figure 3.1-1. After completion of a screening examination, subjects will be hospitalized prior to the evening meal on 3 days before start of tolvaptan administration. Tolvaptan administration will be started at 0.05 mg/kg/day, and subjects with sufficient increase in urine volume will continue administration at 0.05 mg/kg/day for 3 days. For subjects whose urine volume does not sufficiently increase, the dose may be increased to 0.15, 0.3, or 0.5 mg/kg/day according to the specification. In that case, the dose should be decided for each individual subject to obtain sufficient increase in urine volume, and administration at the decided dose will be continued for 3 days. When the dose is increased to 0.5 mg/kg/day, administration at 0.5 mg/kg/day should be continued for 3 days. After final tolvaptan administration, subjects will continue to be hospitalized for 2 days to undergo monitoring of condition. Subjects will also undergo the follow up 5 to 7 days after final tolvaptan administration.

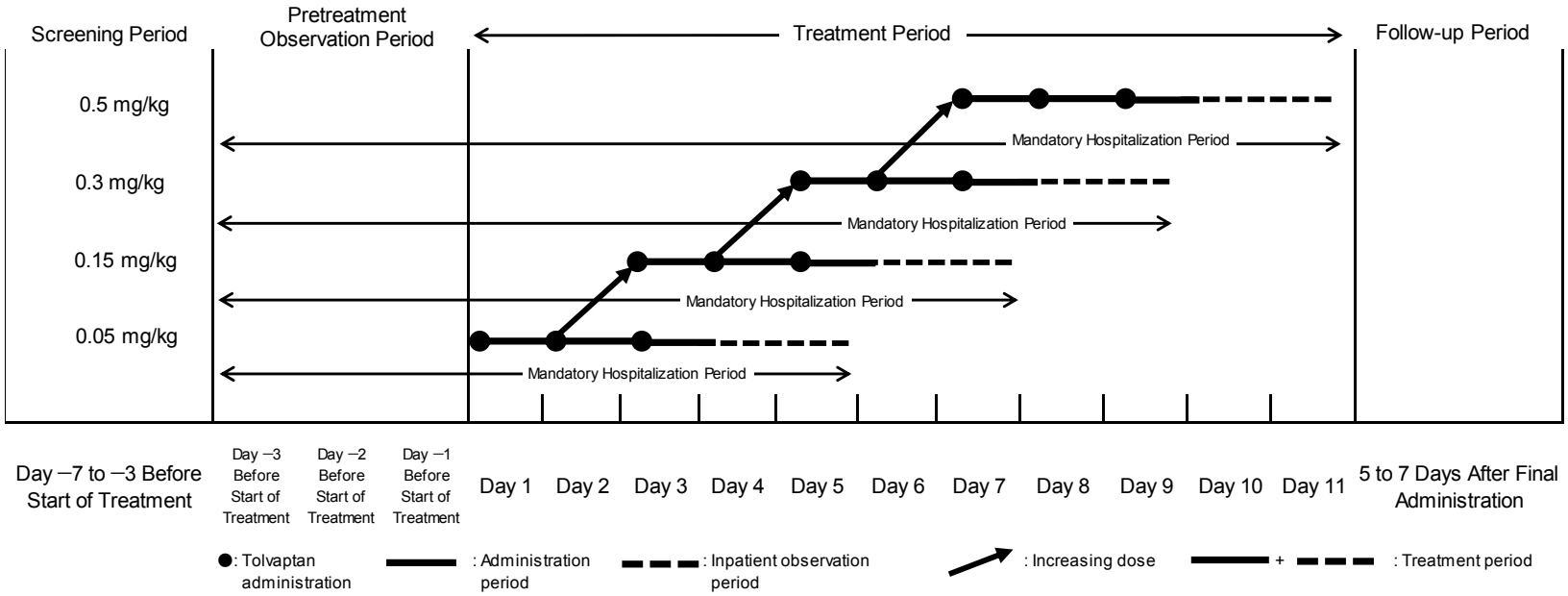


Figure 3.1-1 Basic Trial Design Schematic

3.2 Trial Treatments

3.2.1 Dose and Regimen

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

The initial dose of tolvaptan will be 0.05 mg/kg/day. From the second day of the treatment period and onward, if necessary the dose may be increased to 0.15, 0.3, or 0.5 mg/kg/day according to the rules specified in Section 3.2.2, and then the dose decided for each individual subject will be administered for 3 days. The dose of tolvaptan 1% granules to be administered will be determined depending on the subject's body weight on the day before start of tolvaptan administration; however, the maximum dose is 15 mg/day even if the calculated dose exceeds 15 mg/day. For administration at the maximum dose of 15 mg, tolvaptan 15-mg tablet may be administered in place of tolvaptan 1% granules. If the investigator or subinvestigator judges that there are an excessive aquaresis or safety concerns of subjects, the dose may be reduced (see Section 3.2.3). For subjects who need to continue treatment after 3-day administration at the dose decided individually, extended treatment for up to 4 days is allowed if the aim is to collect data on administration for up to 7 days and if the investigator or subinvestigator considers the safety of subjects to be ensured (including ensuring safety by dose reduction) (see Section 3.2.4). The dose, the date and time of administration, and the reason for dose reduction (for dose reduction, see Section 3.2.3) will be recorded in a source document and a case report form (CRF).

3.2.2 Increasing the Dose of Tolvaptan

Tolvaptan should be administered according to the following procedure. Daily urine volume should be assessed as "insufficient increase in urine volume" when it is less than 150% of that for the pretreatment observation period (1 day before start of tolvaptan administration), and "sufficient increase in urine volume" when it is at least 150%.

1) Tolvaptan administration will be started at 0.05 mg/kg/day, and administration at 0.05 mg/kg/day will be continued for 2 days.
2) For subjects with sufficient increase in urine volume on Day 1 or Day 2 of treatment, administration at 0.05 mg/kg/day will be continued for 3 days. For subjects with an insufficient increase in urine volume on Day 1 and Day 2 of treatment, the dose will be increased to 0.15 mg/kg/day on Day 3.
3) If a sufficient increase in urine volume is observed following 2-day administration at 0.15 mg/kg/day on Day 3 or Day 4 of the treatment period, administration at 0.15 mg/kg/day will be continued for 3 days. For subjects with an insufficient

increase in urine volume on Day 3 and Day 4 of the treatment period, the dose will be increased to 0.3 mg/kg/day on Day 5.

4) If a sufficient increase in urine volume is observed following 2-day administration at 0.3 mg/kg/day on Day 5 or Day 6 of the treatment period, administration at 0.3 mg/kg/day will be continued for 3 days. For subjects with an insufficient increase in urine volume on Day 5 and Day 6 of the treatment period, the dose will be increased to 0.5 mg/kg/day on Day 7, and administration at 0.5 mg/kg/day will be continued for 3 days.

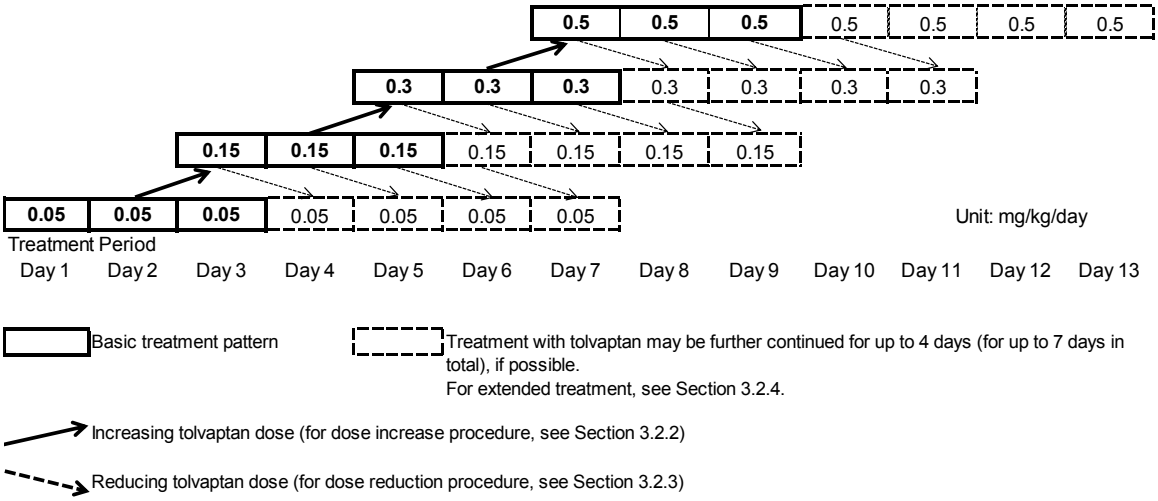
3.2.3 Reducing the Dose of Tolvaptan

If symptoms associated with excessive aquaresis such as persistent sensation of thirst, dehydration, and hypernatremia are observed or there are safety concerns in subjects, at a discretion of the investigator or subinvestigator, the dose may be reduced only to the next lower dose. In that case, however, the dose of conventional diuretics should not be changed. If the dose of tolvaptan needs to be reduced before completion of 3-day administration at the same dose, it should be administered at the reduced dose for 3 days. If the dose of tolvaptan needs to be further reduced after dose reduction to the next lower dose, the subject will be judged to have a problem with tolerability to tolvaptan and should be withdrawn from the trial.

3.2.4 Extended Treatment With Tolvaptan

Patterns of treatment with tolvaptan including extended treatment are shown in Figure 3.2.4-1. If the investigator or subinvestigator judges that the safety of subjects can continue to be ensured (including ensuring safety by dose reduction) after 3-day administration at the dose decided according to the specification for increasing the dose of tolvaptan (see Section 3.2.2), administration at that dose may be continued for up to 4 days (for up to 7 days in total).

In the case of an extended treatment with tolvaptan at reduced dose, the total number of administration days should be up to 7 days, which consists of “the days of administration at the dose just before the dose requiring reduction”, “the days of administration at the dose requiring reduction” and “the days of administration at the dose reduced to the next lower dose” (see examples of dose reduction in Figure 3.2.4-1).



Administration period for extended treatment with tolvaptan at reduced dose	
Dose-reduction example 1: The dose was increased to 0.3 mg/kg/day, but needed to be reduced on the first day of administration at the increased dose. Then, administration at 0.15 mg/kg/day was continued for 3 days. In this case, administration at 0.15 mg/kg/day can be continued for 1 day only. 0.3 0.15 0.15 0.15 0.15 0.15 0.15 0.05 0.05	In the case of dose reduction, the number of administration days should be up to 7 days, which consists of "the days of administration at the dose (0.15) just before the dose requiring reduction (0.3)", "the days of administration at the dose requiring reduction (0.3)", and "the days of administration at the dose reduced to the next lower level (0.15)" (see Section 3.2.4). (Unit: mg/kg/day)
Dose-reduction example 2: The dose was increased to 0.15 mg/kg/day, but needed to be reduced on the second day of administration at the increased dose. Then, administration at 0.05 mg/kg/day was continued for 3 days. In this case, administration at the reduced dose (0.05 mg/kg/day) cannot be continued. 0.15 0.15 0.05 0.05 0.05 0.05 0.05	In the case of dose reduction, the number of administration days should be up to 7 days, which consists of "the days of administration at the dose (0.05) just before the dose requiring reduction (0.15)", "the days of administration at the dose requiring reduction (0.15)", and "the days of administration at the dose reduced to the next lower level (0.05)" (see Section 3.2.4). (Unit: mg/kg/day)

Figure 3.2.4-1 Patterns of Treatment With Tolvaptan Including Extended Treatment

In principle, tolvaptan will be administered while increasing its dose every 2 days, and then, administered at the dose decided for each individual subject for 3 days. If the dose needs to be reduced before completion of 3-day administration, the dose may be reduced only once. The reduced dose should be regarded as the dose decided for each individual subject, and tolvaptan should be administered at the dose for 3 days. The duration of extended treatment at the reduced dose will be limited.

3.2.5 Treatment Period

According to the patterns of treatment with tolvaptan, the duration of treatment period will be 3 days at the shortest, and 13 days at the longest if tolvaptan is administered until the dose is increased to 0.5 mg/kg/day, at 0.5 mg/kg/day for 3 days, and at 0.5 mg/kg/day for additional 4 days.

[Rationale for the Treatment Period]

In a phase 3 trial in adult cardiac edema patients in Japan (Trial 156-06-002), a significant decrease in body weight (−1.27 kg) was seen even on Day 3 although its degree was smaller than that on Day 7 (−1.67 kg). In the retrospective study in pediatric heart failure patients in Japan,[2] an increase in urine volume and a decrease in body weight reached almost a plateau on Day 3 of treatment. Therefore, 3-day administration of tolvaptan is considered to be able to provide adequate data to evaluate its efficacy. In addition, it is considered that the efficacy evaluation needs to be performed for as short a time as possible because the duration to fix the dose and regimen of concomitant drugs cannot be prolonged. In view of this, administration for 3 days in the shortest is appropriate.

