CLINICAL STUDY PROTOCOL

A Multicenter, Uncontrolled, Open-label, Dose-titration Trial to Investigate the Efficacy and Safety of Tolvaptan Tablets in Patients With Hyponatremia in Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

Tolvaptan (OPC-41061)

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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_156-14-003@otsuka.jp
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: Tolvaptan (OPC-41061)	Protocol No.: 156-14-003
Protocol Title:	A multicenter, uncontrolled, open-label, dose-titration trial to investigate the efficacy and safety of tolvaptan tablets in patients with hyponatremia in syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Clinical Phase/Trial Type:	Phase 3
Treatment Indication:	SIADH
Objective(s):	To determine the efficacy and safety of tolvaptan based on the change in serum sodium concentration following administration of tolvaptan oral tablets at 7.5 to 60 mg/day for up to 30 days in Japanese patients with hyponatremia in SIADH
Trial Design:	A multicenter, uncontrolled, open-label, dose-titration clinical trial
Subject Population:	Total of 16 subjects with central measurement value for serum sodium concentration of <135 mEq/L at predose on Day 1 of the treatment period are to be treated with investigational medicinal product (IMP) At least 50% (8/16) of the above subjects should comprise subjects with serum sodium concentration of <130 mEq/L at predose on Day 1 of the treatment period. In addition, the number of subjects with SIADH due to ectopic antidiuretic hormone-producing tumors and the number of subjects with SIADH due to other causes should not be notably different.
Inclusion/Exclusion Criteria:	[Inclusion criteria] 1) Subjects with a definite diagnosis of SIADH in reference to “Diagnostic and Treatment Manual of the Hypersecretion of Vasopressin (SIADH), Revised in 2011” (Appendix 1) 2) Subjects who have been on fluid restriction (total daily fluid intake of ≤20 mL/kg body weight) for at least 7 consecutive days at the time of informed consent and who are showing no improvement of hyponatremia (serum sodium concentration of <135 mEq/L) at the time of the screening examination. 3) Subjects who have been on fluid restriction from the time

of the screening examination until the pretreatment observation (day before start of IMP administration) but whose serum sodium concentration at both the pretreatment observation and at predose on Day 1 of the treatment period is <135 mEq/L and increased by <5 mEq/L compared with that at the screening examination

4) Male and female Japanese subjects age 20 to 85 years, inclusive, at the time of informed consent
5) Subjects from whom informed consent can be obtained before start of the trial

[Exclusion criteria]

1) Subjects who have transient hyponatremia induced by drug administration
2) Subjects with dehydration
3) Subjects with hyponatremia due to heart failure, ascites associated with hepatic cirrhosis, or nephrotic syndrome
4) Subjects with SIADH due to unknown etiology
5) Subjects with substantial sodium transudation due to renal sodium loss, diarrhea, or vomiting
6) Subjects who are unable to sense thirst or who have difficulty with fluid intake
7) Subjects who have impaired consciousness (coma or stupor)
8) Subjects who have AST (GOT) or ALT (GPT) exceeding 3 times the upper limit of normal at the screening examination
9) Subjects who have a history of myocardial infarction within 30 days prior to informed consent
10) Subjects who have a history of persistent ventricular tachycardia or ventricular fibrillation despite having an implantable cardioverter defibrillator within 30 days prior to informed consent
11) Subjects with decubitus angina, exertional angina induced by even mild exertion, or severe angina such as unstable angina
12) Subjects with a history of cerebrovascular disorder within 30 days prior to informed consent
13) Subjects with a severe psychiatric disorder
14) Subjects with systolic blood pressure of <90 mmHg at the time of the screening examination or at the pretreatment observation on the day before start of IMP administration
15) Subjects with a history of hypersensitivity or idiosyncratic

reaction to benzazepine or benzazepine derivatives such as benazepril

16) Subjects with a history of drug abuse within 1 year prior to informed consent or with current alcohol dependence
17) Subjects with poorly controlled diabetes mellitus, defined as fasting blood glucose level of >300 mg/dL
18) Subjects with urinary tract obstruction
19) Subjects who have participated in any other clinical trial within 30 days prior to informed consent
20) Subjects who have participated in another clinical trial of tolvaptan or who have previously received tolvaptan
21) Subjects who are in the terminal stage of the disease or in a moribund state with an expected survival of less than 3 months as judged by the investigator or subinvestigator
22) Subjects with serum sodium concentration of <120 mEq/L associated with neurologic impairment, including apathy, confusion, or seizures
23) Subjects with a progressive or episodic neurological disorder, including multiple sclerosis or with a history of multiple strokes
24) Subjects with acute or transient hyponatremia due to head trauma or postoperative condition
25) Subjects who are receiving intravenous infusion fluid at a keep-vein-open (KVO) volume (at the minimum fluid volume for preventing blood clots after the planned volume of fluid infusion) or higher
26) Subjects with hyponatremia due to an artifact in laboratory tests (eg, a high blood glucose level of >300 mg/dL)
27) Subjects who are receiving arginine vasopressin (AVP) or an AVP analog for the treatment of the disease
28) Subjects who receive any other drugs for the treatment of hyponatremia, including demeclocycline, lithium carbonate, or urea within 7 days prior to start of IMP administration
29) Subjects who have concomitantly used hypertonic saline for correction of serum sodium concentration within 7 days prior to informed consent or who are likely to require intravenous hypertonic saline infusion for correction of symptomatic or asymptomatic severe hyponatremia during the trial period
30) Subjects with severe pulmonary hypertension: subjects whose disease state could be expected to worsen due to sudden changes in body fluid volume and blood pressure

	31) Female subjects who are breast-feeding at the planned start of IMP administration or who are judged by the investigator or subinvestigator to be possibly pregnant based on the results of the pregnancy test at the screening examination. 32) Male subjects or female subjects of childbearing potential who are sexually active and who do not agree to practice birth control as specified or to remain abstinent during the trial and until 30 days after final IMP administration
Trial Site(s):	Approximately 20 trial sites in Japan
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Tolvaptan tablets at 7.5, 15, 30 (one tablet each), or 60 mg (two 30 mg tablets) will be orally administered once daily after breakfast for up to 30 days. The dose will be titrated in sequential order from 7.5 mg as the starting dose until the individual maintenance dose suitable for each subject is determined.
Trial Assessments:	Efficacy: Serum sodium concentration and clinical symptoms associated with hyponatremia Pharmacokinetics: Plasma concentrations of tolvaptan and its metabolites DM-4103 and DM-4107 Pharmacodynamics: Daily urine volume, daily fluid intake, daily fluid balance, urine osmolality, serum osmolality, daily urinary sodium excretion, and plasma AVP concentration Safety: Adverse events (AEs), clinical laboratory tests, body weight, vital signs, 12-lead electrocardiography, liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and serum total bilirubin), and pregnancy test
Criteria for Evaluation:	Primary endpoint: • Percentage of subjects with normalized serum sodium concentration (≥135 mEq/L) on the day after final IMP administration Secondary endpoints: • Change in serum sodium concentration • Time course of serum sodium concentration • Changes in clinical symptoms associated with hyponatremia
Statistical Methods:	The efficacy analysis set and the maintenance dose-setting set will be analyzed as described below. Efficacy will be

comprehensively evaluated based on the following analysis and on individual subject data.

Primary endpoint:

- Percentage of subjects with normalized serum sodium concentration on the day after final IMP administration

  The percentage of subjects with normalized serum sodium concentration, defined as ≥135 mEq/L, on the day after final IMP administration will be calculated versus the number of subjects with serum sodium concentration of <135 mEq/L at baseline on Day 1 of the treatment period.

  The number, percentage, and 95% confidence interval (CI) of subjects with normalized serum sodium concentration on the day of fixing the maintenance dose and on the day after final IMP administration will be calculated. The number and percentage of subjects will also be calculated for each timepoint after start of IMP administration.

Secondary endpoints:

- Change in serum sodium concentration

  The number of subjects and the mean, standard deviation, minimum, median, and maximum values and 95% CI for measured values for serum sodium concentration and the change from baseline (predose on Day 1 of the treatment period) on the day of fixing the maintenance dose and on the day after final IMP administration will be calculated. Descriptive statistics at each timepoint after start of IMP administration will also be calculated.

- Time course of serum sodium concentration

  The individual time courses of measured values and changes from baseline for serum sodium concentration will be plotted.

- Changes in clinical symptoms associated with hyponatremia

  Shift tables of the changes in clinical symptom gradings from baseline (pretreatment observation) to the day of fixing the maintenance dose and from baseline to the day after final IMP administration will be generated. Shift tables of the changes at each postdose timepoint will be generated in the same way.

Trial Duration:	Trial period: Nov 2016 to Mar 2020 Expected duration of trial participation for each subject: Up to 54 days (1 to 13 days for screening, 1 day for pretreatment observation period, up to 30 days for treatment period, and 7 to 10 days for follow up)

Table of Contents

List of In-text Tables

List of In-text Figures

List of Appendices

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AVP	Arginine vasopressin
CI	Confidence interval
CNS	Central nervous system
CRF	Case report form
CYP	Cytochrome P450
DDAVP	1-deamino-8-D-arginine vasopressin
DILI	Drug Induced Liver Injury
EU	European Union
GCP	Good Clinical Practice
GOT	Glutamic-oxaloacetic transaminase
GPT	Glutamic-pyruvic transaminase
hCG	Human chorionic gonadotropin
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
KVO	Keep Vein Open
MedDRA	Medical Dictionary for Regulatory Activities
OPC	Otsuka Pharmaceutical Co., Ltd.
PQC	Product quality complaint
SAE	Serious adverse event
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
TEAE	Treatment-emergent adverse event
QOL	Quality of life
ULN	Upper limit of normal
US	United States

Definitions of Terms

Term	Definition
Screen failure	A patient who provided informed consent but received no IMP
Trial start date for each subject	Date of obtaining signed informed consent from each subject
Trial discontinuation date for each subject	Date on which the investigator or subinvestigator decided to withdraw the subject from the trial, or date of the examination at discontinuation, whichever comes later
Trial completion date for each subject	Trial discontinuation date, or date of the follow-up examination, whichever comes later If 2 or more follow-up examinations were performed, the date of the last examination will be considered as the trial completion date
Trial period for each subject	Period from the date of obtaining signed informed consent to the trial completion date

1 Introduction

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a disease state in which vasopressin is inappropriately released beyond the physiological regulatory mechanism, due to various underlying diseases. The causes of SIADH can be roughly classified into the following 2 types: cases due to the ectopic production of vasopressin (ie, ectopic vasopressin producing tumors [malignant tumors]) and cases due to excess endogenous vasopressin secretion associated with central nervous system (CNS) disorders and pulmonary diseases.[1]

Inappropriately secreted vasopressin causes water retention by increasing water reabsorption at the renal collecting duct through the V_2 receptor, thereby suppressing water clearance from the kidney, which results in dilutional hyponatremia. In mild cases, dilutional hyponatremia may be asymptomatic; however, if left untreated, it may gradually worsen, and present with neurological symptoms (appetite impaired, headache, somnolence, nausea, vomiting, coma, and convulsions) as the condition progresses, ultimately resulting in fatal cerebral edema.[2]

The purpose of treatment of SIADH is to correct the low sodium levels, improve the CNS symptoms, and prevent cerebral edema. For this purpose, elimination of the cause (eg, treatment of the underlying disease) is the first priority. However, as the underlying disease may not be improved, or the symptoms of SIADH may be prolonged after treatment of the underlying disease, palliative therapy is the mainstay for the treatment of hyponatremia. In general, fluid restriction is the treatment of choice for hyponatremia, regardless of the underlying disease; however, fluid restriction commonly has a delayed onset of effect, hinders treatment of the underlying disease, and impairs patient quality of life (QOL) due to severe thirst. Accordingly, patients with severe hyponatremia who require a rapid corrective action are generally treated with a combination of furosemide and hypertonic saline. This combination therapy eliminates excessive water by intravenous furosemide and supplements sodium loss by hypertonic saline, which may cause a rapid elevation of the serum sodium concentration; therefore, the therapy must be administered with extreme caution. In addition, this therapy is of limited use, as it involves intravenous injection and intravenous infusion.[3]

Tolvaptan is a nonpeptidic, cAMP-dependent arginine vasopressin (AVP) V_2-receptor antagonist discovered by Otsuka Pharmaceutical Co., Ltd. It inhibits water reabsorption at the renal collecting duct, thereby enhancing water diuresis without depletion of electrolytes. Tolvaptan was approved in the United States (US) in May 2009 for the treatment of clinically significant hypervolemic and euvolemic hyponatremia, including

patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH), etc., and in the European Union (EU) in August 2009 for the treatment of hyponatremia secondary to SIADH in adults. The recommended starting dose is 15 mg once daily, which may be increased to a maximum of 60 mg once daily.

In Japan, tolvaptan was approved on 27 Oct 2010 under the brand name, "Samsca Tablets 15 mg" for "the treatment of volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics)" (also approved as "Samsca Tablets 7.5 mg" on 04 Feb 2013 for the same indication). It was then approved on 13 Sep 2013 as "Samsca Tablets 7.5 mg" for "the treatment of fluid retention in hepatic cirrhosis when adequate response is not obtained with other diuretics (eg, loop diuretics)." The indications of tolvaptan were further expanded on 24 Mar 2014 under the brand name, "Samsca Tablets 7.5 mg, 15 mg, and 30 mg" to include "suppression of progression of autosomal dominant polycystic kidney disease (ADPKD) in patients with increased kidney volume and a rapid rate of increase."

In December 2013, the Japan Endocrine Society made a development request of tolvaptan to the Ministry of Health, Labour and Welfare for the treatment of improvement of hyponatremia secondary to SIADH as an unapproved and off-label drug of high medical need. The Study Group on Unapproved and Off-label Drugs of High Medical Need accepted the request at the 23th Investigational Committee held on 22 Apr 2015, and requested for the company to develop the drug for the indication of improvement of hyponatremia secondary to SIADH, as an unapproved and off-label drug of high medical need (MHLW/HPB/RDD Notification No. 0521-1 and PFSB/ELD Notification 0521-1, dated 21 May 2015). Subsequently, at the 24th Investigational Committee held on 14 Oct 2015, the Study Group determined that a Japanese clinical trial should be conducted to demonstrate the appropriateness of the proposed dosage regimen (the efficacy and safety of tolvaptan administered at the proposed dosage regimen), and to confirm the safety and other characteristics of the drug under a specified monitoring. Accordingly, the present clinical trial was planned.

1.1 Nonclinical Data

The effects of tolvaptan on hyponatremia were evaluated in rat acute and chronic models of hyponatremia. In the rat model of acutely progressive hyponatremia, combined treatment of subcutaneous infusion (10 ng/hr subcutaneous [SC]) of [deamino-Cys^{1}, $DArg^{8}$]-vasopressin (DDAVP), a peptide V_2 agonist and water loading progressively decreased plasma sodium concentration, resulting in severe hyponatremia associated with high mortality. In this acute hyponatremia model, oral doses of tolvaptan at 1, 3, and

10 mg/kg induced dose-dependent aquaresis, leading to an increase in plasma sodium concentration and a reduction in mortality rate. In the rat model of chronic hyponatremia induced by DDAVP infusion (1 ng/hr SC) and liquid diet, plasma sodium concentration was reduced to about 110 mEq/L and maintained at that level without any deaths. In this chronic hyponatremia model, oral doses of tolvaptan at ascending concentrations from 0.25 to 8 mg/kg nearly normalized the plasma sodium concentration, and improved the wet kidney weight and water content in the brain and heart, which had been increased by chronic hyponatremia. These results suggested the potential of tolvaptan in the treatment of hyponatremia.

For detailed nonclinical data, see the Investigator's Brochure (IB).

1.2 Clinical Data

Among the results of phase 3 trials conducted in the US and EU (156-02-235, 156-03-238),[4] as well as those of the subgroup analyses, data from 110 patients with hypernatremia whose underlying disease was diagnosed as SIADH[5] are presented below. For detailed information on these trials, see the IB.