In 2 phase 3 trials in adult cardiac edema patients in Japan (Trials 156-06-002 and 156-06-006), the safety and efficacy of 7-day administration, and the safety of 14-day administration were confirmed, respectively. Therefore, it is considered to be appropriate to allow extended treatment with tolvaptan for 7 days which may result in administration for up to 13 days including the ascending dose period.

3.2.6 Hospitalization

Subjects will be hospitalized prior to the evening meal on 3 days before start of tolvaptan administration until completion of an examination 2 days after final administration. The investigator or subinvestigator will record the dates of hospitalization and discharge for each individual subject in a source document and a CRF.

3.3 Trial Population

Pediatric heart failure patients age 6 months to less than 15 years with volume overload despite having received conventional diuretic therapy

“Pediatric heart failure patients with volume overload despite having received conventional diuretic therapy” are defined as patients with volume overload despite having received any of the following diuretic therapies 1) in whom sufficient effects cannot be expected even if the dose of the diuretics is increased, or 2) in whom the investigator or subinvestigator judges that increasing the dose of the diuretics is 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 will be calculated as equivalent to furosemide 20 mg.
- Hydrochlorothiazide ≥2 mg/kg/day
- Trichlormethiazide ≥0.05 mg/kg/day
- Spironolactone ≥1 mg/kg/day

3.3.1 Number of Subjects and Description of Population

The subject population includes male or female pediatric heart failure patients with volume overload despite having received conventional diuretic therapy whose age is 6 months to less than 15 years at the time of informed consent by a legal representative. The planned number of subjects for receiving tolvaptan is set at 60.

According to a separately specified procedure, target patients will be 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). Patients in the old age group (7 years to less than 15 years) will be enrolled at first, and a medical advisor will confirm that there is no safety problem in the group when the first 6 subjects complete administration. The enrollment of patients in the middle age group (2 years to less than 7 years) will be started after that (while the enrollment of patients in the old age group will be continued). A medical advisor will confirm that there is no safety problem in the middle age group (2 years to less than 7 years) when the first 6 subjects in the group complete administration, and then, the enrollment of patients in the young age group (6 months to less than 2 years) will be started. The number of patients to be enrolled is up to 24 each for the old age group and the middle age group. For patients in the young age group (6 months to less than 2 years), a medical advisor will confirm the safety when the first 3 subjects in the group complete administration, and then the subsequent enrollment will be started. Underdeveloped patients who are classified into the middle or old age group but weigh less than half the ideal body weight[3] for children at the lower limit of age in each group (2 or 7 years) will be enrolled after start of administration for subjects in the next younger age group.

3.3.2 Subject Selection and Numbering

A subject identifier (subject ID) [site number (3 digits) + S + serial number within the site (5 digits)] will be assigned to each subject for whom a legal representative has given informed consent. The [site number (3 digits)] will be designated by the sponsor. The [serial number within the site (5 digits)] will be assigned from 00001, in the order of

informed consent obtained, within each trial site. The trial site will prepare and retain a list of all subjects for whom a legal representative has given informed consent with their subject identifiers.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Written informed consent will be freely obtained from all subjects' legal representatives (their guardians or legally acceptable representatives, as applicable for laws). If possible, assent (agreement from pediatric subjects who are not subject to legal regulations) will also be obtained from participating subjects themselves. Consent will be documented on a written informed consent form (ICF), and assent will be documented on a written informed assent form (IAF). The ICF and IAF will be approved by the same institutional review board (IRB) that approves this protocol.

Each ICF will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[4] and local regulatory requirements.

Investigators or subinvestigator may discuss trial availability and the possibility for entry with the legal representative without first obtaining consent. However, informed consent must be obtained from the legal representative and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Legal representatives and potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the legal representative by the investigator or subinvestigator, the IRB approved written ICF will be signed and dated by both the legal representative and the person obtaining consent (investigator or subinvestigator). For obtaining assent from the subject himself/herself, full explanation will be given to the potential subject in layman's language according to his/her age, and then, the IRB approved written IAF will be signed and dated by both the subject himself/herself and the person obtaining assent (investigator or subinvestigator). If a clinical trial associate has provided a supplemental explanation, the IRB approved written ICF and IAF will be signed and dated by the

clinical trial associate. The legal representative will receive a copy of the signed ICF and IAF; the originals shall be kept on file by the investigator or subinvestigator.

Legal representatives may be asked to sign additional ICFs if the protocol is amended to significantly add or change procedures.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in Table 3.4.2-1.

Table 3.4.2-1 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 cannot be expected even if the dose of the diuretics is increased or in whom the investigator or subinvestigator judges that increasing the dose of the diuretics is 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 will 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 can also be enrolled in the trial if strict management of fluid intake and excretion is 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 is possible, patients in whom the investigator or subinvestigator judges that tolvaptan cannot be safely administered are to be excluded.
4.	Patients who can be hospitalized from at least 3 days before start of tolvaptan administration until 2 days after final administration

[Rationale for the Inclusion Criteria]

1) In consideration of trial conduct and the fact that many patients, even at the age of less than 1 year, need tolvaptan therapy, the lower limit of age is determined to be 6 months. As adolescent patients may also require tolvaptan therapy, the upper limit of age is determined to be less than 15 years as specified in the package insert of tolvaptan.
2) The criterion is set based on the clinical position of tolvaptan.
3) When tolvaptan therapy produces an excessive diuretic effect and significantly disrupts the balance between fluid intake and excretion, a serum or blood sodium concentration may be rapidly increased. Therefore, this trial can be safely conducted by strictly managing the fluid balance while monitoring serum or blood sodium concentration for patients unable to complain of thirst due to their young age, and taking appropriate actions such as the use of hypotonic solution as needed. The criterion is set from this perspective.
4) The criterion is set to evaluate the efficacy and safety in this trial.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1. Subjects' legal representatives must agree the restriction on medications specified in Section 4.

Table 3.4.3-1 Exclusion Criteria

1.	Patients whose volume overload status shows improvement during the screening period or pretreatment observation period
2.	Patients who are unable to drink fluid (including patients who are unable to sense thirst)
3.	Patients whose circulatory blood flow is 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 have participated in any other trials within 30 days prior to informed consent by a legal representative
12.	Patients who have received tolvaptan therapy before
13.	Female patients who are breastfeeding or who tests positive in pregnancy test prior to tolvaptan administration
14.	Female patients who are pregnant or suspected of being pregnant, or patients who cannot agree to remain fully abstinent during the trial and for 30 days after the last dose of IMP
15.	Breastfed patients (excluding those patients whose fluid intake can be measured by expressed breast milk or other ways, and whose mother does 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 are judged to be ineligible to participate in this trial by the investigator or subinvestigator.

[Rationale for the Inclusion Criteria]
1) The criterion is set because the efficacy evaluation may be affected.
2) The criterion is set because tolvaptan therapy for such patients is contraindicated in the package insert of Samsca®.
3) The criterion is set because treatment through excessive diuresis is unfavorable.
4) The criterion is set because the evaluation of efficacy and safety may be affected.
5) The criterion is set because tolvaptan therapy for such patients is contraindicated in the package insert of Samsca.
6) to 8) The criteria are set because it is difficult to ensure the safety of the patients during the trial.
9) The criterion is set because tolvaptan therapy for such patients is contraindicated in the package insert of Samsca.
10) The criterion is set because it is difficult to ensure the safety of such patients during the trial or

because enrollment of such patients is considered to be inappropriate.
11) The criterion is set because the evaluation of efficacy and safety may be affected.
12) The criterion is set because the evaluation of efficacy may be affected.
13) to 14) The criteria are set because tolvaptan has been shown to be teratogenic and embryo-fetal lethal (in rabbits), and excreted into milk (in rats).
15) The criterion is set because the control of drugs in breast milk and the measurement of fluid intake cannot be performed in such patients.
16) The criterion is set because the evaluation of efficacy and safety may be affected.

3.5 Endpoints

3.5.1 Primary Endpoint

The percentage of subjects who satisfy the following condition:

- Body weight on the day after the third day of treatment with tolvaptan at the evaluation dose (see Section 7.4) is decreased by 1.7% or more from the weight measured before breakfast on the first day of the treatment period

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

<Rationale for the Primary Endpoint>

Body weight in heart failure patients is considered to reflect change in systemic volume overload, and it is therefore regarded as a general index to grasp volume overload status in edematous diseases. Tolvaptan was approved based on the results of trials conducted during its clinical development in adult heart failure patients with volume overload, where body weight was set as a primary efficacy endpoint. In view of the above, body weight is also employed as a safety endpoint in this trial. An increase in daily urine volume is set to confirm that a decrease in body weight is brought by the aquaretic effect of tolvaptan therapy.

3.5.2 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

<Rationale for the Secondary Endpoints>

In this trial, the degree of improvement in each edematous symptom is also set as an efficacy endpoint. Target edematous symptoms include edema (lower limbs, etc), jugular venous distension, pulmonary congestion, and cardiothoracic ratio, which were assessed in tolvaptan trials during its clinical development in adult heart failure patients with volume overload. As a particularly essential item for pediatric heart failure patients, dyspnea, respiration rate at rest, pulse rate, pleural effusion, central venous pressure, and retention of pericardial effusion will also be assessed in this trial.

An increase in urine volume is an index reflecting the pharmacological action of tolvaptan. Body weight, which is set as an efficacy endpoint, may be affected by food intake, vomiting, excretion, or other factors. Therefore, daily urine volume is included in the efficacy endpoints to confirm that a decrease in body weight is caused by increasing the excretion of free water, the pharmacological action of tolvaptan.

3.6 Measures to Minimize/Avoid Bias

As this is an uncontrolled trial in one active treatment group, blinding and randomization are not performed.

3.7 Trial Procedures

Basic trial assessment schedule is shown in Table 3.7-1. See Section 3.7.1.4 for the assessment schedule when extending treatment with tolvaptan at the dose decided for each individual subject from the fourth day, and see Section 3.7.1.5 for the assessment schedule when extending treatment with tolvaptan at a reduced dose.

Table 3.7-1 Basic Assessment Schedule Without Reduction of Dose or Extension of Treatment

	Screening	Pretreatment Observation Period			Treatment Period											Follow-up	Withdrawal
	Day -7 to -3 Before Start of Treatment	Day -3 Before Start of Treatment	Day -2 Before Start of Treatment	Day -1 Before Start of Treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day After Final Administration	2 Days After Final Admnistration	5 to 7 Days After Final Administration	At Withdrawal
Informed Consent	□																
Subject Enrollment				□													
IMP Administration					◊	◊	◊	◊	◊	◊	◊	◊	◊				
Body Weight	□		○	○	○	○	○	○	○	○	○	○	○	○		□	□
Vital sign (Blood Pressure, Pulse Rate, Body Temperature)	□			□	□	□	□	□	□	□	□	□	□	□	□	□	□
12-Lead ECG			□											□		□	□
LaboratoryTests	□			○		○		○		○		○		○		□	□
Serum/Blood Sodicum concentration	□			○	○▼▲	○	○▼[a]▲[a]	○	○▼[a]▲[a]	○	○▼[a]▲[a]	○	○	○		□	□
Serum/Blood Potassium concentration	□			○	○	○	○	○	○	○	○	○	○	○		□	□
Serum Osmolality				○		○		○		○		○		○		□	□
Plasma AVP Concentration (only subjects for whom sample is available)				○										○			
Daily Urine Volume and Fluid Intake, Urine Sodium and Potassium Excretions, and Urine Osmolality[b]				←	→	→	→	→	→	→	→	→	→				
Plasma Drug Concentration[c]							○[d]●[d]■[d]		○[d]●[d]■[d]		○[d]●[d]■[d]		○[d]●[d]■[d]	○			□
Edematous Symptoms	□		□	□	□[e]	□[e]	□[e]	□[e]	□[e]	□[e]	□[e]	□[e]	□[e]	□		□	□
Chest X-ray (Pulmonary Congestion, Cardiacthoracic Ratio, Pleural Effusion)			□											□			
Pregnancy Test (only for female subjects who have begun menstruation)	□																
Adverse Events	←																→
IMP Compliance					□	□	□	□	□	□	□	□	□				□
Concomittant Drugs and Therapies	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□

Assessments should be performed according to the schedules for Days 1 to 9 until completion of 3-day administration at the dose decided for each individual subject, and the schedules for Day After Final Administration and subsequent days after completion of 3-day administration at the dose decided for each individual subject.

The schedule presented in Section 3.7.1.5 Extended Treatment With Tolvaptan at Reduced Dose will be followed when the dose needs to be reduced, and the schedule presented in Section 3.7.1.4 Extended Treatment With Tolvaptan at Dose Decided for Each Individual Subject From Fourth Day will be followed when treatment is extended after completion of 3-day administration at the dose decided for each individual subject.

○ = Before breakfast; ◊ = After breakfast; □ = At a feasible time; ● = At 2 to 4 hours postdose; ▼ = At 4 to 6 hours postdose; ▲ = At 8 to 12 hours postdose; ■ = At 10 to 14 hours postdose.

[a]To be measured at the time of dose increase.

[b]To be measured up until the morning of the day after final IMP administration.

[c]The blood collection for measurement of plasma drug concentration specified for before breakfast (○) may be performed after breakfast as long as it is before IMP administration.

[d]Only on the third day of administration at 0.05, 0.15, 0.3, or 0.5 mg/kg/day.

[e]After IMP administration.

3.7.1 Schedule of Assessments

3.7.1.1 Screening Period (7 to 3 Days Before Start of Tolvaptan Administration)

After obtaining informed consent from the legal representative, the investigator or subinvestigator will assign a subject identifier to the subject according to Section 3.3.2, and record the date of informed consent and the subject identifier in a source document and a CRF.

The investigator or subinvestigator will perform the following examinations and investigations, and confirm that the subject meets all of the inclusion criteria and none of the exclusion criteria to record the result of confirmation in a source document and a CRF.

1) Investigation of subject background
   - Birth date
   - Gender
   - Height
   - Race
   - Complication
   - Medical history
   - Etiology of heart failure
2) Examinations and assessments
   - Concomitant drugs and therapies
   - Body weight
   - Vital signs
   - Laboratory tests
   - Serum or blood sodium concentration
   - Serum or blood potassium concentration
   - Edematous symptoms
   - Pregnancy test (urine human chorionic gonadotropin [hCG] test): Only for female subjects who have begun menstruation
   - Adverse events

3.7.1.2 Pretreatment Observation Period

3.7.1.2.1 Pretreatment Observation Period (3 Days Before Start of Tolvaptan Administration)

The investigator or subinvestigator will admit the subject to the trial site before evening meal to perform the following investigations.

- Concomitant drugs and therapies
- Adverse events

3.7.1.2.2 Pretreatment Observation Period (2 Days Before Start of Tolvaptan Administration)

The investigator or subinvestigator will perform the following procedures.

1) Before breakfast
   - Body weight
2) At a feasible time
   - 12-lead electrocardiogram (ECG) (at any time 1 day before start of tolvaptan administration)
   - Chest x-ray (at any time 1 day before start of tolvaptan administration)
   - Edematous symptoms
   - Concomitant drugs and therapies
   - Adverse events

3.7.1.2.3 Pretreatment Observation Period (1 Day Before Start of Tolvaptan Administration)

The investigator or subinvestigator will perform the following procedures.

The investigator or subinvestigator will confirm that the subject does not meet Exclusion Criteria 1, and record the result of confirmation in a source document and a CRF.

1) Before breakfast
   - Body weight
   - Laboratory tests
   - Serum or blood sodium concentration
   - Serum or blood potassium concentration
   - Serum osmolality
   - Plasma AVP concentration (only subjects from whom samples are available)
2) Approximately 24 hours before the scheduled time of first tolvaptan administration

   The subject will be instructed to completely discharge the urine immediately after breakfast. Urine collection and fluid intake measurement will be started to assess the following items.
   - Daily urine volume
   - Daily fluid intake
   - Daily fluid balance

- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

3) At a feasible time
   - Subject enrollment
   - Vital signs
   - 12-lead ECG (at any time 2 day before start of tolvaptan administration)
   - Chest x-ray (at any time 2 day before start of tolvaptan administration)
   - Edematous symptoms
   - Concomitant drugs and therapies
   - Adverse events

3.7.1.3 Treatment Period

Procedures will be conducted according to the schedules specified in Section 3.7.1.3.1 to Section 3.7.1.3.9 until completion of 3-day administration at the dose decided for each individual subject, and the schedules specified in Section 3.7.1.3.10 and subsequent sections after completion of 3-day administration at the dose decided for each individual subject. If extending treatment at the dose decided for each individual subject from the fourth day, the schedule presented in Section 3.7.1.4 should be followed.

If the dose needs to be reduced, the schedule presented in Section 3.7.1.5 should be followed.

3.7.1.3.1 Day 1 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

   The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.
   - Body weight
   - Serum or blood sodium concentration
   - Serum or blood potassium concentration

   The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.
   - Daily urine volume
   - Daily fluid intake

- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan (0.05 mg/kg/day) with water after breakfast. After administration, the change in serum or blood sodium concentration will be observed. If the change meets the following criteria, the investigator or subinvestigator should discontinue treatment with tolvaptan as specified in Section 3.8.3.1, and perform the withdrawal examination according to Section 3.7.1.6.

- Serum or blood sodium concentration increased by ≥8 mEq/L from that immediately before tolvaptan administration, within 8 to 12 hours after administration
- Serum or blood sodium concentration increased by ≥12 mEq/L from that immediately before tolvaptan administration, within 24 hours after administration
- Serum or blood sodium concentration exceeding 145 mEq/L is observed during the treatment period

3) 4 to 6 hours after tolvaptan administration
   - Serum or blood sodium concentration
4) 8 to 12 hours after tolvaptan administration
   - Serum or blood sodium concentration
5) At a feasible time
   - Vital signs
   - Edematous symptoms (after tolvaptan administration)
   - Concomitant drugs and therapies
   - IMP compliance
   - Adverse events

3.7.1.3.2 Day 2 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Laboratory tests

- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Serum osmolality

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan (0.05 mg/kg/day) with water after breakfast.

3) At a feasible time
   - Vital signs
   - Edematous symptoms (after tolvaptan administration)
   - Concomitant drugs and therapies
   - IMP compliance
   - Adverse events

3.7.1.3.3 Day 3 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Plasma drug concentration (on the third day of administration at 0.05 mg/kg/day)
  Assessment after breakfast is allowed if it is conducted prior to tolvaptan administration.

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) 2 to 4 hours after tolvaptan administration (on the third day of administration at 0.05 mg/kg/day)
   - Plasma drug concentration
4) 4 to 6 hours after tolvaptan administration (at increased dose)
   - Serum or blood sodium concentration
5) 8 to 12 hours after tolvaptan administration (at increased dose)
   - Serum or blood sodium concentration
6) 10 to 14 hours after tolvaptan administration (on the third day of administration at 0.05 mg/kg/day)
   - Plasma drug concentration
7) At a feasible time
   - Vital signs
   - Edematous symptoms (after tolvaptan administration)
   - Concomitant drugs and therapies
   - IMP compliance
   - Adverse events

3.7.1.3.4 Day 4 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Laboratory tests

- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Serum osmolality

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) At a feasible time

- Vital signs
- Edematous symptoms (after tolvaptan administration)
- Concomitant drugs and therapies
- IMP compliance
- Adverse events

3.7.1.3.5 Day 5 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Plasma drug concentration (on the third day of administration at 0.15 mg/kg/day)
  Assessment after breakfast is allowed if it is conducted prior to tolvaptan administration.

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) 2 to 4 hours after tolvaptan administration (on the third day of administration at 0.15 mg/kg/day)
   - Plasma drug concentration
4) 4 to 6 hours after tolvaptan administration (at increased dose)
   - Serum or blood sodium concentration
5) 8 to 12 hours after tolvaptan administration (at increased dose)
   - Serum or blood sodium concentration
6) 10 to 14 hours after tolvaptan administration (on the third day of administration at 0.15 mg/kg/day)
   - Plasma drug concentration
7) At a feasible time
   - Vital signs
   - Edematous symptoms (after tolvaptan administration)
   - Concomitant drugs and therapies
   - IMP compliance
   - Adverse events

3.7.1.3.6 Day 6 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Laboratory tests

- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Serum osmolality

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) At a feasible time

- Vital signs
- Edematous symptoms (after tolvaptan administration)
- Concomitant drugs and therapies
- IMP compliance
- Adverse events

3.7.1.3.7 Day 7 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Plasma drug concentration (on the third day of administration at 0.3 mg/kg/day)
  Assessment after breakfast is allowed if it is conducted prior to tolvaptan administration.

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) 2 to 4 hours after tolvaptan administration (on the third day of administration at 0.3 mg/kg/day)
   - Plasma drug concentration
4) 4 to 6 hours after tolvaptan administration (at increased dose)
   - Serum or blood sodium concentration
5) 8 to 12 hours after tolvaptan administration (at increased dose)
   - Serum or blood sodium concentration
6) 10 to 14 hours after tolvaptan administration (on the third day of administration at 0.3 mg/kg/day)
   - Plasma drug concentration
7) At a feasible time
   - Vital signs
   - Edematous symptoms (after tolvaptan administration)
   - Concomitant drugs and therapies
   - IMP compliance
   - Adverse events

3.7.1.3.8 Day 8 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Laboratory tests

- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Serum osmolality

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) At a feasible time

- Vital signs
- Edematous symptoms (after tolvaptan administration)
- Concomitant drugs and therapies
- IMP compliance
- Adverse events

3.7.1.3.9 Day 9 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Plasma drug concentration (on the third day of administration at 0.5 mg/kg/day)
  Assessment after breakfast is allowed if it is conducted prior to tolvaptan administration.

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) 2 to 4 hours after tolvaptan administration
   - Plasma drug concentration (on the third day of administration at 0.5 mg/kg/day)
4) 10 to 14 hours after tolvaptan administration
   - Plasma drug concentration (on the third day of administration at 0.5 mg/kg/day)
5) At a feasible time
   - Vital signs
   - Edematous symptoms (after tolvaptan administration)
   - Concomitant drugs and therapies
   - IMP compliance
   - Adverse events

3.7.1.3.10 Day After Final Administration

If administration at the dose decided for each individual subject is completed in 3 days, the investigator or subinvestigator will perform the following procedures on the day after final administration.

1) Before breakfast
   - Body weight
   - Laboratory tests
   - Serum or blood sodium concentration
   - Serum or blood potassium concentration
   - Serum osmolality
   - Plasma AVP concentration (only subjects from whom samples are available)

- Plasma drug concentration: Assessment after breakfast is allowed.

2) At a feasible time
   - Vital signs
   - 12-lead ECG
   - Edematous symptoms
   - Chest x-ray
   - Concomitant drugs and therapies
   - Adverse events

3.7.1.3.11 Two Days After Final Administration

If administration at the dose decided for each individual subject is completed in 3 days, the investigator or subinvestigator will perform the following procedures 2 days after final administration.

1) At a feasible time
   - Vital signs
   - Concomitant drugs and therapies
   - Adverse events

3.7.1.4 Extended Treatment With Tolvaptan at Dose Decided for Each Individual Subject From Fourth Day

The schedules presented in Section 3.7.1.4.1 to Section 3.7.1.4.4 should be followed when extending treatment at the dose decided for each individual subject, and the schedules presented in Section 3.7.1.4.5 and subsequent sections should be followed after completion of extended treatment.

If the dose needs to be reduced, the schedule presented in Section 3.7.1.5 should be followed.

3.7.1.4.1 Fourth Day of Administration at Dose Decided for Each Individual Subject

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration
   The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.
   - Body weight
   - Laboratory tests

- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Serum osmolality
- Plasma AVP concentration (only subjects from whom samples are available)
- Plasma drug concentration: Assessment after breakfast is allowed if it is conducted prior to tolvaptan administration.

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration
The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) At a feasible time
- Vital signs
- 12-lead ECG
- Edematous symptoms (after tolvaptan administration)
- Chest x-ray
- Concomitant drugs and therapies
- IMP compliance
- Adverse events

3.7.1.4.2 Fifth Day of Administration at Dose Decided for Each Individual Subject

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration
The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.
- Body weight
- Serum or blood sodium concentration

- Serum or blood potassium concentration

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) At a feasible time

- Vital signs
- Edematous symptoms (after tolvaptan administration)
- Concomitant drugs and therapies
- IMP compliance
- Adverse events

3.7.1.4.3 Sixth Day of Administration at Dose Decided for Each Individual Subject

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Laboratory tests
- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Serum osmolality

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake

- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) At a feasible time

- Vital signs
- Edematous symptoms (after tolvaptan administration)
- Concomitant drugs and therapies
- IMP compliance
- Adverse events

3.7.1.4.4 Seventh Day of Administration at Dose Decided for Each Individual Subject

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Serum or blood sodium concentration
- Serum or blood potassium concentration

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) At a feasible time
   - Vital signs
   - Edematous symptoms (after tolvaptan administration)
   - Concomitant drugs and therapies
   - IMP compliance
   - Adverse events

3.7.1.4.5 Day After Final Administration in Extended Treatment

The investigator or subinvestigator will perform the following procedures.