1.2.1 Foreign Phase 3 Trials (156-02-235, 156-03-238)

Results from 416 evaluable subjects with euvolemic or hypervolemic hyponatremia (serum sodium <135 mEq/L) resulting from a variety of underlying causes (eg, heart failure, liver cirrhosis, SIADH, etc.), who were treated for 30 days with tolvaptan (titrated dose) or placebo in the phase 3 trials (156-02-235, 156-03-238) conducted in the US and EU demonstrated that:

- The average daily area under the concentration-time curve (AUC) for the change in serum sodium from baseline to Day 4 and from baseline to Day 30 (the primary endpoint) was significantly greater in the tolvaptan group than in the placebo group ($p < 0.0001$), when adjusted for multiplicity associated with 2 assessment points.
- A significantly higher serum sodium concentration was noted in the tolvaptan group than in the placebo group, from 8 hours after the first dose (the first assessment point after the start of treatment), which lasted for 30 days.
- The serum sodium concentration in the tolvaptan group declined to a level similar to that in the placebo group, within 7 days after tolvaptan therapy was discontinued.

1.2.2 Subgroup Analyses in Subjects With Syndrome of Inappropriate Secretion of Antidiuretic Hormone in Phase 3 Trials (156-02-235, 156-03-238)

Among the results of the subgroup analyses in phase 3 trials conducted in the US and EU (156-02-235, 156-03-238), data from 110 subjects with hypernatremia whose underlying

disease was diagnosed as SIADH (52 in the tolvaptan group, 58 in the placebo group) are presented below.

- Forty-two subjects (80.8%) in the tolvaptan group and 42 subjects (72.4%) in the placebo group completed the treatment period of up to 30 days. Among these subjects, 30 (57.7%) in the tolvaptan group and 29 (50.0%) in the placebo group had severe hyponatremia (serum sodium concentration <130 mmol/L).
- The average daily AUC for the change in serum sodium concentration from baseline to Day 4 and from baseline to Day 30 (the primary endpoint) was 5.28 ± 3.35 mmol/L (mean ± standard deviation) in the tolvaptan group and 0.47 ± 2.81 mmol/L in the placebo group on Day 4, and 8.07 ± 4.55 mmol/L in the tolvaptan group and 1.89 ± 4.13 mmol/L in the placebo group on Day 30, which indicated a significant increase in the tolvaptan group, compared with the placebo group ($p < 0.0001$) at both assessment points. The serum sodium concentrations observed in the tolvaptan group were significantly higher than those in the placebo group at all of the time points.
- The exposure was 1396 person-days in the tolvaptan group and 1425 person-days in the placebo group. Dry mouth and thirst, the most frequently reported adverse drug reactions (ADRs) in the treatment of tolvaptan, occurred respectively in 9 subjects (17.6%) and 8 subjects (15.7%) in the tolvaptan group, and 5 subjects (8.6%) and 6 subjects (10.3%) in the placebo group. The incidences of dizziness, nausea, hypotension, and nasopharyngitis were slightly higher in the tolvaptan group than in the placebo group. A total of 4 subjects died, 1 subject in the tolvaptan group and 3 subjects in the placebo group.
- Among the 51 subjects treated with tolvaptan, 3 subjects developed a too rapid correction in serum sodium concentration, exceeding the upper limit of the serum sodium correction specified by the protocol (serum sodium increases ≥12 mmol/L within 24 hours or ≥18 mmol/L within 48 hours). Of these 3 subjects, 1 subject experienced a 13 mmol/L increase within 24 hours, and 2 subjects experienced a 14 mmol/L increase within 24 hours. These 3 subjects had severe hyponatremia with a serum sodium concentration of <130 mmol/L at baseline, but no neurological signs suggestive of osmotic demyelination syndrome were reported.

1.3 Known and Potential Risks and Benefits

In clinical trials involving patients with hyponatremia, the most frequently reported adverse events (AEs) with an incidence of >5% in 511 subjects treated with oral tolvaptan were thirst, dry mouth, oedema peripheral, nausea, dizziness, fatigue, constipation, headache, ascites, diarrhoea, pollakiuria, asthenia, hypotension, pyrexia, and hypokalaemia. The most frequently reported AEs with an incidence of >5% in subjects receiving placebo were oedema peripheral, diarrhoea, headache, ascites, vomiting, dyspnoea, nausea, and hypotension. The AEs with a higher incidence in subjects treated with tolvaptan than in subjects receiving placebo were thirst, dry mouth, nausea, dizziness, fatigue, constipation, pollakiuria, asthenia, hypotension, pyrexia, and

hypokalaemia. In 416 evaluable subjects with hyponatremia treated with tolvaptan in the phase 3 trials conducted in the US and EU (156-02-235, 156-03-238), serum sodium concentration improved continuously regardless of the underlying disease, and normalized in most subjects. For the details of the AEs attributable to tolvaptan therapy in clinical trials, see the latest IB.

2 Trial Rationale and Objectives

2.1 Trial Rationale

The mechanism of the onset of hyponatremia in patients with SIADH is the abnormal regulation of nonosmotic AVP release.[6] Hyponatremia in patients with SIADH is primarily treated with fluid restriction and hypertonic saline infusion. Fluid restriction has the advantage of correcting serum sodium concentration safely, but has a delayed onset of effect and is also difficult for patients to accept as an established therapy due to its poor tolerability. Hypertonic saline infusion has a rapid onset of effect, and is therefore appropriate in acute treatment; however, the sustained normalization of serum sodium concentration with a hypertonic saline infusion is difficult.[7] The conventional treatments for hyponatremia are based on fluid restriction. Tolvaptan is expected to ease fluid restriction, thereby exerting its therapeutic effects rapidly as demonstrated by three phase 3 trials conducted overseas, and improving QOL impaired by fluid restriction. Hypertonic saline infusion is an emergency treatment, and is not generally expected to be used concomitantly with tolvaptan. However, tolvaptan with a different administration route may be useful in outpatient management after the correction of serum sodium with hypertonic saline. Unlike mozavaptan, which is limited to the treatment of SIADH secondary to ectopic antidiuretic hormone-producing tumors, tolvaptan has been demonstrated in overseas clinical trials to be clinically effective and safe regardless of the underlying disease, and could be administered to all patients with SIADH. The demonstrated clinical efficacy and safety of tolvaptan are based on the outcome of 30-day treatment, while those of mozavaptan are based on the outcome of 7-day treatment.

Tolvaptan is an ingestible AVP receptor antagonist with a high affinity for the V_2 receptor, and has been shown to produce water diuresis resulting in the increased excretion of free water.

In the US and EU, tolvaptan is approved for the treatment of hyponatremia secondary to SIADH. However, the efficacy and safety of tolvaptan have not been demonstrated in Japanese patients. The present clinical trial was planned to demonstrate the

appropriateness of the proposed dosage regimen (the efficacy and safety of tolvaptan administered at the proposed dosage regimen), and to confirm the safety and other characteristics of the drug under a specified monitoring. This protocol was prepared based on the agreement reached with PMDA regarding the appropriateness of the trial plan at the consultation after completion of the phase 2 trial (19 Apr 2016, Application Number P3962).

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

2.2 Dosing Rationale

The approved dosage regimen of tolvaptan for the treatment of patients with hypernatremia, including those with SIADH, in the US and EU is "The starting dose is 15 mg once daily, which may be increased to a maximum of 60 mg once daily." The European Summaries of Product Characteristics (SmPC) states based on the results of clinical trials, that the frequency of rapid correction of hyponatremia is ≥1% to <10%; however, a higher incidence of 18.4% was observed in a post-marketing safety trial conducted in the EU (156-09-101),[8] with no reports of neurological sequelae in all patients. In addition, the actual dose utilization data showed that 42.1% of patients treated with tolvaptan received at least 1 dose of 7.5 mg/day. Based on these results, the European authorities requested that the company investigate the possibility of a starting dose of 7.5 mg/day, and a clinical pharmacology trial (156-12-203)[9] of the single administration of tolvaptan at 3.75, 7.5, and 15 mg to patients with SIADH was conducted in the EU. In this trial, for serum sodium concentration, either an increase of ≥8 mEq/L at 8 hours postdose or an increase of ≥12 mEq/L at 24 hours postdose was observed in 4 of 28 patients: 1 patient (10 %) at 3.75 mg, 1 patient (10%) at 7.5 mg, and 2 patients (25%) at 15 mg. Regarding safety, no relationship between dose and the incidence of the rapid correction of serum sodium was found. Regarding efficacy, the mean maximum increase in serum sodium concentration increased in a dose-dependent manner: 3.6 mmol/L in the 3.75 group, 5.3 mmol/L in the 7.5 mg group, and 7.9 mmol/L in the 15 mg group. The greatest median increase in serum sodium concentration was observed in the 7.5 mg group (6.0 mmol/L) as compared to the 3.75 and 15 mg group (2.5 mmol/L and 5.0 mmol/L, respectively).

In the present clinical trial, in consideration of subject safety, the starting dose is set at 7.5 mg/day, which is one half of the approved dose in the US and EU, with an increase in dose to 15 mg/day, followed by 30 mg/day and then 60 mg/day, according to the dose titration scheme to determine the optimal dose in each subject.

Tolvaptan will be administered once daily after breakfast, as approved overseas.

2.3 Trial Objective

To determine the efficacy and safety of tolvaptan based on the change in serum sodium concentration following administration of tolvaptan oral tablets at 7.5 to 60 mg/day for up to 30 days in Japanese patients with hyponatremia in SIADH

3 Trial Design

3.1 Type/Design of Trial

This clinical trial is a multicenter, uncontrolled, open-label, dose-titration trial to investigate the efficacy and safety of tolvaptan administered for up to 30 days at a dose of 7.5 to 60 mg/day, based on the change in serum sodium concentration in Japanese patients with hyponatremia secondary to SIADH. The trial design schematic and trial flowchart are shown in Figure 3.1-1 and Figure 3.1-2.

The trial consists of a screening period, pretreatment observation period, treatment period, and follow-up period.

After written informed consent has been obtained, the investigator or subinvestigator will perform the screening examination to confirm the eligibility of the subject within 14 to 2 days before start of IMP administration. The subject will be admitted to the trial site 2 days before start of IMP administration, at which eligibility for trial entry is confirmed during the pretreatment observation (the day before start of IMP administration) and predose on Day 1 of the treatment period.

From Day 1, the IMP will be orally administered once daily after breakfast, and the specified observations, examinations, and investigations will be performed for the efficacy and safety evaluations. The starting dose of the IMP is 7.5 mg/day, which will be increased to 15 mg/day, followed by 30 mg/day then 60 mg/day on or after Day 2, according to Section 3.2.2, to determine the maintenance dose in each subject as specified in Section 3.2.3. Once the maintenance dose has been determined, the IMP will be administered continuously at that dose throughout the period defined by Section 3.2.4, as a rule.

If the subject becomes less responsive to the IMP due to exacerbation of the underlying disease or other causes, and the investigator or subinvestigator concludes that dose escalation is needed and this increase would raise no safety problems, the dose may be increased. When increasing the dose beyond the maintenance dose once it has been determined, the subject should be hospitalized at the trial site to determine a new maintenance dose according to Section 3.2.2.

To prevent a too rapid increase in serum sodium concentration, fluid restriction should be avoided within 24 hours after IMP administration on Day 1 of the treatment period, based on safety considerations. From Day 2 of treatment period and onward, the investigator or subinvestigator will define the upper limit of daily fluid intake for the subject according to Section 4.2, and instruct the subject to take fluids depending on his/her condition.

From the day after the maintenance dose has been determined and onward, a decision regarding switching the subject to outpatient treatment will be made as specified in Section 3.2.5.

The maximum treatment duration is 30 days. If the serum sodium concentration has normalized (≥135 mEq/L), the subject has no subjective symptoms associated with hyponatremia, and the investigator or subinvestigator concludes that the serum sodium concentration is unlikely to decrease on withdrawal of the IMP, the treatment may be completed before the duration of treatment reaches 30 days.

The subject should visit the trial site 7 to 10 days after the completion of IMP treatment to undergo the follow-up examination. Since serum sodium concentration is expected to decrease due to the withdrawal of treatment, serum sodium concentration will be measured 3 to 5 days after completion of IMP treatment.

If hyponatremia recurs after treatment with the IMP has been completed before the duration of treatment reached 30 days (except treatment discontinuations as specified in Section 3.8.3.1), and it is judged by the investigator or subinvestigator that readministration with the IMP is necessary, treatment may be resumed within 30 days after the initial IMP administration (for the readministration procedure, see Appendix 3).

The trial participation period for each subject is from the date of signed informed consent to the trial completion date.

Definition of trial completion date:

The trial completion date is defined as the trial discontinuation date, or the date on which the follow-up examination is completed, whichever comes later (If 2 or more follow-up examinations were performed, the date of the last examination will be taken as the trial completion date.)

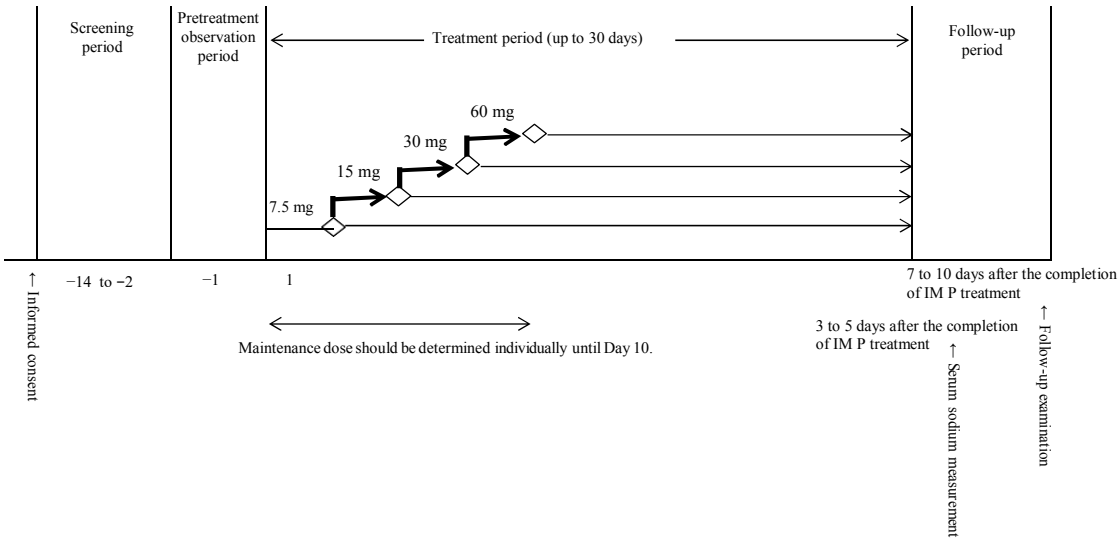

Figure 3.1-1 Trial Design

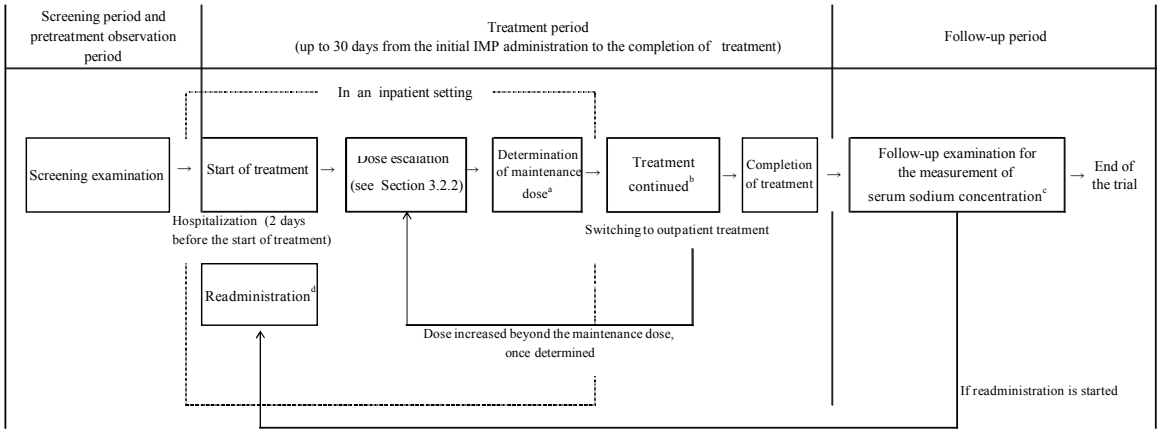

Figure 3.1-2 Trial Flowchart

[a] Dose escalation should be completed to determine the maintenance dose by Day 10 (see Section 3.2.1, Section 3.2.2, and Section 3.2.3)

[b] The IMP will be administered in an inpatient or outpatient setting.