1) Before breakfast
   - Body weight
   - Laboratory tests (Assessment will not be performed if it is completed on the previous day.)
   - Serum or blood sodium concentration
   - Serum or blood potassium concentration
   - Serum osmolality (Assessment will not be performed if it is completed on the previous day.)
2) At a feasible time
   - Vital signs
   - Edematous symptoms
   - Concomitant drugs and therapies
   - Adverse events

3.7.1.4.6 Two Days After Final Administration in Extended Treatment

The investigator or subinvestigator will perform the following procedures.

1) At a feasible time
   - Vital signs
   - Concomitant drugs and therapies
   - Adverse events

3.7.1.5 Extended Treatment With Tolvaptan at Reduced Dose

The schedules presented in Section 3.7.1.5.1 to Section 3.7.1.5.4 should be followed when extending treatment at reduced dose, and the schedules presented in Section 3.7.1.5.5 and subsequent sections should be followed after completion of extended treatment.

3.7.1.5.1 First Day of Administration at Reduced Dose

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Laboratory tests
- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Serum osmolality
- Plasma AVP concentration (on the day after the third day of administration at 0.15, 0.3, or 0.5 mg/kg/day; only subjects from whom samples are available)
- Plasma drug concentration (on the day after the third day of administration at 0.15, 0.3, or 0.5 mg/kg/day): Assessment after breakfast is allowed if it is conducted prior to tolvaptan administration.

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) At a feasible time

- Vital signs
- 12-lead ECG (on the day after the third day of administration at 0.15, 0.3, or 0.5 mg/kg/day)
- Edematous symptoms (after tolvaptan administration)
- Chest x-ray (on the day after the third day of administration at 0.15, 0.3, or 0.5 mg/kg/day)
- Concomitant drugs and therapies

- IMP compliance
- Adverse events

3.7.1.5.2 Second Day of Administration at Reduced Dose

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Serum or blood sodium concentration
- Serum or blood potassium concentration

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) At a feasible time

- Vital signs
- Edematous symptoms (after tolvaptan administration)
- Concomitant drugs and therapies
- IMP compliance
- Adverse events

3.7.1.5.3 Third Day of Administration at Reduced Dose

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Laboratory tests
- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Plasma drug concentration: Assessment after breakfast is allowed if it is conducted prior to tolvaptan administration.
- Serum osmolality

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) 2 to 4 hours after tolvaptan administration
   - Plasma drug concentration
4) 10 to 14 hours after tolvaptan administration
   - Plasma drug concentration
5) At a feasible time
   - Vital signs
   - Edematous symptoms (after tolvaptan administration)
   - Concomitant drugs and therapies
   - IMP compliance
   - Adverse events

3.7.1.5.4 Fourth Day of Administration at Reduced Dose

The investigator or subinvestigator will perform the following procedures.

1) Before tolvaptan administration

The investigator or subinvestigator will perform the following examinations, and then, offer breakfast to the subject.

- Body weight
- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Plasma AVP concentration (only subjects from whom samples are available)
- Plasma drug concentration: Assessment after breakfast is allowed if it is conducted prior to tolvaptan administration.

The investigator or subinvestigator will instruct the subject to completely discharge the urine immediately after breakfast, and start urine collection and fluid intake measurement to assess the following items.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Urine sodium excretion
- Urine potassium excretion
- Urine osmolality

2) Tolvaptan administration

The investigator or subinvestigator will instruct the subject to take tolvaptan with water after breakfast according to Section 3.2.

3) At a feasible time
   - Vital signs
   - 12-lead ECG
   - Edematous symptoms (after tolvaptan administration)
   - Chest x-ray
   - Concomitant drugs and therapies
   - IMP compliance
   - Adverse events

3.7.1.5.5 Day After Final Administration in Extended Treatment at Reduced Dose

The investigator or subinvestigator will perform the following procedures.

1) Before breakfast
   - Body weight
   - Laboratory tests (Assessment will not be performed if it is completed on the previous day.)
   - Serum or blood sodium concentration
   - Serum or blood potassium concentration

- Serum osmolality (Assessment will not be performed if it is completed on the previous day.)
- Plasma AVP concentration (on the day after the third day of administration at reduced dose; only subjects from whom samples are available)
- Plasma drug concentration (on the day after the third day of administration at reduced dose)
  : Assessment after breakfast is allowed if it is conducted prior to tolvaptan administration.

2) At a feasible time
   - Vital signs
   - 12-lead ECG (on the day after the third day of administration at reduced dose)
   - Edematous symptoms
   - Chest x-ray (on the day after the third day of administration at reduced dose)
   - Concomitant drugs and therapies
   - Adverse events

3.7.1.5.6 Two Days After Final Administration in Extended Treatment at Reduced Dose

The investigator or subinvestigator will perform the following procedures.

1) At a feasible time
   - Vital signs
   - Concomitant drugs and therapies
   - Adverse events

3.7.1.6 Treatment Discontinuation

When discontinuation of treatment with tolvaptan is deemed necessary according to the rules specified in Section 3.8.3.1, the investigator or subinvestigator will perform the following examinations or investigations. If the examination or investigation has been completed on the day of treatment discontinuation, it does not have to be repeated. If it is not feasible to perform all of the examinations, observations, and assessments at treatment discontinuation, because of the subject's refusal or at the discretion of the investigator or subinvestigator (eg, in emergencies), only feasible ones should be performed.

- Concomitant drugs and therapies
- Serum or blood sodium concentration
- Serum or blood potassium concentration

- Body weight
- Laboratory tests
- Serum osmolality
- Plasma drug concentration (Assessment does not have to be repeated on the day of treatment discontinuation if it has been conducted after administration.)
- Vital signs
- 12-lead ECG
- Edematous symptoms
- IMP compliance
- Adverse events

3.7.1.7 Follow-up Period (5 to 7 Days After Final Tolvaptan Administration)

The investigator or subinvestigator will perform the following procedures.

1) At a feasible time
   - Body weight
   - Vital signs
   - 12-lead ECG
   - Laboratory tests
   - Serum or blood sodium concentration
   - Serum or blood potassium concentration
   - Serum osmolality
   - Edematous symptoms
   - Concomitant drugs and therapies
   - Adverse events

3.7.2 Efficacy Assessments

3.7.2.1 Body Weight

A calibrated scale (an instrument which can measure body weight to the second decimal point by the kilogram) should be used to determine body weight while minimizing the influence of clothing, at about the same time before breakfast throughout the trial period. The date and time, and result of measurement (to the second decimal point by the kilogram) will be recorded in a source document and a CRF. The result should be rounded to 2 decimal places.

3.7.2.2 Daily Urine Volume

During the pretreatment observation period, daily urine volume will be measured for the time interval starting at urination (an instruction to urinate) after breakfast and ending at complete urination immediately before administration on the following day. After start of tolvaptan administration on the first day of the treatment period, daily urine volume will be determined for each time interval from the point after urination (an instruction to urinate) immediately before administration of the day to the point after urination (an instruction to urinate) immediately before administration on the following day.

For diapered subjects whose urine volume is difficult to determine by urine collection, urine volume may be estimated from the difference in the weight of diaper between before and after use (the weight at 1 g should be converted to 1 mL). The procedure should be established with consideration of measurement time to minimize fluctuations. The method of urine volume measurement (urine collection, diaper, or both) should not be changed throughout the trial period.

The status (measured/not measured), start date and time, and completion date and time of measurement, as well as daily urinary volume will be recorded in a source document and a CRF.

3.7.2.3 Edematous Symptoms (Edema [Lower Limbs, Eyelids, etc], Dyspnea, Jugular Venous Distension, Respiration Rate at Rest, and Pulse Rate)

3.7.2.3.1 Edema (Lower Limbs, Eyelids, etc)

3.7.2.3.1.1 Edema (Lower Limbs)

In principle, the grade of edema at the tibial border or the acrotarsium will be assessed in the sitting position, according to Table 3.7.2.3.1.1-1. The date and time, and result of assessment will be recorded in a source document and a CRF.

Table 3.7.2.3.1.1-1 Criteria for Grading Lower Limb Edema

	Grade	Criterion
0	None	No pit observed
1	Mild	Faint pit observed
2	Moderate	Pit observed
3	Severe	Easily recognizable edema

3.7.2.3.1.2 Edema (Eyelids)

The presence/absence of eyelid edema will be assessed. The date and time, and result of assessment will be recorded in a source document and a CRF.

3.7.2.3.1.3 Edema (Others)

The same criteria as those for lower limb edema will be adopted to assess other edema. The same area of the body will be assessed before and after administration. The area, date and time, and result of assessment will be recorded in a source document and a CRF.

3.7.2.3.2 Dyspnea

The presence/absence of dyspnea will be assessed. The date and time, and result of assessment will be recorded in a source document and a CRF.

3.7.2.3.3 Jugular Venous Distension

The presence/absence of jugular venous distension will be visually assessed. The date and time, and result of assessment will be recorded in a source document and a CRF.

3.7.2.3.4 Respiration Rate at Rest

Respiration rate at rest will be measured by auscultation using a stethoscope, or by observing respiratory movement of the thorax (up-and-down movement of the chest) (times/minute). The date and time, and result of measurement will be recorded in a source document and a CRF.

3.7.2.3.5 Pulse Rate

A calibrated measuring instrument should be used to determine pulse rate after resting for at least 3 minutes. The status (measured/not measured), date and time, and result of measurement will be recorded in a source document and a CRF.

3.7.2.4 Chest X-ray (Pulmonary Congestion, Cardiothoracic Ratio, and Pleural Effusion)

A calibrated instrument should be used to perform chest x-ray, and the date of chest x-ray will be recorded in a source document and a CRF. An obtained radiograph will be assessed for pulmonary congestion, cardiothoracic ratio, and pleural effusion as described below, and the result of assessment will be recorded in a source document and a CRF.

3.7.2.4.1 Pulmonary Congestion

The grade of pulmonary congestion will be assessed according to Table 3.7.2.4.1-1, and the date and result of assessment will be recorded in a source document and a CRF.

Table 3.7.2.4.1-1 Criteria for Grading Pulmonary Congestion		
	Grade	**Criterion**
0	None	No congestion
1	Mild	Pulmonary venous congestion
2	Moderate	Interstitial pulmonary edema
3	Severe	Alveolar pulmonary edema

Modified from the criteria by Forrester JS, et al.[6]

3.7.2.4.2 Cardiothoracic Ratio

Cardiothoracic ratio (%) will be measured, and the date and result of measurement will be recorded in a source document and a CRF. For the result of measurement, a value to the first decimal point should be recorded.

3.7.2.4.3 Pleural Effusion

The presence/absence of pleural effusion will be assessed, and the date and result of assessment will be recorded in a source document and a CRF.

3.7.2.5 Central Venous Pressure (Only Subjects With Central Venous Catheterization)

In subjects with central venous catheterization who can undergo measurement before and after tolvaptan administration, a calibrated instrument should be used to determine central venous pressure (mmHg) in the way specified by each trial site. The date and result of measurement will be recorded in a source document and a CRF.

3.7.2.6 Retention of Pericardial Effusion (Only Subjects Requiring Echocardiography)

For subjects who have been found to have excessive retention of pericardial effusion by echocardiography before tolvaptan administration and have undergone echocardiography again after administration, a change in the degree of retention from that before administration (decrease, no change, or increase from that before administration) will be assessed. The date and result of assessment will be recorded in a source document and a CRF. A calibrated instrument should be used for echocardiography.

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to Section 5.

3.7.3.2 Laboratory tests

For laboratory tests, each trial site should use appropriate equipment and apparatuses with reliable precision, and follow the procedures specified by the site (measurement at the site). When measurement at the site is not feasible, samples may be sent to the contract research organization for clinical laboratory tests (hereafter, central laboratory) for measurement. The central laboratory will measure the following items according to the procedures specified by the laboratory, and report the result of measurement to the sponsor, and the investigator or subinvestigator. The status (with or without blood/urine sampling), the date and time of blood sampling, the date of urine sampling, and the result of measurement will be recorded in a source document and a CRF. The result of measurement by the specified central laboratory does not have to be recorded.