[c] If readministration with the IMP is needed, at the discretion of the investigator or subinvestigator, the subject may visit the trial site after the initial follow-up examination is completed to undergo the second follow-up examination.

[d] Treatment with the IMP may be resumed within 30 days after the initial IMP administration (see Appendix 3).

3.2 Trial Treatments

3.2.1 Dosage Regimen

Subjects will take tolvaptan tablets once daily after breakfast with water.

The starting dose of tolvaptan is 7.5 mg/day (one 7.5 mg tablet), which will be increased to 15 mg/day (one 15 mg tablet) on or after Day 2 of treatment period, followed by 30 mg/day (one 30 mg tablet) and then 60 mg/day (two 30 mg tablets), as specified in Section 3.2.2 to determine the maintenance dose for each subject, according to Section 3.2.3. Once the maintenance dose has been determined, the IMP will be administered continuously at that dose throughout the period defined by Section 3.2.4, as a rule.

The dose may be reduced at any time during the treatment period, if any safety problem arises and the investigator or subinvestigator concludes that a dose reduction is necessary. Dose reduction should be performed as 1 dose level per day.

If the subject becomes less responsive to the IMP due to exacerbation of underlying disease or other causes, and the investigator or subinvestigator concludes that dose escalation is needed and that this increase would raise no safety problems, the dose may be increased. When increasing the dose beyond the maintenance dose once it has been determined, the subject should be hospitalized at the trial site to determine a new maintenance dose according to Section 3.2.2.

The serum sodium concentrations used to determine whether the subject meets the criteria for dose escalation, maintenance dose, and switching to outpatient treatment (Section 3.7.1.17) will be based on serum sodium concentrations measured at each trial site.

3.2.2 Dose Escalation Criteria

1) Day 2 of treatment period
   If the predose serum sodium concentration meets both of the criteria below, the dose will be increased to 15 mg/day.

- The serum sodium concentration is <130 mEq/L.
- The increase in serum sodium concentration from predose on Day 1 is <5 mEq/L.

Even if both of these criteria are met, the same dose as that administered on Day 1 should be administered, if the investigator or subinvestigator concludes that dose escalation is inappropriate due to safety concerns.

2) From Day 3 of treatment period and onward

If the predose serum sodium concentration meets both of the criteria below, the dose will be increased.

- The serum sodium concentration is <135 mEq/L.
- The increase in serum sodium concentration from predose on the previous day is <5 mEq/L.

Even if both of these criteria are met, the same dose as that administered on the previous day should be administered when any of the following are present on the day that dose escalation is determined:

- The dose was increased on the previous day, and the predose serum sodium concentration on the day dose escalation is assessed is ≥130 mEq/L and <135 mEq/L; OR
- The serum sodium concentration has increased continuously during the previous 2 days and is expected to increase further without dose escalation, at the discretion of the investigator or subinvestigator; OR
- The investigator or subinvestigator concludes that dose escalation is inappropriate due to safety concerns.

3.2.3 Criteria for Maintenance Dose Determination

The maintenance dose will be determined if any of the following criteria are met.

- The serum sodium concentration has normalized (≥135 mEq/L)
- Further dose escalation is considered to be inappropriate due to safety concerns.
- The dose of the IMP has reached 60 mg/day.
- None of the above criteria have been met up to Day 10 of the treatment period.

3.2.4 Treatment Period

The maximum treatment duration with the IMP is 30 days. If the serum sodium concentration normalizes (≥135 mEq/L), the subject has no subjective symptoms associated with hyponatremia, and the investigator or subinvestigator concludes that the serum sodium concentration is unlikely to decrease on withdrawal of the IMP, the treatment may be completed before the treatment duration reaches 30 days.

If hyponatremia recurs after treatment with the IMP has been completed (except for treatment discontinuations as specified in Section 3.8.3.1) and the investigator or subinvestigator judges that readministration with the IMP is necessary, treatment may be resumed within 30 days after the initial IMP administration (for the readministration procedure, see Appendix 3).

[Rationale for the treatment duration]

The maximum duration of treatment is set as 30 days, which is the same as that used in the phase 3 trials previously conducted in the US and EU, and is sufficient to evaluate the effect of tolvaptan on correction and maintenance of serum sodium concentration.

Treatments for hyponatremia may become unnecessary after IMP administration is started due to improvement of the etiology of SIADH. To avoid the chronic administration of tolvaptan, the treatment duration is not uniformly specified in this trial, and the completion of IMP treatment is allowed at any time, when treatment with tolvaptan is judged to be unnecessary based on an individual subject's condition at discretion of the investigator or subinvestigator.

3.2.5 Hospitalization

1) Hospitalization required from 2 days before start of IMP administration

The subject is required to be hospitalized before supper 2 days before start of IMP administration.

On the day after the maintenance dose is determined, the investigator or subinvestigator may determine whether the subject meets the following criterion for switching to outpatient treatment. By meeting the criterion, the subject may be transferred to outpatient treatment from the following day of assessment and onward.

Criterion for switching to outpatient treatment

- The predose serum sodium concentration has not increased by >2 mEq/L, as compared with predose on the previous day.

If the criterion for switching to outpatient treatment is not met on the day after the maintenance dose is determined, the serum sodium concentration will be measured again at predose on the following day to determine the switching. The subject may be moved to outpatient treatment on or after the day the criterion for switching to outpatient treatment is met.

The investigator or subinvestigator will record the dates the subject is admitted to and discharged from the trial site in the source document and case report form (CRF).

2) Re-hospitalization after switching to outpatient treatment

A subject who has been switched to outpatient treatment will be rehospitalized by the day before the day dose escalation or readministration is started, if either of the following criteria is met:

- A new increased maintenance dose beyond the fixed maintenance dose, becomes necessary due to the lack of efficacy or other reasons; OR

- Readministration is started after completion of IMP treatment.

The timing of discharge from the trial site after readmission will be decided as specified in 1) Hospitalization required from 2 days before start of IMP administration.

The investigator or subinvestigator will record the dates the subject is admitted to and discharged from the trial site in the source document and CRF.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

In this trial, male and female Japanese patients with hyponatremia secondary to SIADH, aged from 20 to 85, inclusive at the time of consent are eligible. The trial population must include 16 subjects who are evaluable for the primary endpoint, the percentage of subjects with normalized serum sodium concentration (ie, subjects whose predose serum sodium concentration centrally measured on Day 1 is <135 mEq/L). Subject enrollment will be continued until a total of 16 evaluable subjects have been obtained.

At least 50% (8/16) of the above subjects should comprise subjects with serum sodium concentration of <130 mEq/L at predose on Day 1 of the treatment period. In addition, the number of subjects with SIADH due to ectopic antidiuretic hormone-producing tumors and the number of subjects with SIADH due to other causes should not be notably different.

3.3.2 Subject Identification Number

A subject identification number (site number [3 digits] + S + a serial number within the site [5 digits]) will be assigned to each subject. The site number (3 digits) is designated by the sponsor, while the serial number within each site (5 digits) is assigned from 00001, in the order of obtainment of informed consent within that site. The trial site will prepare a list of subjects who have provided informed consent and their subject identification numbers, and retain the list.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Informed consent will be freely obtained from all subjects. By signing the informed consent form (ICF), consent of the subject will be recorded in document form. Both the written information for the subjects and the ICF will be approved by the same Institutional Review Board (IRB) that approves this protocol.

The written information for the subjects and ICF will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[10] and local regulatory requirements.

Before obtaining informed consent, the investigator or subinvestigator may discuss with potential subjects regarding the possibility of participation or enrollment in the trial. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s).

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 subject by the investigator or subinvestigator, the IRB-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or subinvestigator). The ICF will also be signed and dated by a clinical trial associate, in cases where they also provide a supplemental explanation. The subject will receive the written information for subjects and a copy of the signed ICF; the original shall be kept on file by the investigator or subinvestigator.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects.

3.4.2 Inclusion Criteria

The investigator or subinvestigator will confirm that subjects meet all of the inclusion criteria listed in Table 3.4.2-1. Confirmations will be made for criteria 1, 2, 4, and 5 at the screening examination, and for criterion 3 during the pretreatment observation period (the day before start of IMP administration) and predose on Day 1. Serum sodium concentrations measured at each trial site will be used in the eligibility assessment.

Table 3.4.2-1	Inclusion Criteria
1.	Subjects with a definite diagnosis of SIADH in reference to "Diagnostic and Treatment Manual of the Hypersecretion of Vasopressin (SIADH), Revised in 2011" (Appendix 1)
2.	Subjects who have been on fluid restriction (total daily fluid intake of ≤20 mL/kg body weight) for at least 7 consecutive days at the time of informed consent and who are showing no improvement of hyponatremia (serum sodium concentration of <135 mEq/L) at the time of the screening examination.
3.	Subjects who have been on fluid restriction from the time of the screening examination until the pretreatment observation (day before start of IMP administration) but whose serum sodium concentration at both the pretreatment observation and at predose on Day 1 of the treatment period is <135 mEq/L and increased by <5 mEq/L compared with that at the screening examination
4.	Male and female Japanese subjects age 20 to 85 years, inclusive, at the time of informed consent
5.	Subjects from whom informed consent can be obtained before start of the trial

[Rationale for the inclusion criteria]

Criteria 1 to 3 are set to appropriately evaluate the efficacy and safety of tolvaptan in the treatment of hyponatremia secondary to SIADH.

The lower age limit in criterion 4 is set to enroll only adults with a sufficient capability to provide consent to participate in the trial. The upper age limit is set to reflect the considerations for the common development of some underlying diseases of SIADH at an older age as well as to ensure subject safety.

Criterion 5 is set to ensure the ethical conduct of the trial.

When determining whether the subject satisfies criterion 1 in Table 3.4.2-1, the plasma AVP concentration measured at the screening examination will be used, as a rule. If the plasma AVP concentration was measured as part of routine medical practice prior to participation in the trial, that result may be used for the subject's eligibility assessment without measuring the plasma AVP concentration at the screening examination (this only applies if the previous measurement was performed using a blood sample collected within 30 days prior to the scheduled start of IMP administration).

3.4.3 Exclusion Criteria

Subjects who meet any of the exclusion criteria listed in Table 3.4.3-1 at the screening examination will be excluded from the trial. In addition, subjects who meet any of exclusion criteria 14, 22, 28, or 29 in Table 3.4.3-1 during the pretreatment observation period (the day before start of IMP administration) or predose on Day 1 will also be excluded.

Serum sodium concentrations measured at each trial site will be used in the eligibility assessment.

Table 3.4.3-1 Exclusion Criteria	
1	Subjects who have transient hyponatremia induced by drug administration
2	Subjects with dehydration
3	Subjects with hyponatremia due to heart failure, ascites associated with hepatic cirrhosis, or nephrotic syndrome
4	Subjects with SIADH due to unknown etiology
5	Subjects with substantial sodium transudation due to renal sodium loss, diarrhea, or vomiting
6	Subjects who are unable to sense thirst or who have difficulty with fluid intake
7	Subjects who have impaired consciousness (coma or stupor)
8	Subjects who have AST (GOT) or ALT (GPT) exceeding 3 times the upper limit of normal at the screening examination
9	Subjects who have a history of myocardial infarction within 30 days prior to informed consent
10	Subjects who have a history of persistent ventricular tachycardia or ventricular fibrillation despite having an implantable cardioverter defibrillator within 30 days prior to informed consent
11	Subjects with decubitus angina, exertional angina induced by even mild exertion, or severe angina such as unstable angina
12	Subjects with a history of cerebrovascular disorder within 30 days prior to informed consent
13	Subjects with a severe psychiatric disorder
14	Subjects with systolic blood pressure of <90 mmHg at the time of the screening examination or at the pretreatment observation on the day before start of IMP administration
15	Subjects with a history of hypersensitivity or idiosyncratic reaction to benzazepine or benzazepine derivatives such as benazepril
16	Subjects with a history of drug abuse within 1 year prior to informed consent or with current alcohol dependence
17	Subjects with poorly controlled diabetes mellitus, defined as fasting blood glucose level of >300 mg/dL
18	Subjects with urinary tract obstruction
19	Subjects who have participated in any other clinical trial within 30 days prior to informed consent
20	Subjects who have participated in another clinical trial of tolvaptan or who have previously received tolvaptan
21	Subjects who are in the terminal stage of the disease or in a moribund state with an expected survival of less than 3 months as judged by the investigator or subinvestigator
22	Subjects with serum sodium concentration of <120 mEq/L associated with neurologic impairment, including apathy, confusion, or seizures
23	Subjects with a progressive or episodic neurological disorder, including multiple sclerosis or with a history of multiple strokes
24	Subjects with acute or transient hyponatremia due to head trauma or postoperative condition
25	Subjects who are receiving intravenous infusion fluid at a keep-vein-open (KVO) volume (at the minimum fluid volume for preventing blood clots after the planned volume of fluid infusion) or higher
26	Subjects with hyponatremia due to an artifact in laboratory tests (eg, a high blood glucose level of >300 mg/dL)
27	Subjects who are receiving arginine vasopressin (AVP) or an AVP analog for the treatment of the disease
28	Subjects who receive any other drugs for the treatment of hyponatremia, including demeclocycline, lithium carbonate, or urea within 7 days prior to start of IMP administration
29	Subjects who have concomitantly used hypertonic saline for correction of serum sodium concentration within 7 days prior to informed consent or who are likely to require intravenous hypertonic saline infusion for correction of symptomatic or asymptomatic severe hyponatremia during the trial period
30	Subjects with severe pulmonary hypertension: subjects whose disease state could be expected to worsen due to sudden changes in body fluid volume and blood pressure

Table 3.4.3-1	Exclusion Criteria
31	Female subjects who are breast-feeding at the planned start of IMP administration or who are judged by the investigator or subinvestigator to be possibly pregnant based on the results of the pregnancy test at the screening examination.
32	Male subjects or female subjects of childbearing potential who are sexually active and who do not agree to practice birth control as specified or to remain abstinent during the trial and until 30 days after final IMP administration

Subjects who have met any of the exclusion criteria and were thereby excluded from the trial may undergo the screening examination again, if there are changes in the criterion (criteria) that the subjects met. When the screening examination is repeated, the investigator or subinvestigator should obtain a new informed consent from the subject and assign a new subject identification number to that subject, prior to performing the second screening examination.

Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy and/or hysterectomy).

Subjects must agree to the restriction of drug use as specified in Section 4.

[Rationale for the exclusion criteria]

Criteria 1, 20, and 24 to 27 are set considering the effects on the efficacy or safety evaluation.

Criteria 2 to 5 are set according to "Diagnosis and Treatment Manual of Hypersecretion of Vasopressin (SIADH), Revised in 2011" (Appendix 1), to appropriately evaluate the efficacy and safety of tolvaptan in the treatment of hyponatremia secondary to SIADH.

Criteria 6 to 19, 21 to 23, and 30 are set considering the effects on the safety evaluation.

Criteria 28 and 29 are set considering the effects on the efficacy evaluation.

Criteria 31 and 32 are set because tolvaptan has been shown to be teratogenic and embryo-fetal lethal (in rabbits), and excreted into milk (in rats).

3.5 Endpoints

3.5.1 Efficacy

3.5.1.1 Primary Endpoint

- Percentage of subjects with normalized serum sodium concentration on the day after final IMP administration

3.5.1.2 Secondary Endpoints

- Change in serum sodium concentration
- Time course of serum sodium concentration
- Changes in clinical symptoms associated with hyponatremia

3.5.2 Pharmacodynamics

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Serum osmolality
- Urine osmolality
- Daily urinary sodium excretion
- Plasma AVP concentration

3.5.3 Pharmacokinetics

The plasma concentrations of tolvaptan and its metabolites (DM-4103 and DM-4107)

3.5.4 Safety

- AEs
- Clinical laboratory tests
- Body weight and vital signs
- 12-Lead electrocardiography
- Liver function tests

3.6 Measures to Minimize/Avoid Bias

This trial is an uncontrolled trial.