The case where the subject cannot provide urine sample for some reason despite having received an instruction to urinate will not be regarded as a deviation, but the reason should be recorded in a CRF. To ensure the safety of the subject, a sample should be obtained at a different time or day.

Unscheduled laboratory tests, if required at the occurrence of AEs or for the follow-up of AEs, should be performed at each trial site.

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology: Hemoglobin Mean Corpuscular Hemoglobin Concentration Mean Corpuscular Volume Hematocrit Red Blood Cell count White Blood Cell count with differential Platelet count Urinalysis: Color Occult blood Glucose pH Protein Specific gravity	Serum Chemistry: Alkaline Phosphatase ALT AST Bilirubin, total Blood Urea Nitrogen Uric acid Cholesterol Creatinine Gamma Glutamyl Transpeptidase Glucose Lactic Dehydrogenase Potassium Protein, total Albumin Sodium Triglycerides Additional Tests: Urine pregnancy test for all female subjects who have begun menstruation

In all female subjects who have begun menstruation, a pregnancy test will be conducted at screening examination, and results must be available prior to tolvaptan administration.

3.7.3.3 Vital signs

3.7.3.3.1 Body Temperature

A calibrated thermometer should be used to determine body temperature. The status (measured/not measured), date and time, and result of measurement will be recorded in a source document and a CRF. For the result of measurement, a value to the first decimal point should be recorded. The result should be rounded to one decimal place.

3.7.3.3.2 Blood Pressure and Pulse Rate

A calibrated measuring instrument should be used to determine blood pressure (systolic and diastolic) and pulse rate after resting for at least 3 minutes. The status (measured/not measured), date and time, and result of measurement will be recorded in a source document and a CRF.

3.7.3.4 12-lead Electrocardiogram

A 12-lead ECG monitors sent by a central ECG measurement facility should be used to obtain an ECG according to the procedure specified by the laboratory. Based on the obtained ECG, the investigator or subinvestigator will record the status (measured/not measured) and date of 12-lead ECG measurement, and the result of assessment (normal or abnormal) in a source document and a CRF. An abnormal finding should be described in the source document and the CRF. The ECG will be sent to the central ECG measurement facility to measure heart rate, and PR, RR, QRS, QT, and QTc (QTcB, QTcF) intervals. The measurement report for the ECG will be sent to the investigator or subinvestigator, and the sponsor. The investigator or subinvestigator will refer to the measurement report to review the result of 12-lead ECG assessment, and sign and date the measurement report. For the measurement report, an electronic file submitted to the sponsor by the central ECG measurement facility is regarded as a source document, and the entry of the result in the CRF is unnecessary.

3.7.3.5 Pregnancy Test

1) Subjects

All female subjects who have begun menstruation at the time of pregnancy test will undergo the pregnancy test. Subjects with a history of hysterectomy or bilateral ovariectomy are regarded as women of nonchild-bearing potential, and do not have to undergo the pregnancy test.

2) Procedure

Each trial site should use a pregnancy test reagent provided by the sponsor to perform urine hCG test in female subjects of child-bearing potential (see Section 5.5). If the result of test unclear, urine hCG test should be repeated. The investigator or subinvestigator will review the result of test, and record the status, date, and result (positive or negative) of test in a source document and a CRF. For a subject who is urine hCG test positive and suspected to be pregnant by the investigator or subinvestigator, treatment should be discontinued according to the rules specified in Section 5.5.

3.7.4 Pharmacokinetic/Pharmacodynamic Assessments

3.7.4.1 Pharmacokinetic Assessments

3.7.4.1.1 Pharmacokinetic Blood Samples

1) Time points of blood sampling (see Section 3.7.1.5 for time points in treatment at reduced dose)

Before administration, and 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.

2) Procedures for blood sampling and measurement

At time points shown in Section 3.7.4.1.1 1) and Table 3.7-1, a pharmacokinetic blood sample will be collected in a blood-collecting tube containing heparin sodium through an indwelling catheter or direct venipuncture. Cases where the subject cannot provide a blood sample for some reason will not be regarded as a deviation. The status (collected/not collected), and exact date and time of collecting a pharmacokinetic blood sample will be recorded in a CRF.

All samples will be shipped to the bioanalytical laboratory shown in Appendix 1 to determine the plasma concentrations of OPC-41061 (tolvaptan), DM-4103, and DM-4107 according to an established procedure. Detailed handling and shipping instructions are provided in Appendix 1.

3) 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 OPC-41061 and its metabolites (DM-4103 and DM-4107) will 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 peak time [2-4 hours after

administration], and at times in an elimination phase [10-14 hours and 24 hours after administration]) are set so that the pharmacokinetic parameters of OPC-41061 can be determined by population pharmacokinetic analysis which will be separately conducted.

3.7.4.2 Pharmacodynamic Assessments

3.7.4.2.1 Daily fluid intake

At the same interval as that for measurement of daily urine volume, daily fluid intake (beverages [eg, juice, milk, tea], water, and transfusion, etc) will be determined. During the pretreatment observation period, daily fluid intake will be measured for the time interval starting at an instruction to urinate after breakfast and ending at complete urination immediately before administration on the following day. After start of tolvaptan administration on the first day of the treatment period, daily fluid intake will be determined for each time interval from the point after complete urination immediately before administration of the day to the point after complete urination immediately before administration on the following day.

The status (measured/not measured), start date and time, and completion date and time of measurement, as well as daily fluid intake will be recorded in a source document and a CRF. Water the subject drinks with tolvaptan will be included in the fluid intake after administration.

3.7.4.2.2 Daily Fluid Balance

Daily fluid balance will be calculated by subtracting “daily urine volume” from “daily fluid intake”. Daily fluid balance will be calculated by the sponsor, and the entry of daily fluid balance in a CRF is unnecessary.

3.7.4.2.3 Serum Osmolality

For laboratory tests, each trial site should use appropriate equipment and apparatuses with reliable precision, and follow the procedures specified by the site (measurement at the site). When measurement at the site is not feasible, samples may be sent to the specified central laboratory for measurement. The central laboratory will perform measurement according to the procedures specified by the laboratory, and report the result of measurement to the sponsor and the investigator or subinvestigator. Serum osmolality does not necessarily have to be measured if its measurement is difficult due to the volume of collected blood or other problems. The status (collected/not collected) and date of blood sampling, and the result of measurement will be recorded in a source

document and a CRF. The result of measurement by the specified central laboratory does not have to be recorded.

3.7.4.2.4 Serum or Blood Sodium Concentration

For laboratory tests, each trial site should use appropriate equipment and apparatuses with reliable precision, and follow the procedures specified by the site (measurement at the site). When measurement at the site is not feasible, samples may be sent to the specified central laboratory for measurement. In that case, however, the same measurement procedure should be followed for each subject. The status (collected/not collected), and date and time of blood sampling, as well as the result of measurement will be recorded in a source document and a CRF. The result of measurement by the specified central laboratory does not have to be recorded.

3.7.4.2.5 Serum or Blood Potassium Concentration

For laboratory tests, each trial site should use appropriate equipment and apparatuses with reliable precision, and follow the procedures specified by the site (measurement at the site). When measurement at the site is not feasible, samples may be sent to the specified central laboratory for measurement. In that case, however, the same measurement procedure should be followed for each subject. The status (collected/not collected), and date and time of blood sampling, as well as the result of measurement will be recorded in a source document and a CRF. The result of measurement by the specified central laboratory does not have to be recorded.

3.7.4.2.6 Urine Osmolality

1) Urine sample processing (pretreatment observation period and treatment period)
Approximately 5 mL aliquot of cumulative urine sample will be taken into a sample stock tube and stored in a refrigerator as needed. The date of sampling will be recorded in a source document. Daily urine volume should be determined before taking the aliquot. If spot urine sample has been obtained from a diapered subject, approximately 5 mL aliquot of the spot urine sample will be taken into a sample stock tube. For spot urine sample, urine volume at the interval of urine collection that the spot urine sample has been obtained, as well as the start and completion times of urine collection, will be recorded in a source document.

Cases where the subject cannot provide a urine sample for some reason despite having received the instruction to urinate will not be regarded as a deviation, but the reason should be recorded in a CRF.

2) Measurement

For laboratory tests, each trial site should use appropriate equipment and apparatuses with reliable precision, and follow the procedures specified by the site (measurement at the site). When measurement at the site is not feasible, samples may be sent to the specified central laboratory for measurement. The central laboratory will perform measurement according to the procedures specified by the laboratory, and report the result of measurement to the sponsor and the investigator or subinvestigator. The status (collected/not collected) and date of urine sampling, and the result of measurement will be recorded in a source document and a CRF. The result of measurement by the specified central laboratory does not have to be recorded.

3.7.4.2.7 Daily Urine Sodium Excretion

1) Urine sample processing

Approximately 5 mL aliquot of cumulative urine sample will be taken into a sample stock tube. The date of sampling will be recorded in a source document. Daily urine volume should be determined before taking the aliquot. If spot urine sample has been obtained from a diapered subject, approximately 5 mL aliquot of the spot urine sample will be taken into a sample stock tube. For spot urine sample, urine volume at the interval of urine collection that the spot urine sample has been obtained, as well as the start and completion times of urine collection, will be recorded in a source document.

Cases where the subject cannot provide a urine sample for some reason despite having received the instruction to urinate will not be regarded as a deviation, but the reason should be recorded in a CRF.

2) Measurement of urine sodium concentration

For laboratory tests, each trial site should use appropriate equipment and apparatuses with reliable precision, and follow the procedures specified by the site (measurement at the site). When measurement at the site is not feasible, samples may be sent to the specified central laboratory for measurement. The central laboratory will perform measurement according to the procedures specified by the laboratory, and report the result of measurement to the sponsor and the investigator or subinvestigator. The status (collected/not collected) and date of urine sampling, and the result of measurement will be recorded in a source document and a CRF. The result of measurement by the specified central laboratory does not have to be recorded.

3) Calculation of urinary excretion

Daily urinary excretion will be calculated by multiplying urinary concentration by daily urine volume. Urinary excretion will be calculated by the sponsor, and the entry of urinary excretion in a CRF is unnecessary.

3.7.4.2.8 Daily Urine Potassium Excretion

1) Urine sample processing

Approximately 5 mL aliquot of cumulative urine sample will be taken into a sample stock tube. The date of sampling will be recorded in a source document. Daily urine volume should be determined before taking the aliquot. If spot urine sample has been obtained from a diapered subject, approximately 5 mL aliquot of the spot urine sample will be taken into a sample stock tube. For spot urine sample, urine volume at the interval of urine collection that the spot urine sample has been obtained, as well as the start and completion times of urine collection, will be recorded in a source document.

Cases where the subject cannot provide a urine sample for some reason despite having received the instruction to urinate will not be regarded as a deviation, but the reason should be recorded in a CRF.

2) Measurement of urine potassium concentration

For laboratory tests, each trial site should use appropriate equipment and apparatuses with reliable precision, and follow the procedures specified by the site (measurement at the site). When measurement at the site is not feasible, samples may be sent to the specified central laboratory for measurement. The central laboratory will perform measurement according to the procedures specified by the laboratory, and report the result of measurement to the sponsor and the investigator or subinvestigator. The status (collected/not collected) and date of urine sampling, and the result of measurement will be recorded in a source document and a CRF. The result of measurement by the specified central laboratory does not have to be recorded.

3) Calculation of urinary excretion

Daily urinary excretion will be calculated by multiplying urinary concentration by daily urine volume. Urinary excretion will be calculated by the sponsor, and the entry of urinary excretion in a CRF is unnecessary.

3.7.4.2.9 Plasma AVP Concentration

Blood sample for measurement of plasma AVP concentration will be obtained, and the date of blood sampling will be recorded in a source document for the subject from whom

the sample is available. The sample will be shipped to the specified central laboratory for central measurement. The central laboratory will measure the above item according to the procedure specified by the laboratory, and report the result of measurement to the sponsor and the investigator or subinvestigator. The status (collected/not collected) and date of blood sampling, and the result of measurement will be recorded in a CRF. The result of measurement by the specified central laboratory does not have to be recorded.

3.7.5 End of Trial

The end of trial date is defined as the date on which the last subject completes the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to the heads of the trial sites and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site Discontinuation

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and GCP. The head of the trial site will notify the sponsor promptly if the trial is terminated by the investigator or the IRB at the site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

Treatment with the IMP should be discontinued, and the withdrawal examination specified in Section 3.7.1.6 should be performed, in the cases listed below. Each investigator or subinvestigator will comprehensively review the circumstances and record the date and reason of discontinuation in a source document and a CRF.

1) Legal representative or subject requests to be withdrawn
2) After start of IMP administration, a deviation from the inclusion or exclusion criteria is discovered for the subject
3) Continuation of treatment is deemed unfeasible due to the occurrence of AEs
4) Any of the prohibited concomitant medications are used
5) The dose and regimen of restricted concomitant medication were changed within 24 hours before and after start of IMP administration

6) Excessive aquaresis is observed, or dose reduction to ≥2 dose steps lower is required due to concerns regarding the safety of the subject
7) Liver function test value (AST or ALT) increased by ≥3 times the upper limit of the reference range for the subject's age and gender
8) Serum or blood sodium concentration increased by ≥12 mEq/L from that immediately before IMP administration, within 24 hours after administration
9) Serum or blood sodium concentration increased by ≥8 mEq/L from that immediately before IMP administration, within 8 to 12 hours after administration
10) Serum or blood sodium concentration exceeding 145 mEq/L is observed during the treatment period
11) Serum or blood potassium concentration exceeds the upper limit of the reference range for the subject's age and gender during the treatment period
12) Subject's pregnancy is confirmed or suspected
13) The investigator or subinvestigator judges that withdrawal is necessary for any other reasons

After start of treatment with the IMP, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment, when medically necessary due to AEs, when requiring treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, options for continued treatment should be offered to the legal representative or subject to the degree possible as described in Section 3.8.3.4.

3.8.3.2 Documenting Reasons for Treatment Discontinuation

A subject may discontinue the IMP for a number of reasons including those listed below.

- Reasons related to AEs:
  - Legal representative or subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing treatment with the IMP places the subject at undue risk as determined by the investigator or subinvestigator
- Serious adverse event (SAE)
- Other safety concerns or AEs that may possibly be related to the IMP
- Death
- Lost to follow-up
- Poor IMP compliance
- Pregnancy (see Section 5.5)
- Major protocol deviations
- Withdrawal of informed consent (complete written consent to withdrawal form)

- Termination of all or part of the trial by the sponsor
- Other reasons unrelated to medical condition
  (including the case where the subject was found to deviate from any of the inclusion criteria or to meet any of the exclusion criteria, after start of IMP administration)

If treatment is discontinued due to an AE, the investigator or subinvestigator will follow up the event according to Section 5.7.

3.8.3.3 Withdrawal of Consent

All legal representatives and subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Legal representatives and subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator or subinvestigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the legal representative provides his/her written withdrawal of consent or there is other written documentation by the investigator confirming the legal representative's verbal intent to completely withdraw from the trial, the subject should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires the regal representative's or subject's refusal of ALL of the following procedures of follow-up (these procedures of follow-up will also be noted in the trial ICF).

- Participation in all follow-up procedures specified in the protocol (whether in-site, by telephone, or by an in-home visit)
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by legal representative and trial personnel)
- Contact of the legal representative and subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, legal representative, friend, neighbor, or physician)
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources)

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a legal representative's intended withdrawal need to be completely

understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A legal representative may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.1). A legal representative may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator or subinvestigator should follow the procedures outlined in Section 3.8.3.2 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only legal representatives who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent for subject's participation in the trial.

3.8.3.4 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, the investigator or subinvestigator will meet/phone and discuss with the legal representative about options of continuing in the trial, preferably on therapy. The investigator or subinvestigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, a legal representative signs an ICF), but who is not started on treatment.

A subject for whom a legal representative signs an ICF, but who is not started on treatment is permitted to be re-screened as specified in Section 3.4.3.

For a subject who meets the definition of screen failure, the following items will be recorded in a CRF for screen failure.

- Date of investigation
- Date on which the subject was determined to be a screen failure
- Date of informed consent
- Birth date
- Gender
- Race
- Compliance with the inclusion criteria (Record the criterion number the subject did not meet, if any)

- Deviation from the exclusion criteria (Record the criterion number the subject met, if any)
- Reason for screen failure

3.10 Definition of Completed Subjects

Subjects who have received IMP administration at evaluation dose (see Section 7.4) for 3 days will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the day of last observation, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status on the end of trial date cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The investigator, subinvestigator, or designee will make 3 documented attempts to contact the subject by telephone, and in the event he/she is unable to reach the subject by telephone, he/she will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

The investigator or subinvestigator will record the following items for the subject lost to follow-up in a source document and a CRF.

- Date of investigation
- Investigation method
- Contact with the subject (successful/unsuccessful)
- Reason why the subject does not (cannot) visit
- Presence or absence of AEs. If present, specify its name, dates of onset and resolution, severity, and IMP causality.
- Action taken with the IMP, treatment for the event, and outcome
- If the investigation is impossible, specify the reason

3.12 Legal Representative or Subject Compliance

During the trial period, a subject will be placed under the management of the investigator or subinvestigator. The investigator or subinvestigator will instruct a legal representative and subject to adhere to the following.

- The IMP should be taken according to the specified dose and regimen
- The specified schedule should be followed during the trial period
- Prohibited concomitant medications (see Section 4.1) should not be used
- The dose and regimen of restricted concomitant medications (see Section 4.2) should not be changed
- Information obtained as a result of participation in the trial should not be divulged to a third party

3.13 Protocol Deviations

The investigator or subinvestigator must not make deviations from or changes to the protocol without prior written agreement with the sponsor, as well as prior review and written approval by the IRB.

The investigator or subinvestigator may make deviations from or changes to the protocol without prior written agreement with the sponsor or prior review and written approval by the IRB, if the deviations or changes cannot be avoided to eliminate immediate hazards to subjects or for other medical reasons. In such cases, the investigator should promptly submit a document stating the details and reason of deviation or change to the sponsor and the head of the trial site, and obtain approval from the IRB. In addition, the investigator should obtain approval from the head of the trial site and a written agreement from the sponsor through the head of the trial site.

1) Reporting to the sponsor
In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator, subinvestigator, or designee will contact the sponsor at the earliest possible time by telephone. The investigator or subinvestigator and the sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator or subinvestigator and the sponsor, and reviewed by the site monitor.

2) Recording deviations

The investigator or subinvestigator will record all deviations from the protocol in a source document.

In addition, the investigator or subinvestigator will record certain specified items of the protocol deviations in a CRF according to the procedures for preparing a CRF provided by the sponsor.

4 Restrictions

4.1 Prohibited Concomitant Medications

If any medication other than the IMP was used from the date of informed consent to the end of trial date, its name, indication, regimen, daily dose, administration route, and start and end dates should be recorded in a source document and a CRF. For therapy other than medication, its name, indication, and start and end dates should be recorded in a source document and a CRF.

Concomitant use of medications and other substances listed in Table 4.1-1 and Table 4.1-2 is prohibited from the pretreatment observation period (3-1 days before start of tolvaptan administration) through the completion of an examination 2 days after final administration. This shall not apply to inevitable cases such as treatment for AEs.

Table 4.1-1 List of Medications Prohibited Before the Trial

- Drugs and foods that may be a strong inhibitors or inducers of CYP3A4 (see Table 4.1-2)
- Tolvaptan-containing drug products other than the IMP, mozavaptan hydrochloride
- Drugs unapproved in Japan

Table 4.1-2 Drugs and Foods That May Be a Strong Inhibitors or Inducers of CYP3A4

Drug class	Drug
1) CYP3A4 inhibitors (excluding external agents)	
Antimicrobials	Clarithromycin, erythromycin, fluconazole, itraconazole, miconazole, norfloxacin, chloramphenicol, voriconazole, telithromycin, ciprofloxacin, fosfluconazole, clotrimazole
Calcium antagonists	Diltiazem, verapamil
Therapeutic drugs for gastritis/peptic ulcer	Cimetidine
Immunosuppressants	Cyclosporine
Anticancer drugs	Imatinib, crizotinib

Table 4.1-2 Drugs and Foods That May Be a Strong Inhibitors or Inducers of CYP3A4	
Anti-HIV drugs	Indinavir, nelfinavir, ritonavir, saquinavir, delavirdine, atazanavir, fosamprenavir, lopinavir, darunavir, telaprevir, cobicistat
Autonomic drugs	Tofisopam
Adenosine A2A receptor antagonists	Istradefylline
Antimetics	Aprepitant
Selective serotonin reuptake inhibitors	Fluvoxamine
2) CYP3A4 inducers (excluding external agents)	
Barbiturates	Phenobarbital, amobarbital, pentobarbital, barbital, secobarbital
Antiepileptics	Carbamazepine, phenytoin
Antitubercular drugs	Rifampicin, rifabutin
Psychostimulants	Modafinil
Anti-HIV drugs	Efavirenz, nevirapine, etravirine
Endothelin receptor antagonists	Bosentan
Anticancer drugs	Enzalutamide
Corticosteroid synthesis inhibitors	Mitotane
3) Foods containing substances that inhibit CYP3A4	Grapefruit, Seville orange, star fruit, and their processed products
4) Foods containing substances that induce CYP3A4	Foods containing St. John's wort

HIV = human immunodeficiency virus

4.2 Restricted Concomitant Medications

The dose and regimen of the following medications should not be changed from the pretreatment observation period through the completion of an examination 2 days after final administration in principle. Change of dose and regimen during this period is allowed if it is required for safety reasons. In such cases, "the reason of change" and "the details of change" should be recorded. Within 24 hours before and after first tolvaptan administration, however, the dose and regimen of restricted concomitant medications should not be changed (if changed, the subject's participation in the trial should be discontinued).

- Therapeutic drugs for heart failure (injectables): Catecholamine preparations, human atrial natriuretic peptide preparations, phosphodiesterase 3 inhibitors, colforsin preparations, etc
- Diuretics (oral preparations and injectables)

5 Reporting of Adverse Events

5.1 Definitions

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

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE.

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator or subinvestigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions
- Requires in-patient hospitalization or prolongs hospitalization
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a “serious” AE.

Immediately Reportable Event (IRE):

- Any SAE
- Any AE related to occupational exposure
- Potential drug induced liver injury (see Section 5.4)
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented in the "Adverse event" section of a CRF if there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's or subinvestigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's or subinvestigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator or subinvestigator needs to ascertain if this is an abnormal (ie, clinically significant) change from the baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator or subinvestigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant by the investigator or subinvestigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated in a CRF. The intensity of an AE is defined as follows:

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	There is no temporal or causal relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject from informed consent to the end of trial must be recorded in source documents and CRFs provided by the sponsor.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition. If an AE that has been previously reported worsens and its severity or seriousness changes, it should be reported as a new AE in a CRF.

In addition, the sponsor must be notified immediately by e-mail of any IRE which occurred from the time of informed consent by a legal representative to the end of trial, according to the procedure outlined in Section 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

In a CRF, the following items should be recorded according to the procedures for preparing a CRF provided by the sponsor.

- Event name
- Date of onset (also time of onset, if possible, during hospitalization) and date of resolution
- Severity
- Seriousness (if serious, specify the details)
- IMP causality
- Action taken with the IMP
- Outcome

5.3 Immediately Reportable Events

The investigator or subinvestigator must immediately report after either the investigator, subinvestigator, or designee becomes aware of any IRE, by e-mail to the sponsor using the contact information on the cover page of this protocol.

An IRE form must be completed and sent by e-mail to the sponsor. Please note that the IRE form is NOT the "Adverse event" section of the CRF. Due regard should be paid to privacies when sending the IRE form or other documents by e-mail, etc.

Subjects experiencing SAEs should be followed until the events are resolved, stabilized, or the subject is lost to follow-up. Resolution means that the subject has returned to the baseline state of health, and stabilized means that the investigator or subinvestigator does not expect any further improvement or worsening of the subject's condition. It is expected that the investigator or subinvestigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Drug Induced Liver Injury

For a subject who experiences an elevation in AST or ALT that is ≥3 times the upper limit of the reference range for their age and gender, a total bilirubin level should also be evaluated. If the total bilirubin is ≥2 times the upper limit of the reference range for their age and gender, the investigator or subinvestigator should record all these values in an IRE form and promptly report to the sponsor according to the procedure specified in Section 5.3 Immediately Reportable Events.

5.5 Pregnancy

Before enrolling a female who has begun menstruation in this trial, the investigator or subinvestigator must review the guidelines about trial participation with all female subjects who have begun menstruation. The topics should generally include:

- Informed consent form
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, the legal representative of the female subject (potential female subject) who has begun menstruation must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The legal representative must sign an informed consent form stating that the above-mentioned risk factors and consequences were discussed with her.

A urine pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening on all females who have begun menstruation. If a urine test is performed and is positive, the investigator or subinvestigator will follow up with a confirmatory serum test.