3.7 Trial Procedures

The assessment schedule is presented in Table 3.7-1.

Table 3.7-1 Schedule of Assessments (1/2)

	Screening Period		Pretreatment Observation Period	Treatment Period				
	Day −14 to Day −2	Day −2	Day −1	Day 1	Day 2	Day 3	Day 4	Day 5
Informed Consent	●							
Hospitalization[a,b]		●						
Subject Background	●							
Eligibility Assessment	●		●	●[c]				
IMP Administration[d]				←	←	←	←	→
Confirmation of Concomitant Drugs and Therapies	●	●	●	●	●	●	●	●
Clinical Symptoms Associated with Hyponatremia	●		●	●		●		●
Fluid intake restriction (≤20 mL/kg/day)	←	←	→					
Fluid intake restriction[e]					←	←	←	→
IMP Compliance			●	●	●	●	●	●

	Day −14 to Day −2	Day −2	Day −1	Day 1		Day 2	Day 3	Day 4	Day 5
				Predose	Postdose	Predose[f]	Predose[f]	Predose[f]	Predose[f]
Serum Sodium Concentration[g]	●		●	●	●	●	●	●	●
Body Weight	●		●	●		●	●	●	●
Daily Urine Volume, Fluid Intake, and Fluid Balance, and Urinary Sodium Excretion[h]	●		←						→
Urine Osmolality[i]	●								
Serum Osmolality	●			●		●	●	●	●
Plasma Drug Concentration (Blood Sampling)									
Laboratory Tests (Blood/Urine Sampling)	●			●					●
Liver Function Test (Blood Sampling)[j]	●			●			●		●
Vital Sign[k]	●		●	●		●	●	●	●
12-Lead Electrocardiography	●		●						
Serum Cortisol	●								

Table 3.7-1 Schedule of Assessments (1/2)

	Screening Period		Pretreatment Observation Period	Treatment Period					
	Day −14 to Day −2	Day −2	Day −1	Day 1		Day 2	Day 3	Day 4	Day 5
Plasma AVP Concentration	•[l]			•					
Pregnancy Test[m]	•								
Adverse Events	←								→

Table 3.7-1 Schedule of Assessments (2/2)

	Treatment Period							Day After Final IMP Administration	Follow-up Exam After the End-of-Treatment	
	Day 7 (±1 day)	Day 14 (±1 day)	Day 21 (±1 day)	Until the Maintenance Dose Determination	At the Time of Maintenance Dose Determined	When Determining Possibility of Switching to Outpatient Treatment	At Withdrawal		Measurement of serum sodium concentration 3 to 5 days after completion	Follow-up examination 7 to 10 days after completion
Informed Consent										
Hospitalization										
Subject Background										
Eligibility Assessment										
IMP Administration	p	p	p							
Confirmation of Concomitant Drugs and Therapies	●	●	●				●	●		●
Clinical Symptoms Associated with Hyponatremia	●	●	●		●		●	●	●	●
Fluid intake restriction (≤20 mL/kg/day)								←	→	→
Fluid intake restriction	←	→	→	→	→	→	→	→		
IMP Compliance	●	●	●				●	●		
Serum Sodium Concentration	●	●	●	●		●	●	●	●	●
Body Weight	●	●	●				●	●		●
Daily Urine Volume, Fluid Intake, and Fluid Balance, and Urinary Sodium Excretion				●						
Urine Osmolality				●						
Serum Osmolality	●	●	●				●	●		●
Plasma Drug Concentration (Blood Sampling)			●				●	●		

Table 3.7-1 Schedule of Assessments (2/2)

	Treatment Period							Day After Final IMP Administration	Follow-up Exam After the End-of-Treatment	
	Day 7 (±1 day)[n]	Day 14 (±1 day)[o]	Day 21 (±1 day)[o]	Until the Maintenance Dose Determination	At the Time of Maintenance Dose Determined	When Determining Possibility of Switching to Outpatient Treatment	At Withdrawal		Measurement of serum sodium concentration 3 to 5 days after completion	Follow-up examination 7 to 10 days after completion
Laboratory Tests (Blood/Urine Sampling)[q]	●	●	●				●	●		●
Liver Function Tests (Blood Sampling)[q]	●	●	●				●	●		●
Vital Sign	●	●	●				●	●		●
12-Lead Electrocardiography	●						●	●		●
Serum Cortisol										
Plasma AVP concentration[q]	●	●	●				●	●		●
Pregnancy Test										●
Adverse Events	←									→

[a] Hospitalization: Required from before supper 2 days prior to start of IMP administration. Possibility of switching to outpatient treatment will be determined for each subject on the day after the maintenance dose is determined as specified in Section 3.2.5.

[b] Hospitalization: As specified in Section 3.2.5, subjects who have switched to the outpatient treatment will be re-hospitalized if it becomes necessary to increase their dose of the IMP from the determined maintenance dose due to lack of efficacy or other reasons. Subjects will also be re-hospitalized if treatment is to be resumed after completion of IMP treatment.

[c] Eligibility assessment will be performed before IMP administration on Day 1 of the treatment period.

[d] IMP administration:

IMP administration will be performed once daily after breakfast from Day 1 of the treatment period. The timing for the end of treatment will be individually determined for each subject as specified in Section 3.2.4. The maximum treatment duration will be 30 days.

[e] From Day 2 to the completion of the examination on the day after the final IMP administration: Fluid intake from immediately before IMP administration on Day 1 to immediately before IMP administration on Day 2 will be the upper limit of the daily fluid intake. However, if thirst or dehydration, and other unfavorable symptoms develop, the subject should be instructed to take more fluids, irrespective of the upper limit, to ensure the safety of the subject.

[f] On Days 2 through 5 of the treatment period, predose laboratory tests and examinations will be performed at 21 to 24 hours after IMP administration on the previous day.

[g] Serum sodium concentration

- Pretreatment observation period (day before start of IMP administration): Blood sampling will be performed at approximately 24 hours before the scheduled initial IMP administration.
- Day 1 of the treatment period: Blood sampling will be performed at predose and at 4 to 6 hours and 8 to 12 hours postdose.
- Days 2 to 5 of the treatment period: Until the maintenance dose is determined, blood sampling will also be performed at 4 to 6 hours postdose on days on which the dose is increased.

[h] Daily urine volume, fluid intake, and fluid balance and urinary sodium excretion

- Screening period (Day −14 to −2): Only urinary sodium excretion will be measured.
- Pretreatment observation period (day before start of IMP administration): Cumulative 24-hour urine volume and fluid intake volume will be measured from after complete urination after breakfast until after complete urination immediately before IMP administration on Day 1 of the treatment period.
- Treatment period: Measurement of cumulative urine volume and fluid intake will start after complete urination after breakfast on Day 1. The time until after complete urination immediately before IMP administration on the following day will be defined as one collection period, and the measurement of daily urine volume and fluid intake volume for each collection period will continue until the maintenance dose is determined.

[i] Urine osmolality:

In the pretreatment observation period and treatment period, measurement will be performed using urine samples from the cumulatively collected urine.

[j] Liver function tests (blood sampling): AST (GOT), ALT (GPT), and serum total bilirubin will be measured.

[k] Vital signs: Blood pressure, pulse rate, and body temperature will be measured.

[l] Plasma AVP concentration:

For determining whether the subject satisfies the inclusion criteria, in principle, plasma AVP concentration measured at the time of screening examination will be used. However, if plasma AVP concentration has already been measured at a regular visit prior to the subject's participation in the trial, that result may be used for assessment without measuring plasma AVP concentration at the screening examination (this only applies if the previous measurement was performed using a blood sample collected within 30 days prior to the scheduled start of IMP administration).

[m] Pregnancy test: Performed in only females of childbearing potential.

[n] Day 7 of the treatment period:

If subjects who have switched to outpatient treatment have difficulty coming to the trial site on the day of the scheduled visit for some reason, a margin of +1 day is allowed.

[o] Days 14 and 21 of the treatment period:

If subjects who have switched to outpatient treatment have difficulty coming to the trial site on the day of the scheduled visit for some reason, a margin of ±1 day is allowed.

[p] IMP administration:
On Days 7, 14, and 21, if subjects visit the trial site for examination, IMP administration is to be performed in the morning after blood sampling.

[q] Serum sodium concentration, serum osmolality, plasma drug concentrations (blood sampling), laboratory tests (blood/urine sampling), liver function test (blood sampling), and plasma AVP concentration:
For measurement on Day 21 of the treatment period and on the day after final IMP administration, blood sampling will be performed at 22 to 24 hours after IMP administration on the previous day. For other measurement timepoints, blood sampling will be performed at 21 to 24 hours after IMP administration on the previous day. If it is difficult to perform blood sampling at 22 to 24 hours after IMP administration on the previous day for subjects who have switched to outpatient treatment, blood sampling for days other than the day after final IMP administration can be performed anytime in the morning before IMP administration.

- Serum sodium concentration:
  Days 7, 14, and 21 of the treatment period, the day after final IMP administration, and 3 to 5 days after completion of treatment
- Serum Osmolality:
  Days 7, 14, and 21 of the treatment period and the day after final IMP administration
- Plasma drug concentrations (blood sampling):
  Day 21 of the treatment period and the day after final IMP administration
- Laboratory tests (blood/urine sampling):
  Days 7, 14, and 21 of the treatment period and the day after final IMP administration
- Liver function tests (blood sampling):
  Days 7, 14, and 21 of the treatment period and the day after final IMP administration
- Plasma AVP concentration:
  Days 7, 14, and 21 of the treatment period and the day after final IMP administration

[r] Serum sodium concentration: Blood sampling will be performed at predose every day until the maintenance dose will be determined. Blood sampling will also be performed at 4 to 6 hours postdose on days which the dose is increased.

3.7.1 Schedule of Assessments

3.7.1.1 Screening Period (14 to 2 Days Before Start of IMP Administration)

After informed consent has been obtained, the investigator or subinvestigator will assign a subject identification number to the subject according to Section 3.3.2, and record the date of acquisition of informed consent and the assigned subject identification number in the source document and CRF.

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

1) Assessment of subject background

The investigator or subinvestigator will investigate the subject background for the following items, and record the results in the source document and CRF.

- Birth date
- Gender
- Height
- Race
- Ethnicity
- Complications
- Medical history
- Etiology of SIADH
- Date of diagnosis of SIADH
  (Date on which the latest diagnosis of SIADH was made [or the date on which hyponatremia requiring treatment was diagnosed])
- Diagnoses and treatments of SIADH prior to participation in the trial
  (Perform an investigation, as specified in 2) Investigation of diagnoses and treatments prior to participation in the trial.)

2) Investigation of diagnoses and treatments prior to participation in the trial

The investigator or subinvestigator will investigate the following items, and record the results in the source document and CRF.

- Serum sodium concentrations before participation in the trial

  The investigator or subinvestigator will identify the following serum sodium concentrations measured within 30 days before the day of informed consent acquisition, and record each value, along with the date on which the value was measured.

- The highest serum sodium concentration observed after SIADH was diagnosed
- The lowest serum sodium concentration observed after SIADH was diagnosed
- The serum sodium concentration just after fluid intake restriction was started

- Clinical symptoms associated with hyponatremia before participation in the trial

The investigator or subinvestigator will identify the following clinical symptoms observed within 30 days before the day of informed consent acquisition, and record the presence/absence of each symptom and its severity, along with the date on which each symptom was observed.

- Anorexia associated with hyponatremia
- Vomiting associated with hyponatremia
- Headache associated with hyponatremia
- Consciousness disturbed associated with hyponatremia
- Malaise associated with hyponatremia
- Other symptoms associated with hyponatremia, if any

- Treatments of hyponatremia secondary to SIADH before participation in the trial

The investigator or subinvestigator will identify the following treatments given within 30 days before the day of informed consent acquisition, and record the dates on which the treatment was started and completed.

- Fluid intake restriction
- Treatments other than fluid intake restriction, if any

3) Examinations and assessments

- Confirmation of concomitant drugs and therapies
- Clinical symptoms associated with hyponatremia
- Serum sodium concentration
- Body weight
- Urine osmolality
- Serum osmolality
- Laboratory tests (blood/urine sampling)
- Liver function tests (blood sampling)
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-Lead electrocardiography
- Serum cortisol concentration
- Plasma AVP concentration
- Urine sodium concentration
- Pregnancy test (human chorionic gonadotropin [hCG]) for female subjects of childbearing potential

If the plasma AVP concentration was measured as part of routine medical practice prior to participation in the trial, that result may be used for the subject's eligibility assessment, without measuring the plasma AVP concentration at the screening examination (this only applies if the previous measurement was performed using a blood sample collected within 30 days prior to the scheduled start of IMP administration).

3.7.1.2 Screening Period (2 Days Before Start of IMP Administration)

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

- Confirmation of concomitant drugs and therapies
- AEs

3.7.1.3 Pretreatment Observation Period (Day Before Start of IMP Administration)

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

1) Approximately 24 hours before the scheduled time of the initial IMP administration

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

- Serum sodium concentration

Subjects are required to urinate completely immediately after breakfast, and then the investigator or subinvestigator will start urine collection and fluid intake measurement to assess the following items.

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

2) At a feasible time

- Confirmation of concomitant drugs and therapies
- Clinical symptoms associated with hyponatremia
- Body weight
- Vital signs (blood pressure, pulse rate, body temperature)

- 12-Lead electrocardiography
- AEs

3.7.1.4 Day 1 of Treatment Period

The investigator or subinvestigator will perform the following procedures. Fluid intake must not be restricted within 24 hours from immediately after the initial IMP administration on Day 1 of treatment period.

1) Before IMP administration

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

- Serum sodium concentration
- Body weight
- Serum osmolality
- Laboratory tests (blood/urine sampling)
- Liver function tests (blood sampling)
- Vital signs (blood pressure, pulse rate, body temperature)
- Plasma AVP concentration

Subjects are required to urinate completely immediately after breakfast, and then the investigator or subinvestigator will start urine collection and fluid intake measurement to assess the following items.

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

2) IMP administration

The investigator or subinvestigator will confirm that the subject meets all of the inclusion criteria and none of the exclusion criteria, and then administer one 7.5 mg tolvaptan tablet with water. After administration, the investigator or subinvestigator will observe the change in serum sodium concentration, and if the following criterion is met, discontinue treatment with the IMP as specified in Section 3.8.3.1, followed by performance of the examination at withdrawal according to Section 3.7.1.19.

- Serum sodium concentration increased by ≥12 mEq/L from predose, within 24 hours after the IMP administration.

3) 4 to 6 hours after IMP administration

- Serum sodium concentration

4) 8 to 12 hours after IMP administration

- Serum sodium concentration

5) At a feasible time

- Confirmation of concomitant drugs and therapies
- Clinical symptoms associated with hyponatremia
- IMP compliance
- AEs

3.7.1.5 Day 2 of Treatment Period

The investigator or subinvestigator will perform the following procedures. Fluid intake must not be restricted within 24 hours after IMP administration on Day 1 of the treatment period. On or after Day 2 of treatment period, if the serum sodium concentration has increased by ≥12 mEq/L within 24 hours from immediately before IMP administration, treatment with the IMP should be discontinued as specified in Section 3.8.3.1, and the examination at withdrawal will be performed according to Section 3.7.1.19.

1) Before IMP administration (21 to 24 hours after IMP administration on the day before)

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

- Serum sodium concentration
- Body weight
- Serum osmolality
- Vital signs (blood pressure, pulse rate, body temperature)

Subjects are required to urinate completely immediately after breakfast, and the investigator or subinvestigator will start urine collection and fluid intake measurement to assess the following items. If the maintenance dose has already been determined, tolvaptan tablets should be administered at the maintenance dose with water after breakfast, without performing the measurements below.

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

2) IMP administration

The investigator or subinvestigator will select the dose of the IMP based on the change in serum sodium concentration from predose of the IMP administration on the day before as specified in Section 3.2.2, and administer tolvaptan tablets to subjects at that dose with water, unless the maintenance dose has already been determined.
The investigator or subinvestigator will confirm the fluid intake within 24 hours after the IMP administration on Day 1 of treatment period, and instruct the subject to adhere to Section 4.2 on or after Day 2 of treatment period.

3) 4 to 6 hours after IMP administration

If the maintenance dose is not determined on Day 2 of treatment period and the dose is increased on that day according to Section 3.2.2, the investigator or subinvestigator will perform the following examinations 4 to 6 hours after IMP administration.

- Serum sodium concentration

4) At a feasible time

- Confirmation of concomitant drugs and therapies
- IMP compliance
- AEs

5) When the maintenance dose is determined

If the maintenance dose is to be determined on Day 2 of treatment period, the investigator or subinvestigator will perform the procedures as specified in Section 3.7.1.16.

3.7.1.6 Day 3 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before IMP administration (21 to 24 hours after IMP administration on the day before)

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

- Serum sodium concentration
- Body weight
- Serum osmolality
- Liver function tests (blood sampling)
- Vital signs (blood pressure, pulse rate, body temperature)

Subjects are required to urinate completely immediately after breakfast, and the investigator or subinvestigator will start urine collection and fluid intake measurement to assess the following items. If the maintenance dose has been already

determined, tolvaptan tablets should be administered at the maintenance dose with water after breakfast, without performing the measurements below.

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

2) IMP administration

The investigator or subinvestigator will select the dose of the IMP based on the change in serum sodium concentration from predose of the IMP administration on the day before as specified in Section 3.2.2, and administer tolvaptan tablets to subjects at that dose with water, unless the maintenance dose has already been determined.

In addition, the investigator or subinvestigator will instruct the subject to adhere to Section 4.2.

3) 4 to 6 hours after IMP administration

If the maintenance dose is not determined on Day 3 of treatment period and the dose is to be increased on the same day according to Section 3.2.2, the investigator or subinvestigator will perform the following examinations 4 to 6 hours after IMP administration.

- Serum sodium concentration

4) At a feasible time

- Confirmation of concomitant drugs and therapies
- Clinical symptoms associated with hyponatremia
- IMP compliance
- AEs

5) When the maintenance dose is determined

If the maintenance dose is determined on Day 3 of treatment period, the investigator or subinvestigator will perform the procedures specified in Section 3.7.1.16.

6) When determining possibility of switching to outpatient treatment

When determining possibility of switching to outpatient treatment as specified in Section 3.2.5 is needed for subjects whose maintenance dose were determined on the day before, the investigator or subinvestigator is to perform the procedures as specified in Section 3.7.1.17.

3.7.1.7 Day 4 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before IMP administration (21 to 24 hours after IMP administration on the day before)

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

- Serum sodium concentration
- Body weight
- Serum osmolality
- Vital signs (blood pressure, pulse rate, body temperature)

Subjects are required to urinate completely immediately after breakfast, and the investigator or subinvestigator will start urine collection and fluid intake measurement to assess the following items. If the maintenance dose has been already determined, tolvaptan tablets should be administered at the maintenance dose with water after breakfast, without performing the examinations below.

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

2) IMP administration

The investigator or subinvestigator will select the dose of the IMP based on the change in serum sodium concentration from predose of the IMP administration on the day before as specified in Section 3.2.2, and administer tolvaptan tablets to subjects at that dose with water, unless the maintenance dose has already been determined.

In addition, the investigator or subinvestigator will instruct the subject to adhere to Section 4.2.

3) 4 to 6 hours after IMP administration

If the maintenance dose is not determined on Day 4 of treatment period and the dose is to be increased on the same day according to Section 3.2.2, the investigator or subinvestigator will perform the following examinations 4 to 6 hours after IMP administration.

- Serum sodium concentration

4) At a feasible time

- Confirmation of concomitant drugs and therapies
- IMP compliance
- AEs

5) When the maintenance dose is determined

If the maintenance dose is to be determined on Day 4 of treatment period, the investigator or subinvestigator will perform the procedures specified in Section 3.7.1.16.

6) When determining possibility of switching to outpatient treatment

When determining possibility of switching to outpatient treatment as specified in Section 3.2.5 is needed for subjects whose maintenance dose were determined on the day before, the investigator or subinvestigator is to perform the procedures as specified in Section 3.7.1.17.

3.7.1.8 Day 5 of Treatment Period

The investigator or subinvestigator will perform the following procedures.

1) Before IMP administration (21 to 24 hours after IMP administration on the day before)

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

- Serum sodium concentration
- Body weight
- Serum osmolality
- Laboratory tests (blood/urine sampling)
- Liver function tests (blood sampling)
- Vital signs (blood pressure, pulse rate, body temperature)

Subjects are required to urinate completely immediately after breakfast, and the investigator or subinvestigator will start urine collection and fluid intake measurement to assess the following items. If the maintenance dose has been already determined, tolvaptan tablets should be administered at the maintenance dose with water after breakfast, without performing the examinations below.

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

2) IMP administration

The investigator or subinvestigator will select the dose of the IMP based on the change in serum sodium concentration from predose of the IMP administration on the day before as specified in Section 3.2.2, and administer tolvaptan tablets to subjects at that dose with water, unless the maintenance dose has already been determined.

In addition, the investigator or subinvestigator will instruct the subject to adhere to Section 4.2.

3) 4 to 6 hours after IMP administration

If the maintenance dose is not determined on Day 5 of treatment period and the dose is to be increased on the same day according to Section 3.2.2 on the same day, the investigator or subinvestigator will perform the following examinations 4 to 6 hours after IMP administration.

- Serum sodium concentration

4) At a feasible time

- Confirmation of concomitant drugs and therapies
- Clinical symptoms associated with hyponatremia
- IMP compliance
- AEs

5) When the maintenance dose is determined

If the maintenance dose is to be determined on Day 5 of treatment period, the investigator or subinvestigator will perform the procedures specified in Section 3.7.1.16.

6) When determining possibility of switching to outpatient treatment

When determining possibility of switching to outpatient treatment as specified in Section 3.2.5 is needed for subjects whose maintenance dose were determined on the day before, the investigator or subinvestigator is to perform the procedures as specified in Section 3.7.1.17.

3.7.1.9 Day 6 of Treatment Period

Subjects with an individual maintenance dose (including subjects who have already switched to outpatient treatment after determination of the maintenance dose) will receive tolvaptan tablets according to the individually determined maintenance dose with water after breakfast, and are not required to undergo the following examinations as described in items 1) and 2) on Day 6 of treatment period.

1) Procedures (if the maintenance dose has not been determined)
Follow the procedures specified in Section 3.7.1.15.

2) When the maintenance dose is determined
If the maintenance dose is to be determined on Day 6 of treatment period, the investigator or subinvestigator will perform the procedures as specified in Section 3.7.1.16.

3) When determining possibility of switching to outpatient treatment
When determining possibility of switching to outpatient treatment as specified in Section 3.2.5 is needed for subjects whose maintenance dose were determined on the day before, the investigator or subinvestigator is to perform the procedures specified in Section 3.7.1.17.

3.7.1.10 Day 7 of Treatment Period

The investigator or subinvestigator is to perform the following procedures on Day 7 of treatment period. If subjects who have switched to outpatient treatment have difficulty coming to the trial site on the day of the scheduled visit for some reason, a margin of +1 day is allowed.

If the investigator or subinvestigator judges to terminate treatment with the IMP according to the specifications in Section 3.2.4, the subjects should not receive the IMP administration on that day but undergo the examinations according to the procedures specified in Section 3.7.1.14.

1) Before IMP administration (21 to 24 hours after the IMP administration on the day before)
The investigator or subinvestigator will perform the following examinations. If the examinations that require a visit to the trial site cannot be performed within 21 to 24 hours after the IMP administration on the day before, the examinations may be performed in the morning before IMP administration on Day 7.

- Serum sodium concentration
- Serum osmolality
- Laboratory tests (blood/urine sampling)
- Liver function tests (blood sampling)
- Plasma AVP concentration

Subjects are required to urinate completely immediately after breakfast, and the investigator or subinvestigator will start urine collection and fluid intake measurement to assess the following items. However, subjects with already determined maintenance doses (including subjects who have already switched to

outpatient treatment after determination of the maintenance dose) will receive tolvaptan tablets at the individually determined maintenance dose with water after breakfast, without undergoing the following measurements.

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

2) IMP administration

The investigator or subinvestigator will select the dose of the IMP based on the change in serum sodium concentration from predose of the IMP administration on the day before as specified in Section 3.2.2, and administer tolvaptan tablets to subjects at that dose with water, unless the maintenance dose has already been determined.

In addition, the investigator or subinvestigator will instruct the subject to adhere to Section 4.2.

3) 4 to 6 hours after administration

If the maintenance dose is not determined on Day 7 of treatment period and the dose is to be increased on the same day according to Section 3.2.2, the investigator or subinvestigator will perform the following examinations 4 to 6 hours after IMP administration.

- Serum sodium concentration

4) At a feasible time

- Confirmation of concomitant drugs and therapies
- Clinical symptoms associated with hyponatremia
- Body weight
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-Lead electrocardiography
- IMP compliance
- AEs

5) When the maintenance dose is determined

If the maintenance dose is to be determined on Day 7 of treatment period, the investigator or subinvestigator will perform the procedures specified in Section 3.7.1.16.

6) When determining possibility of switching to outpatient treatment
When determining possibility of switching to outpatient treatment as specified in Section 3.2.5 is needed for subjects whose maintenance dose were determined on the day before, the investigator or subinvestigator is to perform the procedures as specified in Section 3.7.1.17.

3.7.1.11 Days 8 to 10 of Treatment Period

Subjects with an individual maintenance dose (including subjects who have already switched to outpatient treatment after determination of the maintenance dose) will receive tolvaptan tablets at the individually determined maintenance dose with water after breakfast, and are not required to undergo the following examinations as described in items 1) and 2) on Days 8 to 10 of treatment period.

1) Procedures (if the maintenance dose has not been determined)
Follow the procedures specified in Section 3.7.1.15.

2) When the maintenance dose is determined
If the maintenance dose is to be determined on Days 8 to 10 of treatment period, the investigator or subinvestigator will perform the procedures specified in Section 3.7.1.16.

3) When determining possibility of switching to outpatient treatment
When determining possibility of switching to outpatient treatment as specified in Section 3.2.5 is needed for subjects whose maintenance dose were determined on the day before, the investigator or subinvestigator is to perform the procedures as specified in Section 3.7.1.17.

3.7.1.12 Day 14 of Treatment Period

The investigator or subinvestigator is to perform the following procedures on Day 14 of treatment period. If subjects who have switched to outpatient treatment have difficulty coming to the trial site on the day of the scheduled visit for some reason, a margin of ±1 day is allowed.

If the investigator or subinvestigator judges to terminate treatment with the IMP according to the specification in Section 3.2.4, the subjects should not receive the IMP administration on that day but undergo the examinations according to the procedures specified in Section 3.7.1.14.

1) Before IMP administration (21 to 24 hours after the IMP administration on the day before)

The investigator or subinvestigator will perform the following examinations. If the examinations that require a visit to the trial site cannot be performed within 21 to 24 hours after the IMP administration on the day before, the examinations may be performed in the morning before IMP administration on Day 14.

- Serum sodium concentration
- Serum osmolality
- Laboratory tests (blood/urine sampling)
- Liver function tests (blood sampling)
- Plasma AVP concentration

2) IMP administration

Subjects will take tolvaptan tablets with water. In addition, the investigator or subinvestigator will instruct the subject to adhere to Section 4.2.

3) At a feasible time

- Confirmation of concomitant drugs and therapies
- Clinical symptoms associated with hyponatremia
- Body weight
- Vital signs (blood pressure, pulse rate, body temperature)
- IMP compliance
- AEs

3.7.1.13 Day 21 of Treatment Period

The investigator or subinvestigator is to perform the following procedures on Day 21 of treatment period. If subjects who have switched to outpatient treatment have difficulty coming to the trial site on the day of the scheduled visit for some reason, a margin of ±1 day is allowed.

If the investigator or subinvestigator judges to terminate treatment with the IMP according to the specification in Section 3.2.4, the subjects should not receive the IMP administration on that day but undergo the examinations according to the procedures specified in Section 3.7.1.14.

1) Before IMP administration (22 to 24 hours after IMP administration on the day before)

The investigator or subinvestigator will perform the following examinations. If the examinations that require a visit to the trial site cannot be performed within 22 to 24

hours after the IMP administration on the day before, the examinations may be performed in the morning before IMP administration on Day 21.

- Serum sodium concentration
- Serum osmolality
- Plasma drug concentration (blood sampling)
- Laboratory tests (blood/urine sampling)
- Liver function tests (blood sampling)
- Plasma AVP concentration

2) IMP administration

Subjects will take tolvaptan tablets with water. In addition, the investigator or subinvestigator will instruct the subject to adhere to Section 4.2.

3) At a feasible time

- Confirmation of concomitant drugs and therapies
- Clinical symptoms associated with hyponatremia
- Body weight
- Vital signs (blood pressure, pulse rate, body temperature)
- IMP compliance
- AEs

3.7.1.14 Day After the Final IMP Administration

On the day after the final IMP administration (the day following Day 30, or the day after the investigator or subinvestigator has decided to complete treatment with the IMP as specified in Section 3.2.4), the investigator or subinvestigator will perform the following procedures.

If the investigator or subinvestigator makes a judgement to discontinue treatment with the IMP according to Section 3.8.3.1, the procedures as specified in Section 3.7.1.19 should be performed rather than the specifications as below.

1) 22 to 24 hours after the final IMP administration

The investigator or subinvestigator will perform the following examinations. If the examinations that require a visit to the trial site cannot be performed within 22 to 24 hours after the IMP administration on the day before, the examinations may be performed on the morning of the day after the final IMP administration.

- Serum sodium concentration
- Serum osmolality
- Plasma drug concentration (blood sampling)

- Laboratory tests (blood/urine sampling)
- Liver function tests (blood sampling)
- Plasma AVP concentration

2) At a feasible time

- Confirmation of concomitant drugs and therapies
- Clinical symptoms associated with hyponatremia
- Body weight
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-Lead electrocardiography
- IMP compliance
- AEs

Subjects are to visit the trial site 3 to 5 days and 7 to 10 days after the final IMP administration (the completion of treatment) to undergo the examinations specified in Section 3.7.1.20. Even if treatment with the IMP is terminated before the duration of treatment reached 30 days, the examinations specified in Section 3.7.1.20 should be performed regardless of whether or not treatment maybe resumed.

3.7.1.15 Procedures to Be Performed Until the Maintenance Dose Is Determined

The investigator or subinvestigator will perform the following procedures until the maintenance dose is determined (see Section 3.2.1 and Section 3.2.3), except for scheduled assessment days (Days 1 to 5, 7, 14, and 21), on which the specified procedures for each day should be performed.

1) Before IMP administration (21 to 24 hours after the IMP administration on the day before)

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

- Serum sodium concentration

Subjects are required to urinate completely immediately after breakfast, and the investigator or subinvestigator will start urine collection and fluid intake measurement to assess the following items.

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

2) IMP administration

The investigator or subinvestigator will select the dose of the IMP based on the change in serum sodium concentration from predose of the IMP administration on the day before as specified in Section 3.2.2, and administer tolvaptan tablets to subjects at that dose with water.

The investigator or subinvestigator will record the date that the dose increase is assessed, along with the reasons if the dose is not increased in the source document and CRF.

If the investigator or subinvestigator judges to reduce the dose of the IMP due to any tolerability problem (eg, the occurrence or deterioration of AEs), the dose should be down-titrated (to the next lower dose level than that on the previous day). If the tolerability problem continues after dose reduction, the dose may be further reduced. The dose at the time that the investigator or subinvestigator judges to be tolerable will be determined as the maintenance dose.