During the trial period, all female subjects and legal representatives should be instructed to contact the investigator or subinvestigator immediately if they suspect they might be pregnant.

If a subject is suspected to be pregnant before she receives the IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking the IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risk) until the result of serum pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for the subject's safety) and the subject will be withdrawn from the trial.

The investigator or subinvestigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial period and for 30 days after final IMP administration, and record the event on an IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator or subinvestigator must report to the sponsor, on appropriate Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.6 Procedure for Breaking the Blind

Not applicable

5.7 Follow-up of Adverse Events

For this trial, information on AEs will be collected until the follow-up examination performed 5-7 days after final IMP administration (hereinafter referred to as "the end of trial date").

After the end of trial date, an AE falling into any of categories in Section 5.7.1, Section 5.7.2, and Section 5.7.3 will be followed as specified.

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial period must be recorded on the "Adverse event" section of the CRF with the current status noted. If a subject has an AE or has not recovered from an AE at the end of trial date, follow-up contacts will be scheduled at least every 4 weeks until the event is resolved, stabilized, or the subject is lost to follow-up. All nonserious AEs that are ongoing at the end of trial date will be recorded as ongoing in a CRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation). The follow-up information after the end of trial date will be recorded in the subject's medical record.

5.7.2 Follow-up of Serious Adverse Events

This trial requires that subjects be actively monitored for SAEs up to the end of trial date. If a subject has an AE or has not recovered from an AE at the end of trial date, follow-up contacts will be scheduled at least every 4 weeks until the event is resolved, stabilized, or the subject is lost to follow-up.

Serious AEs that are identified or ongoing at the end of trial date must be recorded on the "Adverse event" section of the CRF and reported to the sponsor according to the reporting procedure outlined in Section 5.3. All SAEs that are ongoing at the end of trial date will be recorded as ongoing in a CRF. This may include unresolved previously reported SAEs, or new SAEs. The investigator or subinvestigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up. The investigator or subinvestigator will continue to report any significant follow-up information to the sponsor until the event is resolved or stabilized, or the subject is lost to follow-up with and IRE form.

5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring After End of Trial Date (Last Scheduled Contact)

Any new SAE reported by the subject to the investigator or subinvestigator that occur after the end of trial date, and are determined by the investigator or subinvestigator to be related to the IMP, should be reported to the sponsor. The investigator or subinvestigator should follow SAEs identified after the end of trial date until the events are resolved, stabilized, or the subject is lost to follow-up. The investigator or subinvestigator should continue to report any significant follow-up information to the sponsor until the event is resolved or stabilized, or the subject is lost to follow-up with and IRE form.

6 Pharmacokinetic/Pharmacodynamic Analysis

6.1 Pharmacokinetic Analysis

In the pharmacokinetic analysis set (see Section 7.2), the plasma concentrations of OPC-41061 and its metabolites (DM-4103 and DM-4107) will be summarized by descriptive statistics, in the following 2 ways.

- Summarization for each compound, time point of blood sampling, and dose per unit of body weight
- Summarization for each compound, time point of blood sampling, dose per unit of body weight, 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 are the number of subjects, mean, standard deviation, coefficient of variation, minimum, median, and maximum.

The population pharmacokinetic analysis of OPC-41061 will be separately performed and reported.

6.2 Pharmacodynamic Analysis

A pharmacodynamic analysis will be performed in the pharmacodynamic analysis set (see Section 7.2). For the items listed below, descriptive statistics (the number of subjects, mean, standard deviation, minimum, median, and maximum) of measured values and changes from baseline (immediately before tolvaptan administration) at each time point after start of administration at evaluation dose (see Section 7.4) will be determined.

As a subgroup analysis, the items will also be analyzed for each 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).

The same analysis will be performed for each evaluation dose (0.05, 0.15, 0.3, and 0.5 mg/kg/day) (in the entire and each age group).

In the subgroup analysis and the analysis by evaluation dose, data collected on the day after the third day of administration at evaluation dose, the day after final administration at evaluation dose, and the day after final administration will be analyzed.

An analysis will also be performed using data collected immediately before start of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

- Daily fluid intake
- Daily fluid balance
- Serum osmolality
- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Urine osmolality
- Daily urine sodium excretion
- Daily urine potassium excretion
- Plasma AVP concentration

7 Statistical Analysis

7.1 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 will be 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.

7.2 Datasets for Analysis

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 dataset.

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.

7.3 Handling of Missing Data

If data on body weight and edematous symptoms cannot be obtained at assessment on the day after the third day of administration at evaluation dose, the missing data will be imputed using the last available data obtained by that day. If data on body weight on the day after the third day of administration at evaluation dose cannot be obtained, the definition of primary endpoint, "the mean daily urine volume for the 3 days of treatment at evaluation dose" (Section 3.5.1), will be changed to "the mean daily urine volume from start of administration at evaluation dose to the day on which the imputed data on body weight is obtained".

7.4 Definition of Evaluation Dose

Of the doses administered as specified in Section 3.2.2 and Section 3.2.3, the dose meeting the following criteria is defined as an evaluation dose.

1) If sufficient increase in urine volume was obtained during the course of dose escalation, or if the dose was increased to 0.5 mg/kg/day because sufficient increase in urine volume was not obtained:
   - If the dose was not subsequently reduced, then that dose
   - If the dose was reduced without having been administered for 3 days, then the reduced dose
   - If the dose was reduced after having been administered for 3 days, then the dose before reduction

2) If IMP administration was discontinued before sufficient increase in urine volume was obtained during the course of dose increase:
   - The dose at final IMP administration

Other definitions of evaluation dose will be considered if necessary.

7.5 Primary and Secondary Endpoint Analyses

The following analyses will be performed in the full analysis set. As a subgroup analysis, the items will also be analyzed for each 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).

The same analysis will be performed for each evaluation dose (0.05, 0.15, 0.3, and 0.5 mg/kg/day) (in the entire and each age group).

In the subgroup analysis and the analysis by evaluation dose, data collected on the day after the third day of administration at evaluation dose, the day after final administration at evaluation dose, and the day after final administration will be analyzed.

The same analysis will be performed in the dose maintenance analysis set.

Efficacy will be comprehensively assessed based on the results of primary and other endpoints.

7.5.1 Primary Endpoint Analysis

The definition of primary endpoint is presented in Section 3.5.1.

The number and percentage of subjects as well as exact 95% CI based on binomial distribution will be calculated. The same calculations will be performed regarding body weight on the day after final administration at evaluation dose and the day after final administration. The number and percentage of subjects will also be calculated for each time point after the start of administration at evaluation dose.

An analysis will also be performed using data collected on the first day of administration at evaluation dose as a baseline.

7.5.2 Secondary Endpoint Analysis

7.5.2.1 Percent Change in Body Weight

For body weight measured on the day after the third day of administration at evaluation dose, the day after final administration at evaluation dose, and the day after final

administration, and their percent changes from baseline (before start of tolvaptan administration on the first day of the treatment period), the number of subjects, mean, standard deviation, minimum, median, maximum, and 95% CI will be calculated. The descriptive statistics will also be calculated for each time point after start of administration at evaluation dose.

An analysis will also be performed using data collected on the first day of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

7.5.2.2 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)

7.5.2.2.1 Edema (Lower Limbs, etc) and Pulmonary Congestion

A shift table will be prepared for changes in the degree of each symptom from baseline (the pretreatment observation period) to the day after third day of administration at evaluation dose, the day after final administration at evaluation dose, and the day after final administration. In addition, the percentages of subjects who show remarkable improvement or improvement, and the percentages of subjects whose symptoms observed before tolvaptan administration is resolved after administration on the day after third day of administration at evaluation dose, the day after final administration at evaluation dose, and the day after final administration will be determined.

An analysis will also be performed using data collected immediately before start of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

Table 7.5.2.2.1-1 Degree of Improvement for Edema and Pulmonary Congestion

	Degree of improvement	Criterion
1	Remarkable improvement	Symptom resolution or improvement to at least 2 grades better
2	Improvement	Symptom improvement to 1 grade better (symptom resolution should be assessed as remarkable improvement)
3	No change	No change in the degree of symptom, or no symptom observed throughout the trial period
4	Worsening	Symptom worsening to at least 1 grade worse

7.5.2.2.2 Edema (Eyelids), Jugular Venous Distension, Dyspnea, and Pleural Effusion

A shift table will be prepared for changes in the degree of each symptom from baseline (the pretreatment observation period) to the day after third day of administration at evaluation dose, the day after final administration at evaluation dose, and the day after final administration. In addition, the percentages of subjects whose symptoms observed before tolvaptan administration is resolved after administration on the day after third day of administration at evaluation dose, the day after final administration at evaluation dose, and the day after final administration will be determined.

An analysis will also be performed using data collected immediately before start of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

7.5.2.2.3 Cardiothoracic Ratio, Respiration Rate at Rest, and Pulse Rate

Descriptive statistics of measured values and changes from baseline (the pretreatment observation period) on the day after third day of administration at evaluation dose, the day after final administration at evaluation dose, and the day after final administration will be calculated. The same calculations will be performed for each time point after start of administration at evaluation dose.

An analysis will also be performed using data collected immediately before start of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

7.5.2.2.4 Central Venous Pressure

Descriptive statistics of postdose measured values and changes from baseline (the pretreatment observation period) will be calculated.

7.5.2.2.5 Retention of Pericardial Effusion

The frequency distribution of postdose measured values (decrease, no change, or increase) will be determined.

7.5.2.3 Daily Urine Volume

Descriptive statistics of measured values and changes from baseline (the pretreatment observation period) will be calculated for each time point after start of administration at evaluation dose.

An analysis will also be performed using data collected immediately before start of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

7.6 Analysis of Demographic and Baseline Characteristics

In the safety analysis set, frequency distributions or descriptive statistics of the following subject characteristics will be determined.

- Age
- Gender
- Height
- Race
- Presence/absence of complication
- Presence/absence of medical history
- Etiology of heart failure

7.7 Safety Analysis

7.7.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities preferred term. The incidence of the following events will be summarized.

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

The above AEs will also be summarized by evaluation dose. In addition, summaries by evaluation dose after start of administration at evaluation dose and by age group will be prepared.

7.7.2 Clinical Laboratory Data

For clinical laboratory tests other than qualitative urinalysis, descriptive statistics of measured values and changes from baseline (immediately before tolvaptan administration) at each time point after start of administration at evaluation dose and at

final administration will be calculated. For qualitative urinalysis parameter, shift tables at each time point after start of administration at evaluation dose and at final administration compared with baseline will be prepared. For clinical laboratory test parameters other than qualitative urinalysis, a specified reference range will be used to classify measurements into measurement “within the reference range”, “below the reference range”, or “above the reference range”, and shift tables of classifications at each time point after start of administration at evaluation dose and at final administration compared with baseline will be prepared.

An analysis will also be performed using data collected immediately before start of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

7.7.3 Vital Signs Data

For vital signs, descriptive statistics of measured values and changes from baseline (the pretreatment observation period) at each time point after start of administration at evaluation dose and at final administration will be calculated.

An analysis will also be performed using data collected immediately before start of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

7.7.4 12-lead Electrocardiogram Data

For each 12-lead ECG parameters, descriptive statistics of measured values and changes from baseline (the pretreatment observation period) will be calculated at each time point after start of administration at evaluation dose and at final administration.

For QTc interval, the number and percentage of subjects with a QTc interval of >450, >480, or >500 ms at any time point from baseline through the day after final administration will be calculated. The number and percentage of subjects with a change in QTc interval from baseline of >30 or >60 ms at any time point from start of treatment through the day after final administration will also be calculated. A shift table for QTc interpretation (normal or abnormal) will be prepared from baseline through the day after final administration.

In addition, data will be summarized by the number of days elapsed since start of administration.

8 Management of Investigational Medicinal Product

For full details on IMP management, refer to the IB and clinical operation manual.

8.1 Packaging and Labeling

The IMP will be provided to an IMP manager by the sponsor or a designated agent. The IMP will be supplied in bottles and packages. Each bottle and package for the IMP used in the treatment period will be labeled clearly stating “For trial use only”, protocol number, IMP name, quantity, lot number, expiration date, storage conditions, and sponsor’s name and address.

8.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP manager. The IMP manager should not provide the IMP to any subject not participating in this protocol. The IMP will be stored at room temperature. A trial site staff will measure and record a temperature in the IMP storage area at least once each work day and maintain a temperature log.

8.3 Accountability

The IMP manager must maintain an inventory record of IMP (investigational drug, active control drug, or placebo) received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused and/or partially used IMP must be returned to the sponsor or a designated agent.