3) 4 to 6 hours after IMP administration

If the dose of the IMP is increased according to Section 3.2.2, the investigator or subinvestigator will perform the following examinations 4 to 6 hours after IMP administration.

- Serum sodium concentration

3.7.1.16 When the Maintenance Dose of the IMP Is Determined

On the day the maintenance dose of the IMP is determined according to Section 3.2.3, the investigator or subinvestigator will perform the following investigation. If the investigation has already been performed on the same day, it does not need to be repeated after the maintenance dose is determined.

- Clinical symptoms associated with hyponatremia

The investigator or subinvestigator will record the maintenance dose, the date the maintenance dose is determined, and the reasons for the determination in the source document and CRF.

If dose adjustment is required after the maintenance dose has been determined, the investigator or subinvestigator will record the date on which the dose adjustment is made, along with the reason for the decision in the source document and CRF.

3.7.1.17 When Switching to Outpatient Treatment

The investigator or subinvestigator will make a judgement for switching the trial treatment to outpatient treatment according to the following procedures on the day after the maintenance dose is determined. If the examination has already been performed on the same day, it does not need to be repeated for the judgment regarding switching to outpatient treatment.

1) Before IMP administration (21 to 24 hours after the IMP administration on the day before)

- Serum sodium concentration

2) Judgement for switching subjects to outpatient treatment

The investigator or subinvestigator will make a judgement for switching to outpatient treatment according to the criterion for switching to outpatient treatment as specified in Section 3.2.5. If the criterion for switching to outpatient treatment is met, the subject may be discharged from the trial site on or after the day the judgement is made.

Criterion for switching to outpatient treatment

- The predose serum sodium concentration on the day of judgement has not increased by >2 mEq/L compared with predose on the day before.

If switching to outpatient treatment is not allowed because the criterion for switching to outpatient treatment is not met as specified in Section 3.2.5, the predose serum sodium concentration on the following day will be evaluated for a reassessment of the possibility of switching to outpatient treatment.

3.7.1.18 Change in the Maintenance Dose of the IMP

If the dose of the IMP has to be increased beyond the maintenance dose after it has been determined due to lack of efficacy or other reasons, and a new maintenance dose must be determined, the investigator or subinvestigator should perform the following procedures in an inpatient setting.

1) Day before the start of dose escalation

Subjects who have already switched to outpatient treatment should be rehospitalized by the day before dose escalation is scheduled to start as specified in Section 3.2.5.

The investigator or subinvestigator will perform the following assessments on the day before the dose escalation is scheduled to start. If these procedures have already been performed on the same day, they do not need to be repeated.

- Serum sodium concentration (at predose)
- Clinical symptoms associated with hyponatremia (at a feasible time)

2) Start of dose escalation to determination of the maintenance dose

On and after the day of start of an additional dose escalation beyond the once fixed maintenance dose,, the investigator or subinvestigator will perform the procedures as specified in Section 3.7.1.15, however, measurements of cumulative urine volume and fluid intake (daily urine volume, daily fluid intake, daily fluid balance, and urine osmolarity) are not required. On scheduled assessment days, the procedures specified for each day should be performed.

3) Redetermination of maintenance dose

The investigator or subinvestigator will perform the procedures as specified in Section 3.7.1.16, when the new maintenance dose is determined.

On or after the day on which a new maintenance dose is determined, the investigator or subinvestigator will perform the procedures specified in Section 3.7.1.17 to make a judgement for possibility of switching to outpatient treatment.

3.7.1.19 Treatment Discontinuation

When discontinuation of treatment with the IMP is judged to be necessary according to Section 3.8.3.1, the investigator or subinvestigator will perform the following assessments. If these assessments have already been performed on the same day, they do not need to be repeated. If it is not feasible to perform all of the examinations, observations, and assessments at discontinuation of treatment, due to the subject's refusal or based on the judgment of the investigator or subinvestigator (eg, in emergencies), only those that are feasible should be performed.

- Confirmation of concomitant drugs and therapies
- Clinical symptoms associated with hyponatremia
- Serum sodium concentration
- Body weight
- Serum osmolality
- Plasma drug concentration (blood sampling)
- Laboratory tests (blood/urine sampling)
- Liver function tests (blood sampling)
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-Lead electrocardiography
- Plasma AVP concentration

- IMP compliance
- AEs

The subject will visit the trial site 3 to 5 days and 7 to 10 days after the final IMP administration to undergo the procedures specified in Section 3.7.1.20.

3.7.1.20 Follow-up

3.7.1.20.1 Serum Sodium Concentration (3 to 5 Days After the Final IMP Administration)

The subject will visit the trial site 3 to 5 days after the final IMP administration (the completion of treatment) to undergo the following examinations and investigations.

- Clinical symptoms associated with hyponatremia
- Serum sodium concentration
- AEs

3.7.1.20.2 Follow-up Examination (7 to 10 Days After the Final IMP Administration)

The subject will visit the trial site 7 to 10 days after the final IMP administration (the completion of treatment) to undergo the following examinations and investigations.

- Confirmation of concomitant drugs and therapies
- Clinical symptoms associated with hyponatremia
- Serum sodium concentration
- Body weight
- Serum osmolality
- Laboratory tests (blood/urine sampling)
- Liver function tests (blood sampling)
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-Lead electrocardiography
- Plasma AVP concentration
- Pregnancy test
- AEs

If treatment with the IMP was completed before the duration of treatment reached 30 days (except for treatment discontinuations specified in Section 3.8.3.1) and hyponatremia then recurred, and the investigator or subinvestigator concludes that readministration of IMP is necessary, treatment may be resumed within 30 days after the initial IMP administration (for the readministration procedure, see Appendix 3). If the

investigator or subinvestigator judges not to resume treatment with the IMP, the follow-up period for the subject is to be completed.

The subject may be asked to revisit the trial site to repeat the follow-up examination, if those examinations are necessary for the investigator or subinvestigator to determine whether readministration should be started.

3.7.2 Efficacy Assessments

3.7.2.1 Serum Sodium Concentration

For the efficacy evaluation, serum sodium concentrations will be measured centrally at the contract research organization for clinical laboratory tests (hereafter, central laboratory). In addition, because the investigator or subinvestigator must be apprised of the serum sodium concentrations in a timely manner to conduct the assessment of eligibility, decisions of switching to outpatient treatment, and the dose selection of tolvaptan, as well as to ensure subject safety, serum sodium concentrations will also be measured at each trial site from the screening period to the follow-up period.

The central laboratory will measure serum sodium concentrations according to the procedures specified by the laboratory, and provide the measurement results to the sponsor and the investigator or subinvestigator. The investigator or subinvestigator will document blood sampling, as well as the date and time of sampling in the CRF. The electronic file submitted to the sponsor by the central laboratory will be regarded as the source document; therefore, recording of the results in the CRF is unnecessary. At the same blood sampling points as those specified in Section 3.7.3.2, the serum sodium concentration data obtained as part of the clinical laboratory tests at the central laboratory will be used.

In the measurement of serum sodium concentrations, each trial site should use appropriate equipment and apparatuses, with reliable precision, and follow the procedures specified by the site. Measured values (with the unit) obtained at the trial site, as well as the time and date of measurement, should be recorded in the source document and CRF.

3.7.2.2 Clinical Symptoms Associated With Hyponatremia

The investigator or subinvestigator will interview the subject to confirm whether the clinical symptoms associated with hyponatremia (anorexia, vomiting, headache, consciousness disturbed, and malaise)[11,12] are present and their severities along with the general condition of subjects, and record whether the interview was conducted, the date of interview, and presence or absence of clinical symptoms (if present, its severity of

each symptom is to be recorded based on the following gradings) in the source document and CRF.

1) Anorexia[11]

- Grade 1
  Loss of appetite without an alteration in eating habits
- Grade 2
  Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated
- Grade 3
  Associated with significant weight loss or malnutrition (eg, inadequate oral caloric and/or fluid intake); intravenous fluid, tube feeding, or TPN indicated

2) Vomiting[11]

- Grade 1
  1 to 2 episodes (separated by 5 minutes) in 24 hours
- Grade 2
  3 to 5 episodes (separated by 5 minutes) in 24 hours
- Grade 3
  ≥6 episodes (separated by 5 minutes) in 24 hours

3) Headache[11]

- Grade 1
  Mild pain
- Grade 2
  Moderate pain; limits instrumental activities of daily living (ADL)
- Grade 3
  Severe pain; limits self care ADL

4) Consciousness disturbed[12]

- I = Awakens in the absence of a stimulus
  - 1. Not fully conscious
  - 2. Disoriented
  - 3. Not able to say one's own name or birth date
- II = Awakens in the presence of a stimulus
  - 10. Opens eyes easily when addressed with a regular speaking voice.

  - 20. Opens eyes when addressed with a loud voice or continuously shaken.
  - 30. Opens eyes slightly when repeatedly addressed, while giving a pain stimulus.
- III = Does not awaken in the presence of a stimulus
  - 100. Motions as if brushing away a pain stimulus
  - 200. Moves a limb slightly or winces at a pain stimulus
  - 300. Displays no response to a pain stimulus

5) Malaise[11]

- Grade 1

  Uneasiness or lack of well being

- Grade 2

  Uneasiness or lack of well being; limits instrumental ADL

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

See Section 5.

3.7.3.2 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be collected, and the time and date of blood sampling, and the date of urine collection will be recorded in the source document. The samples will be sent to the specified central laboratory for central measurements. The central laboratory will measure the laboratory test parameters presented in Table 3.7.3.2-1 according to the procedures specified by the laboratory, and provide the results of the measurements to the sponsor and the investigator or subinvestigator. The investigator or subinvestigator will document blood or urine samplings, as well as the dates and times for blood samples and the dates for urine samples in the CRF. The electronic file submitted to the sponsor by the central laboratory will be regarded as the source document; therefore, recording of the results in the CRF is unnecessary.

Unscheduled clinical laboratory tests, if required at the occurrence of AEs or for the follow-up of AEs, should be performed centrally at the specified central laboratory, except in emergencies, in which case clinical laboratory tests may be performed at each trial site.

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology Red blood cell count Hemoglobin Hematocrit Leucocyte count Differential leukocyte count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) Platelet count PT (seconds, INR)[a] Urinalysis Qualitative urinalysis pH Protein Glucose Occult blood Ketone bodies Bilirubin Urobilinogen	Serum Chemistry Alkaline phosphatase γ-GTP[b] Lactic dehydrogenase CK (CPK)[c] Total protein Albumin Random glucose Total cholesterol Triglycerides Urea nitrogen Creatinine Uric acid Serum electrolytes (Na, K, Cl) Transferrin Serum cortisol[d] Liver function tests AST (GOT) ALT (GPT) Serum total bilirubin Additional tests Serum hCG pregnancy test for female subjects of childbearing potential

[a] PT: Prothrombin time
[b] γ-GTP: gamma glutamyl transpeptidase
[c] CK (CPK): Creatine kinase (creatine phosphokinase)
[d] Serum cortisol: measured only at the screening examination

The total volume of blood collected throughout the trial from a subject treated with the IMP for 30 days is at least approximately 175 mL (for hematology, serum chemistry [including central measurements of serum sodium concentration], and measurements of serum osmolality, plasma AVP concentration, and plasma drug concentration). In addition, the following blood samplings may be added.

- Blood samplings for central measurements of serum sodium concentration for the efficacy evaluation
- Blood samplings for measurements of serum sodium concentration at the trial site (see Section 3.7.2.1)
- Blood sampling for pregnancy tests (only in female subjects of childbearing potential)

If the subject is a woman of childbearing potential, a pregnancy test should be performed at the screening examination and the result must be obtained before start of IMP administration.

3.7.3.3 Body Weight

Body weight will be measured using a scale with appropriate maintenance with a minimum division of 0.1 kg, while minimizing the influence of clothing. The date, time, and result (expressed in 0.1 kg intervals) of the measurement will be recorded in the source document and CRF. The result should be rounded to 1 decimal place.

When body weight is measured during an outpatient visit, the influence of clothing should be minimized.

3.7.3.4 Vital Signs

3.7.3.4.1 Body Temperature

Axillary temperature will be measured using an appropriately maintained thermometer, and the completion status (with or without measurement), date, time, and result of the measurement will be recorded in the source document and CRF. The result should be rounded to 1 decimal place.

3.7.3.4.2 Blood Pressure and Pulse Rate

Blood pressure (systolic and diastolic) and pulse rate will be measured after the subject has been sitting for at least 3 minutes, using appropriately inspected instruments. The status (measured/not measured), date, time, and results of the measurements will be recorded in the source document and CRF.

3.7.3.5 12-Lead Electrocardiography

A resting 12-lead electrocardiogram will be recorded using an appropriately inspected electrocardiograph, according to the procedures specified by the trial site. The status (measured/not measured) and date of the recording, along with the heart rate, PR interval, QRS axis, and QT interval, as well as the interpretation (normal or abnormal [detailed findings, if abnormal]) of the investigator or subinvestigator will be recorded in the source document and CRF.

3.7.3.6 Pregnancy Test

1) Subjects requiring a pregnancy test

Female subjects of childbearing potential at the time of the pregnancy test

The following female subjects are considered to be women of nonchildbearing potential, and do not need to undergo pregnancy test.

- Women who have undergone a hysterectomy or bilateral ovariectomy

2) Methods

A blood sample for a serum hCG pregnancy test will be collected from a female subject of childbearing potential. The sample will be sent to the specified central laboratory for central measurement. The central laboratory will perform the test according to the procedures specified by the laboratory, and report the result to the sponsor and the investigator or subinvestigator. The investigator or subinvestigator will record the date and time of blood sampling, and the interpretation of the investigator or subinvestigator (pregnancy suspected/not suspected) in the source document. The investigator or subinvestigator will record the status (with or without blood sampling), date, and time of blood sampling, and the interpretation of the investigator or subinvestigator in the CRF. The electronic file submitted to the sponsor by the central laboratory will be regarded as the source document; therefore, recording of the result in the CRF is unnecessary. If the investigator or subinvestigator suspects pregnancy, administration of the IMP to the subject should be discontinued as 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

On Day 21 of treatment period and the day after the final IMP administration, and at discontinuation of treatment, a blood sample will be collected using a heparin sodium-containing test tube.

All of the blood samples will be sent to and analyzed at the bioanalytical laboratory. For detailed procedures regarding handling and shipment of the blood samples, see Appendix 2.

3.7.4.2 Pharmacodynamic Assessments

3.7.4.2.1 Daily Urine Volume

During the pretreatment observation period, daily urine volume will be measured for the time interval starting at immediately after complete urination after breakfast and ending at complete urination immediately before the IMP administration on the following day. After the initial IMP administration on Day 1 of treatment period through determination of the maintenance dose, daily urine volume will be determined for each time interval from the point after complete urination immediately before the IMP administration of the day to the point after complete urination immediately before the IMP administration on the following day.

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

3.7.4.2.2 Daily Fluid Intake

Daily fluid intake (juice, milk, tea, water, transfusion, etc.) will be determined for the same intervals as the measurement of daily urine volume. During the pretreatment observation period, daily fluid intake will be determined for the time interval starting at immediately after complete urination after breakfast and ending at complete urination immediately before the IMP administration on the following day. After the initial IMP administration on Day 1 of treatment period through the determination of maintenance dose, daily fluid intake will be determined for each time interval from the point after complete urination immediately before the IMP administration of the day to the point after complete urination immediately before the IMP administration on the following day.

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

3.7.4.2.3 Daily Fluid Balance

Daily fluid balance will be calculated by deducting “daily urine volume” from “daily fluid intake.” The daily fluid balance will be calculated by the sponsor; therefore, entry of daily fluid balance in the CRF is unnecessary.

3.7.4.2.4 Serum Osmolality

A blood sample will be collected for the measurement of serum osmolality, and the date and time of blood sampling will be recorded in the source document. Serum osmolality will be measured centrally by the central laboratory according to the procedures specified by the laboratory. The central laboratory will report the result of the measurement to the sponsor and the investigator or subinvestigator. The investigator or subinvestigator will document blood sampling, as well as the date and time of sampling in the CRF. The electronic file submitted to the sponsor by the central laboratory will be regarded as the source document; therefore, entry of the result in the CRF is unnecessary.