All IMP returned to the sponsor must be accompanied by appropriate documentation and be identified by protocol number and trial site number on an outermost shipping container. Returned supplies should be in their original containers. The assigned trial monitor will facilitate the return of unused and/or partially used IMP.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to the identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or

performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blister)
- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator, subinvestigator or designee must record all PQCs identified through any mean during the period from the receipt of the IMP from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator, subinvestigator, or designee must provide the sponsor (or sponsor's designee) with information listed in Section 8.5.2 (Information Required for Reporting Product Quality Complaints) by e-mail (destination address: PQC_156-102-00123@otsuka.jp) immediately after becoming aware of a PQC.

Identification of a PQC by the subject should be reported to the investigator or subinvestigator, who should then follow the reporting mechanisms listed above.

8.5.2 Information Required for Reporting Product Quality Complaints

- Description of compliant
- Reporter identification (eg, subject, investigator/subinvestigator, trial site)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, Kit number or bottle number)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Complaint sample availability for return

8.5.3 Return Process for Product Quality Complaints

At the time of reporting a PQC, the availability of complaint sample for return should be notified. If complaint sample is available for return, the sponsor will provide instructions for sample return, when applicable.

It must be documented in a site accountability record that the complaint sample has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents include but are not limited to medical records, electronic data, screening logs, and recorded data from automated instruments. Source documents for measurements of plasma drug concentration will be retained by the bioanalytical laboratory. The sponsor will retain an electronic file submitted by the bioanalytical laboratory as a copy.

All source documents pertaining to this trial will be maintained by the trial site and made available for direct inspection by authorized persons. The investigator or trial site will permit trial-related monitoring, audit, IRB review, and regulatory inspection by providing direct access to source data/documents. Persons with direct access will be presented in an ICF. In all cases, subject privacy must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

During each subject's visit to the trial site, the investigator or subinvestigator will keep a medical record to document all significant observations. At a minimum, the medical record should contain:

- Documentation of informed consent process, including any revised consent
- Documentation of the investigator's or subinvestigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and the confirmation of IMP administration commencement

- Date of the visit and the corresponding Visit or Day in the trial schedule
- Subject's general status remarks, including any significant medical finding. The severity, frequency, duration, action taken, and outcome of any AE, and the investigator's or subinvestigator's assessment of relationship to the IMP must also be recorded.
- Any change in concomitant medications or their doses
- General reference to procedures completed
- Signature (or initials) and date of the investigator or subinvetigator (or designee) who made an entry in the medical record (if an electronic data system is used, a full audit trail must be maintained)

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical record as described above. Any change to information in the medical record and other source documents will be initialed and dated on the day the change is made by a trial site staff authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source document by the investigator or subinvestigator. If an electronic data system is used, a full audit trail of changes must be maintained.

Information from the medical record and other source documents will be entered by a trial site staff directly into electronic CRFs in the sponsor's electronic data capture (EDC) system. Changes to the data will be captured by an automatic audit trail.

Data on plasma drug concentration measured by the bioanalytical laboratory and ECG measurement result obtained by the central ECG reading facility will be directly transferred from each facility to the sponsor or the Clinical Research Organization. Data the sponsor will collect include:

- Case report form (data collected after informed consent)
- 12-lead ECG measurement report
- Table of drug concentration measurements (copy)
- Measurements of laboratory tests, urine osmolality, plasma AVP concentration, etc

9.3 File Management at the Trial Site

The head of the trial site will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline and as required by applicable local regulations.

The trial site will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

The trial site will retain all trial-related documents and records for the period of time indicated below, whichever is longer. However, if the sponsor requires a longer period of archiving, the trial site will consult with the sponsor on the period and procedure of record retention.

- Period until 2 years after manufacturing and marketing approval date. However, if the trial site receives notification from the sponsor that development has been terminated or that the results of the trial will not be submitted with an approval application, period until 3 years after receipt of such notification.
- Period until 3 years after termination or completion of the trial

The trial site must not dispose of any record relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to collect such record. The trial site will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial, including a data clarification form received from the sponsor. Such documents are subject to inspection by the sponsor and relevant regulatory authorities.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and local regulatory requirements. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the trial site during the trial, as well as communicate periodically via telephone, e-mail, and written communications. In addition, all investigators or subinvestigators and trial site staff will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audit items include, but are not limited to, IMP supply, the presence of required

documents, informed consent process, and comparison of data in CRFs with those in source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the trial site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Sciences guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to local requirements, and provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific and medical appropriateness of the trial. In preparing and handling documents such as a CRF and IRE form, the investigator or subinvestigator and his/her staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identifier will be used to identify each subject. Financial aspects, subject insurance, and the publication policy for the trial will be documented in the agreement between the sponsor and the trial site.

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region where the trial is conducted should be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy trial-related records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject identifier in CRFs. If further subject identification is required, subjects' full names may be made known to regulatory authorities or other authorized officials if necessary, according to local regulations.

13 Amendment Policy

The investigator should not make any change to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "non-substantial" amendments, the investigator or subinvestigator should wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as changes that have no effect on the safety of subjects, the conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately and notified to the IRB within a local applicable timelines. The sponsor will submit the protocol amendments to applicable regulatory agencies within a local applicable timelines.

When the IRB, investigator, and/or sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to subjects, the currently approved ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, informed consent will be obtained again from the legal representatives of enrolled subjects before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on the International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

15 References

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Appendix 1 Handling and Shipment of Bioanalytical Samples

1) Handling of pharmacokinetic blood samples

All sample stock tubes will be labeled to provide necessary information including the protocol number, subject identifier, and time point of blood sampling. Approximately 1 mL of blood will be collected in a blood-collecting tube containing heparin sodium (for blood sampling of 2 mL) through an indwelling catheter or direct venipuncture. The tube will slowly be turned upside down several times to mix the blood and put into ice water. The status (collected/not collected), and exact date and time of collecting a pharmacokinetic blood sample will be recorded in a CRF. Then, the blood will immediately (within 60 minutes after sampling) be centrifuged at approximately 1710 × g for approximately 10 minutes at approximately 4°C. Separated plasma will be taken into a sample stock tube. The plasma sample will be stored at −15°C or lower temperature.

2) Shipment of bioanalytical samples

The central laboratory will collect frozen samples with dry ice from trial sites and store them at −15°C or lower temperature. Then, the samples will be shipped with dry ice to the bioanalytical laboratory according to the shipment schedule decided after consultation with the sponsor.

Appendix 2 Protocol Amendment(s)/Administrative Change(s)

Amendment Number: 1

Issue Date: 31 Mar 2017

PURPOSE:

To correct entry omissions, clerical errors, etc

BACKGROUND:

Corrections were made because entry omissions, clerical errors, etc were found.

MODIFICATIONS TO PROTOCOL:

- Entire Protocol: "Serum potassium concentration" was changed to "serum or blood potassium concentration".
- Protocol Synopsis (Trial Duration): The durations for the treatment period and follow-up period were corrected.
- Section 3.4.3 (Exclusion Criterion 15):
  "Breastfed patients" was changed to "Breastfed patients (excluding those patients whose fluid intake can be measured by expressed breast milk or other ways, and whose mother does not use any of prohibited/restricted concomitant medications from 1 week before informed consent to completion of an examination 2 days after final administration)" (for clarification).
- Section 3.7.1.16.1 Fourth Day of Administration at Dose Decided for Each Individual Subject: The following test items were added (due to entry omissions).
  Before tolvaptan administration: Plasma AVP concentration (only subjects from whom samples are available), plasma drug concentration (when blood sample for measurement of plasma drug concentration was collected on the previous day), daily urine volume, daily fluid intake, daily fluid balance, urine sodium excretion, urine potassium excretion, urine osmolality
  At a feasible time: 12-lead ECG, chest x-ray
- Section 3.7.1.16.2 to Section 3.7.1.16.4 Fifth to Seventh Day of Administration at Dose Decided for Each Individual Subject: The following test items were added (due to entry omissions).
  Before tolvaptan administration: Daily urine volume, daily fluid intake, daily fluid balance, urine sodium excretion, urine potassium excretion, urine osmolality
- Section 3.7.1.17.1 First Day of Administration at Reduced Dose: The following test items were added (due to entry omissions).
  At a feasible time: 12-lead ECG
- Section 3.7.1.17.4 Fourth Day of Administration at Reduced Dose (the fourth day of administration at reduced dose and the day after): The following test items were added (due to entry omissions).

Before tolvaptan administration: Plasma AVP concentration (only subjects from whom samples are available), plasma drug concentration (when blood sample for measurement of plasma drug concentration was collected on the previous day)
At a feasible time: 12-lead ECG, chest x-ray

- Section 3.7.4.2.4 and Section 3.7.4.2.5:
  "In that case, however, the same measurement procedure should be followed for each subject." was added.
- Section 3.7.4.2.6: 1) Urine sample processing (screening period) was deleted (due to clerical error).
- Section 3.11: "Treatment compliance" was deleted (due to clerical error).
- Others: Scheduled assessment procedures were clarified.

Amendment Number: 2

Issue Date: 06 Jun 2017

PURPOSE:

To correct entry omissions, clerical errors, etc

BACKGROUND:

Corrections were made because entry omissions, clerical errors, etc were found.

MODIFICATIONS TO PROTOCOL:

- Entire Protocol: Sections to describe procedures when treatment at the dose decided for each individual subject is completed in 3 days, when treatment at the dose decided for each individual subject is extended, and on the day and 2 days after extended treatment at reduced dose were created (for clarification).
- Section 3.7.1.2.3: Confirmation that a subject does not meet Exclusion Criterion 1 was added (due to entry omission).
- Section 3.7.1.7: 12-lead ECG was added (due to entry omission).
- Section 3.7.2.4.1: Items to be recorded was changed from “the date and time of assessment” to “the date of assessment” (due to inconsistency with description in Section 3.7.2.4).
- Section 7.3: It is described that the missing data on body weight and edematous symptoms will be imputed using the last available data when the data on the day after the third day of administration at evaluation dose cannot be obtained, without limiting the case to treatment discontinuation. Correspondingly, it is also described that the definition of primary endpoint (mean daily urine volume) will be changed to the mean of measurements collected until the day on which the imputed data is obtained (due to entry omissions regarding missing data for reasons other than treatment discontinuation).
- Section 15 (Reference 3): The cited literature was changed (to more appropriate one).
- Appendix 1, 1): The period from blood sampling to centrifugation was set longer (to increase the procedure feasibility).
- Others: Scheduled assessment procedures were clarified.

Amendment Number: 3

Issue Date: 03 Feb 2021

PURPOSE:

To make corrections due to extended trial duration, collection of spot urine data in pharmacodynamic assessments, entry omissions, clerical errors, etc

BACKGROUND:

The trial duration was corrected because the period of subject enrollment is extended. Corrections were also made because entry omission (a note that data collected centrally does not have to be entered in the EDC system), clerical errors, etc were found.

MODIFICATIONS TO PROTOCOL:

- Protocol Synopsis (Trial Duration): The end date for the duration of the trial was changed from Jun 2021 to Nov 2021 (due to extended trial duration).
- Section 3.7.1.3.10 "1) Before tolvaptan administration" Plasma drug concentration: was deleted (due to clerical error).
- Section 3.7.3.2, Section 3.7.4.2.3, Section 3.7.4.2.4, Section 3.7.4.2.5, Section 3.7.4.2.6, Section 3.7.4.2.7, Section 3.7.4.2.8, Section 3.7.4.2.9: "The result of measurement by the specified central laboratory does not have to be recorded." was added (due to entry omission).
- Section 3.7.4.2.6, Section 3.7.4.2.7, Section 3.7.4.2.8 [1) Urine sample processing (pretreatment observation period and treatment period)]: It is additionally described that data on spot urine sample will be collected when an examination is conducted using spot urine, and some clerical errors were corrected.
- Section 5.3, Section 11: Descriptions about an IRE form were added (Because an IRE form becomes available for reporting, in addition to a SAE form).
- Section 9.2: "Measurements of laboratory tests, urine osmolality, plasma AVP concentration, etc" was added (due to entry omission).

Agreement

I, the undersigned investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal, and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational medicinal product, tolvaptan (OPC-41061), the concomitant medications, the efficacy and safety parameters, and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the trial site where tolvaptan (OPC-41061) will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered in case report forms by me, the subinvestigator, or my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other trial sites, whenever applicable. I agree to allow the sponsor, its designee monitors and auditors full access to all medical records at the trial site for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendment to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB within the required local applicable timeline. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experience in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

Investigator Print Name	Trial Site Name
Signature	DD Mon YYYY Date

This agreement is digitally signed. The electronic signature is attached to the agreement.