3.7.4.2.5 Urine Osmolality

1) Urine sample processing (screening period)

A urine sample will be collected for the measurement of urine osmolality and stored in a refrigerator. The status (urine sample collected/not collected) and date of urine collection will be recorded in the source document and CRF.

2) Urine sample processing (pretreatment observation period and treatment period)

An approximately 5 mL aliquot of cumulative urine sample will be taken in a sample stock tube and stored in a refrigerator. The date of urine collection will be recorded in the source document. Before taking the aliquot, the cumulative urine volume will be measured.

3) Measurement of urine osmolality

The urine samples will be sent to the specified central laboratory where urine osmolality is measured centrally according to the procedures specified by the laboratory. The central laboratory will report the measurement results to the sponsor and the investigator or subinvestigator. The electronic file submitted to the sponsor by the central laboratory will be regarded as the source document; therefore, entry of the result in the CRF is unnecessary.

3.7.4.2.6 Daily Urinary Sodium Excretion

1) Urine sample processing (screening period)

A urine sample will be collected for the measurement of urine sodium concentration and stored in a refrigerator. The date of urine collection will be recorded in the source document.

2) Urine sample processing (pretreatment observation period and treatment period)

An approximately 5 mL aliquot of cumulative urine sample will be taken in a sample stock tube and stored in a refrigerator. The date of urine collection will be recorded in the source document. Before taking the aliquot, the cumulative urine volume will be measured.

3) Measurement of urine sodium concentration

The urine samples will be sent to the specified central laboratory where urine sodium concentration is measured centrally according to the procedures specified by the laboratory. The central laboratory will report the measurement results to the sponsor and the investigator or subinvestigator. The electronic file submitted to the sponsor by the central laboratory will be regarded as the source document; therefore, entry of the result in the CRF is unnecessary.

4) Calculation of urinary sodium excretion

Daily urinary sodium excretion will be calculated by multiplying the urinary sodium concentration by the daily urine volume. Daily urinary sodium excretion will be calculated by the sponsor; therefore, entry of the daily urinary sodium excretion in the CRF is unnecessary.

3.7.4.2.7 Plasma Arginine Vasopressin Concentration

A blood sample will be collected for the measurement of plasma AVP concentration, and the date of blood sampling will be recorded in the source document. The sample will be sent to the specified central laboratory for central measurement. The central laboratory will measure the plasma AVP concentration according to the procedures specified by the laboratory, and report the result to the sponsor and the investigator or subinvestigator. The investigator or subinvestigator will record the status (blood sample collected or not collected), date, and time of blood sampling in the CRF. The electronic file submitted to the sponsor by the central laboratory will be regarded as the source document; therefore, entry of the result in the CRF is unnecessary.

If the plasma AVP concentration was measured as part of routine medical practice at the trial site prior to a subject's participation in the trial, and that result was used for the subject's eligibility assessment, the date of the blood sampling and the results will be recorded in the source document and CRF.

3.7.5 End of the Trial

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

3.8 Discontinuation 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 Trial Sites

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 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

In the cases listed below, treatment with the IMP should be discontinued and the examination at withdrawal specified in Section 3.7.1 should be performed. In such cases, the investigator or subinvestigator will find out the situation in detail, and record the date and reason for discontinuation in the source document and CRF.

1) 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 infeasible due to the occurrence of AEs.
4) Laboratory test results (AST [GOT] or ALT [GPT]) were ≥3 times the upper limit of normal (ULN) at the trial site or the specified central laboratory.
5) Serum sodium concentration increased by ≥12 mEq/L from predose, within 24 hours after IMP administration.
6) Serum sodium concentration exceeding 145 mEq/L is observed during the treatment period.
7) The subject becomes poorly compliant with treatment without taking the IMP for ≥7 consecutive days.
8) Pregnancy is suspected or confirmed.
9) The investigator or subinvestigator judges that withdrawal is necessary for any other reason.

Administration of the IMP to the subject may be discontinued after the start of treatment for a variety of reasons. Treatment may be discontinued due to an unsatisfactory effect of the IMP (at the subject's request), due to the occurrence of an AE, because the use of prohibited concomitant medications or therapies has become necessary, or because the investigator or subinvestigator has concluded discontinuation of treatment to be medically necessary for other reasons. In any case, the option to continue treatment with the IMP should be offered to the subject, whenever possible, as described in Section 3.8.3.4.

3.8.3.2 Documenting Reasons for Treatment Discontinuation

Subjects may discontinue treatment for the reasons listed below.

- Reasons related to AEs:
  - Subject decides to discontinue due to annoyance or discomfort resulting from a nonserious AE that is not otherwise determined to be an undue hazard
  - Continuing treatment with the IMP places the subject at an undue risk as determined by the investigator or subinvestigator

  - A serious adverse event (SAE)
  - Laboratory test results (AST [GOT] or ALT [GPT]) becomes ≥3 times the ULN at the trial site or the specified central laboratory.
  - Serum sodium concentration increased by ≥12 mEq/L from predose, within 24 hours after IMP administration.
  - Serum sodium concentration exceeds 145 mEq/L during the treatment period.
  - Other safety concerns or AEs that may possibly be related to the IMP
- Death
- Loss to follow-up of the subject
- Poor treatment compliance
- Pregnancy (see Section 5.5)
- Major protocol deviations
- Withdrawal of informed consent (complete written withdrawal of consent form)
- Premature termination of all or part of the trial by the sponsor
- Other reasons unrelated to medical condition
  (including cases in which the subject has been found, after the start of treatment to deviate from any of the inclusion criteria or meet any of the exclusion criteria)

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 subjects have the right to withdraw their consent from further participation in the trial at any time and without prejudice. 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 subject provides their written withdrawal of consent or there is other written documentation by the investigator or subinvestigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow up (these methods of follow up will also be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether at the trial 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 subject and staff)

- Contact of the subject by trial personnel, even if only by telephone, to assess the subject's 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, spouse, partner, legal representative, friend, neighbor, or physician)
- Access to medical information from alternative sources (eg, hospital/clinic medical records, the referring doctor's notes, public records, dialysis, transplantation or vital registries, or 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 used in initially obtaining informed consent. The reasons for a subject'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 subject may initially express a 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 subject 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 subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate 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 and discuss with the subject at the trial site or by telephone the option of continuing participation 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 Failure

A screen failure is defined as a subject who consented to participate in the trial and signed informed consent, but received no dose of the IMP.

A subject who signed an informed consent but received no dose of the IMP may be rescreened according to Section 3.4.3.

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

- Day of investigation
- Date the subject was determined to be a screen failure
- Date the subject provided informed consent
- Birth date
- Gender
- Race
- Ethnicity
- Compliance with the inclusion criteria (Record the number of the criterion the subject did not meet, if any)
- Deviation from the exclusion criteria (Record the number of the criterion the subject met, if any)
- Reasons for screen failure

3.10 Definition of Completed Subjects

A trial completer is defined as a subject who received at least 1 dose of the IMP and underwent the examination on the day after the final IMP administration.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Day 30 during the treatment period, who does not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom survival status at the end of the trial 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 of death (ie, death certificate, medical records, public records, or a 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, a 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. Further, in the event the investigator, subinvestigator, or designee is unable to reach the subject by telephone, they 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 items listed below for a subject who is lost to follow-up in the source document and CRF.

- Day of investigation
- Investigation methods
- Contact with the subject (successful/unsuccessful)
- Reason why the subject does not (cannot) visit
- Confirmation of treatment compliance
- Presence or absence of an AE (if present, specify the name, dates of onset and disappearance, severity, and causal relationship with the IMP, of the event)
- Action taken with the IMP, and treatment for and outcome of the event
- If an investigation is impossible, specify the reason.

3.12 Subject Compliance

The subject will be placed under the management of the investigator or subinvestigator during the trial. The investigator or subinvestigator will instruct the subject to adhere to the following.

- The subject should take the IMP according to the specified dosage regimen.
- The subject should adhere to the specified schedule during the trial.
- The subject should not use the prohibited concomitant medications (see Section 4.1).
- The subject should adhere to the specified fluid intake restriction (see Section 4.2).
- The subject should not divulge information obtained as a result of participation in the trial 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 from the sponsor, and 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 the subjects. In such cases, the investigator or subinvestigator should promptly submit a document stating the details of and reasons for the deviation or change to the sponsor and the head of the trial site, and obtain the approval of the IRB. In addition, the investigator or subinvestigator should receive approval from the head of the trial site, and obtain the written agreement of 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, a violation of the informed consent process, IMP dispensing

or dosing error, treatment assignment error, subject enrollment in violation of the 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 sponsor will come as quickly as possible to a joint decision regarding the subject's continued participation in the trial. This decision will be documented by the investigator or subinvestigator and the sponsor, and reviewed by the site monitor.

2) Record of deviations

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

In addition, the investigator or subinvestigator will record certain specified protocol deviations in the CRF, according to the written procedures for preparation of the CRF supplied by the sponsor.

3.14 Investigation of Treatment Compliance

The investigator or subinvestigator will ask the subject if the IMP was taken as specified, and record the date of dosing (as well as the time during hospitalization) and daily dose taken in the source document and CRF.

4 Restrictions

4.1 Prohibited Concomitant Medications

If any medication other than the IMP was used from the day informed consent was obtained to the day the trial was completed, the name, indication, dosage regimen, daily dose, administration route, and dates the medication started and ended will be recorded in the source document and CRF. For therapies other than medications, the name, indication, and dates the therapy started and ended will be recorded in the source document and CRF.

From the pretreatment observation period (the day before start of IMP administration) to the completion of the final IMP treatment, the concomitant use of the drugs listed in Table 4.1-1 and Table 4.1-2 is prohibited. The use of hypertonic saline to correct serum sodium concentration is prohibited from the time informed consent is obtained until the completion of IMP administration, except in cases of absolute necessity (eg, treatment for AEs).

Table 4.1-1 List of Medications Prohibited During the Trial

- Demeclocycline
- Lithium carbonate
- Urea
- The following drugs used to correct serum sodium concentration:
  - Intravenous saline
  - Hypertonic saline
- Drugs and foods that may be a strong inhibitor or inducer of CYP3A4 (see Table 4.1-2)
- Drug products containing tolvaptan other than the IMP, mozavaptan hydrochloride
- Drugs unapproved in Japan

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

Drug class	Drugs
1) CYP3A4 inhibitors (excluding external use agents)	
Antimicrobials	Clarithromycin, erythromycin, fluconazole, itraconazole, miconazole, norfloxacin, chloramphenicol, voriconazole, telithromycin, ciprofloxacin, fosfluconazole
Ca antagonists	Diltiazem, verapamil
Antidiabetic	Glibenclamide
Immunosuppressant	Cyclosporine
Anticancer agents	Imatinib, crizotinib
Anti-H_{IV}[a] drugs	Indinavir, nelfinavir, ritonavir, saquinavir, delavirdine, atazanavir, fosamprenavir, lopinavir, darunavir, telaprevir, cobicistat
Autonomic drug	Tofisopam
Adenosine A2A receptor antagonist	Istradefylline
Antimetic	Aprepitant
Drug for a pituitary ACT_H[b] secretion test	Metyrapone
2) CYP3A4 inducers (excluding external use agents)	
Barbiturates	Phenobarbital, amobarbital, pentobarbital, barbital, secobarbital
Antiepileptics	Carbamazepine, phenytoin
Antitubercular agents	Rifampicin, rifabutin
Psychostimulant	Modafinil
Anti-HIV drugs	Efavirenz, nevirapine, etravirine
Endothelin receptor antagonist	Bosentan
3) Foods containing substances that inhibit CYP3A4	Grapefruit, Seville orange, star fruit, and their processed products
4) Foods containing substances that induce CYP3A4	St. John's Wort-containing foods

[a] Human immunodeficiency virus

[b] Adrenocorticotropic hormone

4.2 Fluid Intake Restriction

1) From the acquisition of informed consent to the end of the pretreatment observation period (the day before start of IMP administration)

Fluid intake will be restricted to a daily fluid intake of ≤20 mL/kg.

2) Within 24 hours after the IMP administration on Day 1 of treatment period

Fluid intake must not be restricted.

3) From the IMP administration on Day 2 of treatment period to the day after the final IMP administration

Setting the fluid intake volume from immediately before IMP administration on Day 1 of treatment period to immediately before IMP administration on Day 2 of treatment period as the upper limit of daily fluid intake, subjects will be instructed to restrict fluid intake. Fluid intake is the total volume of beverages (eg, juice, milk, tea), water, and transfusions, not including solid food-derived fluids.

The investigator or subinvestigator should pay attention to an excessive increase in urine volume or rapid increase in serum sodium concentration. If thirst or dehydration, and other unfavorable symptoms develop, the investigator or subinvestigator should instruct the subject to take more fluids, regardless of the upper limit of daily fluid intake to ensure the safety of the subject.

The investigator or subinvestigator will ask the subject whether he/she has complied with the fluid intake restriction, and record the period of assessment (dates of start and completion) and the result in the source document and CRF.

4) From the completion of the examination on the day after the final IMP administration to the completion of the follow-up examination

Fluid intake will be restricted to a daily fluid intake of ≤20 mL/kg.

5 Reporting of Adverse Events

5.1 Definition

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered an IMP 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 pre-planned 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
- Requires inpatient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical 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. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or 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 (DILI) (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 be documented on the "Adverse event" section of the CRF only if there is an abnormality or complication.

Changes in clinical laboratory tests: It is the investigator or subinvestigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator 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 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 (the 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 on the CRF. The intensity of an adverse experience 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 regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject from the time of the acquisition of informed consent to the completion of the trial must be recorded in the source document and CRF provided by the sponsor.

Medical terminology should be used for 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, not 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 will be recorded as a new AE in the CRF.

In addition, the sponsor must be notified immediately by e-mail, as a rule, of any IREs, according to the procedure outlined in Section 5.3 Immediately Reportable Events. Special attention should be paid to recording hospitalization and concomitant medications.

In the CRF, the following items should be recorded according to the written procedures for preparation of the CRF provided by the sponsor.

- Name of the event
- Dates of onset (as well as time, if possible, during hospitalization) and recovery/resolution
- Severity
- Seriousness (if serious, specify the details)
- Causal relationship with the IMP
- 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, as a rule, to the sponsor using the contact information on the cover page of this protocol.

An immediately reportable event:

- Any SAE.
- Any AE related to occupational exposure.
- Potential drug-induced liver injury (DILI) (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 be documented in the "Adverse event" section of the CRF only if there is an abnormality or complication.

In addition, the IRE form should be filled out and sent to the sponsor by e-mail, as a rule. It should be noted that the IRE form is not the "Adverse event" section of the CRF.

A subject experiencing an SAE should be followed until the event has been resolved or clinically stabilized, or until the subject is lost to follow-up. When the subject's health condition returns to baseline status, the event is considered to have been resolved. When no further improvement or deterioration of the subject's health condition is expected, in the opinion of the investigator or subinvestigator, the event is considered to have

stabilized. The investigator or subinvestigator will provide appropriate treatment for the subject and convey prompt updates on the subject's status to the sponsor.

5.4 Potential Drug-Induced Liver Injury

The total bilirubin level should also be evaluated for any subject who experiences an elevation in AST or ALT that is ≥3 times the ULN. If the subject's total bilirubin is ≥2 times the ULN, the investigator or subinvestigator should record all of the laboratory values in an IRE form, and promptly send it to the sponsor according to the procedures specified in Section 5.3.

5.5 Pregnancy

Women of child-bearing potential are defined as female subjects for whom menstruation has started and who have not been documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy).

For both women of child-bearing potential and men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures to prevent pregnancy during the course of the trial and for 30 days after the l final IMP administration. Unless the subject is sterile (ie, women who received a bilateral oophorectomy and/or hysterectomy, or men who have had a bilateral orchidectomy) or remains abstinent, at least one of the following contraceptive measures must be used: a vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, or condom with spermicide.

Before enrolling a woman of childbearing potential in this clinical trial, the investigator or subinvestigator must review the guidelines regarding trial participation for women of childbearing potential. The topics should generally include:

- General information
- Informed consent form
- Information on contraception
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before enrollment in the trial, a woman of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy, and must sign an ICF stating that the above mentioned risk factors and the consequences were discussed with her.

A serum hCG pregnancy test will be performed at the time of screening on all female subjects of childbearing potential. If the investigator or subinvestigator suspects pregnancy based on the test result, the subject should be excluded from the trial according to Section 3.4.3, without administering the IMP to the subject.

During the trial, all female subjects of childbearing potential should be instructed to contact the investigator or subinvestigator immediately if they suspect that they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy test 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, treatment with the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for 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 exposure to the IMP during the trial and for at least 30 days after the final dose of the IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the 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 studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator or subinvestigator must report to the sponsor, on the 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

In this trial, information on AEs will be collected until the follow-up examination, performed 7 to 10 days after the final IMP administration (hereinafter, referred to as the "trial completion day").

If any of Section 5.7.1, Section 5.7.2, or Section 5.7.3 are met, the AEs will be followed up as specified, after the trial completion day.

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded in the Adverse Event section of the CRF. A subject who has any AE or has not recovered from any AE at the trial completion day will be followed up at least every 4 weeks, until the AE has resolved or clinically stabilized, or until the subject is lost to follow-up. All nonserious events that are persistent on the trial completion day will be recorded as ongoing in the CRF. For any AE that has been identified throughout the trial, during the analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation). Follow-up information collected after the trial completion day will be recorded in the medical record.

5.7.2 Follow-up of Serious Adverse Events

This trial requires that subjects be actively monitored for SAEs up to the trial completion day. A subject who has any AE or has not recovered from any AE at the trial completion day will be followed up at least every 4 weeks, until the AE has resolved or clinically stabilized, or until the subject is lost to follow-up.

An SAE that is identified or is persistent on the trial completion day should be recorded in the Adverse Event section of the CRF and reported to the sponsor, according to the procedures specified in Section 5.3. All SAEs that are persistent on the trial completion day will be recorded as ongoing in the CRF. The SAEs to be reported are those that have been previously reported but have not yet resolved, and those that are newly identified. The investigator or subinvestigator should follow up these SAEs until the events have resolved or clinically stabilized, or until the subjects are lost to follow-up, and report important update information to the sponsor through the IRE form.

5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring After the Trial Completion Day

Any new SAE that is reported to the investigator or subinvestigator by a subject, which occurs after the trial completion day and is determined by the investigator or subinvestigator to be related to the IMP, should be reported to the sponsor. The investigator or subinvestigator should follow up all SAEs identified after the trial completion day until the events have resolved or clinically stabilized, or until the subjects are lost to follow-up, and report important update information to the sponsor through an IRE form.

6 Pharmacokinetic/Pharmacodynamic Analysis

6.1 Pharmacokinetic Analysis

In the pharmacokinetic analysis set (see Section 7.2.4), the plasma concentrations of tolvaptan and its metabolites, DM-4103 and DM-4107, on Day 21, at discontinuation of treatment, and on the day after the final IMP administration will be adjusted for the dose administered immediately before each timepoint to calculate descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) by timepoint and by compound.

6.2 Pharmacodynamic Analysis

In the pharmacodynamic analysis set (see Section 7.2.5), descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) for the following parameters will be calculated by timepoint.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Serum osmolality
- Urine osmolality
- Daily urinary sodium excretion
- Plasma AVP concentration

7 Statistical Analysis

7.1 Sample Size

The target sample size was determined with respect to the percentage of subjects with a normalized serum sodium concentration (≥135 mEq/L) at the final administration of tolvaptan.

Sample size determination was based on the results from patients with SIADH as the underlying disease of hyponatremia (“the SIADH subpopulation”) in the efficacy analysis sets of 2 overseas phase 3, placebo-controlled, randomized, double-blind trials in patients with hyponatremia due to SIADH and other causes (Trials 156-02-235 and 156-03-238, with an optional up-titration of 15, 30, and 60 mg for 30 days). To determine the sample size of this trial, a threshold percentage was set based on the results of the placebo group in the SIADH subpopulation of the overseas trials. Considering the distribution of the

point estimates which are calculated based on multiple sample sizes, in the percentage of subjects with a normalized serum sodium concentration after the final IMP administration in the tolvaptan group, a sample size for which the probability of obtaining a point estimate exceeding the threshold percentage was kept at ≥80% was sought. In addition, since this trial intends to evaluate the efficacy and safety of tolvaptan in patients with SIADH due to a variety of etiologies, and to investigate the appropriateness of the dose-titration approach adopted as the dosage regimen, the various etiologies of SIADH and the expected number of subjects at each maintenance dose level were also taken into consideration in determination of the sample size.

In the SIADH subpopulation of the 2 overseas phase 3 trials, the percentage of subjects with a normalized serum sodium concentration (Day 30, Last Observation Carried Forward) was 64.6% (31 of 48 subjects) in the tolvaptan group and 30.2% (16 of 53 subjects) in the placebo group. Therefore, the threshold percentage was set at 44.3% (the upper limit of the exact 95% CI for the percentage of normalized subjects in the placebo group). When a binomial distribution with a parameter of 64.6% (the point estimate of the percentage of normalized subjects in the tolvaptan group) is assumed, the probability that the expected point estimate of the percentage of normalized subjects will exceed the threshold percentage is kept at ≥80% with a sample size of ≥8 subjects.

The underlying diseases of SIADH are diverse, and it is difficult to evaluate the efficacy of tolvaptan for each of all SIADH etiologies. Therefore, patients with SIADH will be divided into those with SIADH due to ectopic vasopressin producing tumors and those due to other etiologies to evaluate the efficacy of tolvaptan. Since the prevalence of these 2 categories of patients is presumed to be nearly equivalent, a sample size of 16 subjects (8 subjects x 2) for the entire trial would enable an efficacy evaluation by SIADH etiology.

In this trial, the following 4 maintenance dose levels have been established: 7.5, 15, 30, and 60 mg/day. A sample size for which the probability of obtaining at least 1 subject for each maintenance dose level is kept at ≥80% was calculated by applying the multinomial distribution. Since the proportion of subjects with each maintenance dose level in the trial is unpredictable, the subjects are assumed to be equally distributed to the 4 maintenance dose levels. By applying a polynomial distribution with a common parameter of 25% across the 4 maintenance dose levels, the sample size required to obtain at least 1 subject at each maintenance dose level with a ≥80% probability was 11 subjects.

Based on the above results, the target sample size has been set as 16 subjects.

7.2 Datasets for Analysis

7.2.1 Efficacy Analysis Set

The efficacy analysis set consists of all subjects who received at least 1 dose of the IMP and have postdose serum sodium concentration data.

7.2.2 Maintenance Dose-setting Set

Of the efficacy analysis set, the subpopulation comprised of the subjects for whom maintenance doses of the IMP were determined is defined as the maintenance dose-setting set.

7.2.3 Safety Analysis Set

The safety analysis set consists of all subjects who received at least 1 dose of the IMP.

7.2.4 Pharmacokinetic Analysis Set

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

7.2.5 Pharmacodynamic Analysis Set

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

7.3 Handling of Missing Data

Missing data on the day after the final IMP administration will be imputed using the last available data obtained by the day after the final administration.

7.4 Primary and Secondary Endpoint Analyses

The following analyses will be performed in the efficacy analysis set.

To evaluate the efficacy of tolvaptan in patients who achieved an appropriate maintenance dose, the same analyses will also be performed in the maintenance dose-setting set.

In addition, subgroup analyses by SIADH etiology (subjects with SIADH due to ectopic antidiuretic hormone-producing tumors/those due to other etiologies) and by serum sodium concentration (<130 mEq/L, ≥130 mEq/L) at predose on Day 1 of the treatment period will be performed.

A similar analysis will also be conducted by the dose administered at determination of the maintenance dose (7.5, 15, 30, and 60 mg).

In the subgroup analyses and the analysis by dose administered at determination of the maintenance dose, data obtained at fixing of maintenance dose and the day after the final IMP administration will be analyzed.

In patients receiving readministration with the IMP, similar analyses using the data immediately before treatment was resumed as baseline data will be performed, as well as a comparison of efficacy between initial treatment and readministration to demonstrate the absence of significant differences (For details, see "Statistical Analysis Plan"). Data collected during readministration will not be included in analyses of data collected during initial treatment.

The day of fixing maintenance dose is the day on which the initial maintenance dose was determined (Similarly, the day of fixing the maintenance dose for readministration is the day on which the initial maintenance dose was determined after the start of readministration).

Serum sodium concentrations that were measured centrally will be used in these analyses.

Efficacy will be comprehensively evaluated based on the following analysis and on individual subject data.

7.4.1 Primary Endpoint Analysis

The primary endpoint is the percentage of subjects with normalized serum sodium concentration the day after the final IMP administration.

The percentage of subjects with normalized serum concentration, defined as ≥135 mEq/L, on the day after final IMP administration will be calculated versus the number of subjects with serum sodium concentration of <135 mEq/L at baseline (predose on Day 1 of the treatment period).

The number, percentage, and 95% CI of subjects with normalized serum sodium concentration on the day of fixing the maintenance dose and on the day after final IMP administration will be calculated. The number and percentage of subjects will also be calculated for each timepoint after start of IMP administration.

7.4.2 Secondary Endpoint Analyses

7.4.2.1 Change in Serum Sodium Concentration

The number of subjects and the mean, standard deviation, minimum, median, and maximum values and 95% CI for measured values for serum sodium concentration and the change from baseline (predose on Day 1 of the treatment period) on the day of fixing the maintenance dose and on the day after final IMP administration will be calculated.

Descriptive statistics at each timepoint after start of IMP administration will also be calculated.

7.4.2.2 Time Course of Serum Sodium Concentration

The individual time courses of measured values and changes from baseline for serum sodium concentration will be plotted.

7.4.2.3 Changes in Clinical Symptoms Associated With Hyponatremia

Shift tables of the changes in clinical symptom gradings from baseline (pretreatment observation) to the day of fixing the maintenance dose and from baseline to the day after final IMP administration will be generated. Shift tables of the changes at each postdose timepoint will be generated in the same way.

7.5 Analyses of Demographic and Baseline Characteristics

In the safety analysis set, the frequency distribution and descriptive statistics will be determined for the following subject characteristics.

- Age
- Gender
- Height
- Race
- Ethnicity
- Complications
- Medical history
- Etiology of SIADH
- Duration of SIADH

(Number of days from the latest date on which SIADH was diagnosed [or the date treatment of hyponatremia was judged to be needed] to the date of acquisition of informed consent)

7.6 Safety Analysis

7.6.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidences of the following events will be summarized by treatment group:

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs with an outcome of death

- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

TEAEs related to the IMP will be summarized, in the same manner as TEAEs.

In addition to summarization of the data collected over the entire period of the trial, AE data will be summarized by time period (during the treatment period, from the day of the initial IMP administration to the day after the maintenance dose is determined, from 2 days after the maintenance dose is determined to the day after the final IMP administration, and from 2 days after the final IMP administration to the follow-up examination).

7.6.2 Clinical Laboratory Tests

For clinical laboratory tests other than the qualitative urinalysis, descriptive statistics of measured values and changes from baseline (predose on Day 1 of the treatment period) will be calculated at each timepoint. For the qualitative urinalysis parameter, shift tables at each timepoint, compared to baseline, will be prepared. For laboratory test parameters other than qualitative urinalysis, shift tables of subjects with values below, within, or above the normal range at each timepoint, compared to baseline, will be prepared.

7.6.3 Body Weight and Vital Signs

For body weight and vital signs, descriptive statistics of measured values and changes from baseline (predose on Day 1 of the treatment period) will be calculated at each timepoint.

7.6.4 12-Lead Electrocardiography

For 12-lead electrocardiographic parameters, the descriptive statistics of measured values and changes from baseline (pretreatment observation) will be calculated at each timepoint.

The numbers and percentages of subjects who have a QTc interval of >450, >480, or >500 ms at any timepoint from baseline through the day after the final IMP administration will be calculated. In addition, the numbers and percentages of subjects who have a change in QTc interval from baseline of >30 and >60 ms at any timepoint from start of IMP administration through the day after the final IMP administration will be calculated. Shift tables for QTc interval interpretation (normal or abnormal) will be prepared from baseline through the day after the final IMP administration.

7.6.5 Liver Function Tests

The numbers and percentages of subjects who have a serum total bilirubin value of ≥2 times the ULN, or an AST or ALT value of ≥3 times the ULN, at any timepoint after start of IMP administration will be calculated.

8 Management of Investigational Medicinal Products

For full details on IMP management, see the tolvaptan investigator's brochure and clinical operation manual.

8.1 Packaging and Labeling

The IMP will be provided to the IMP manager by the sponsor or designated agent. The IMP will be supplied as package boxes. Each package box used in the treatment period will be labeled to clearly state "For clinical trial use only" as well as the protocol number, IMP name, quantity, Lot No., expiration date, storage conditions, subject ID, 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 may not provide the IMP to any patient who is not participating in this trial.

The IMP will be stored at room temperature.

The trial site staff will measure and record a temperature in the IMP storage area at least once each workday and maintain a temperature log.

8.3 Accountability

The IMP manager must maintain an inventory record of IMP received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused IMP and 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 the outermost shipping container. Returned IMP should be in the original package boxes. The assigned trial monitor will facilitate the return of unused IMP and 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 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, or missing product)
- Blister defects (eg, missing, empty blisters)
- 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 means 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 notify the sponsor by e-mail within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- PQC_156-14-003@otsuka.jp

The information specified in Section 8.5.2 will be sent to the above e-mail address.

Identification of a PQC by the subject should be reported to the investigator or subinvestigator, who should then report it to the sponsor according to the above-mentioned procedure.

8.5.2 Information Required for Reporting Purposes

- Description of the compliant
- Reporter identification (eg, subject, investigator or subinvestigator, trial site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)

- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process

During the report of the PQC, indicate whether the sample involved in the complaint is available for return. If the complaint sample is available for return, return it to the sponsor.

Forwarding of the complaint sample to the sponsor for investigation must be documented in the site accountability record.

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 will include but are not limited to medical records, electronic data, screening logs, and recorded data from automated instruments. Original source documents of the results of plasma drug concentration measurements will be retained by the bioanalytical laboratory. The sponsor will retain copies of all electronic file submitted by the bioanalytical laboratory.

All source documents pertaining to this trial will be maintained by the trial sites and made available for direct inspection by authorized persons. The investigators/trial sites will permit trial-related monitoring, audits, IRB reviews, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality 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 and findings. At minimum, the medical record will contain:

- Documentation of the informed consent process, including any revised consents;

- Documentation of the investigator or subinvestigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of IMP administration commencement;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any significant medical findings. The severity, frequency, duration, action taken, and outcome of any AEs, and the investigator or subinvestigator's assessment of causal relationship with the IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- Medical activities provided; and,
- The signature (or initials) and date of each investigator or subinvestigator who made an entry in the medical record (When using an electronic trial data system, a full audit trail should 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 or other source documents will be initialed and dated on the day the change is made by a trial site staff member who is 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, the investigator or subinvestigator will write a brief explanation for the change in the source documents. If an electronic trial data system is used, a full audit trail should be maintained.

The information recorded on the medical record or other source documents should be directly entered in the sponsor's electronic data capture system by the authorized trial site staff member. Changes to the data will be captured by an automatic audit trail.

Results of clinical laboratory tests, urine osmolality, serum osmolality, urine sodium excretion, serum sodium concentration, and drug concentration measured by the central laboratory or bioanalytical laboratory will be directly transferred to the sponsor or contract research organization. Data that the sponsor will collect shall include:

- Case report forms (data collected after the acquisition of informed consent)
- Results of laboratory tests, urine osmolality, serum osmolality, etc.
- Result table of the drug concentration (copy)

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: Consolidated Guideline (E6) and as required by

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

9.4 Records Retention at the Trial Site

The trial site should maintain all documents and records pertaining to the trial for the longer of the following 2 periods: In cases where the sponsor requires maintenance for a longer period, the trial site will discuss the storage period and method with the sponsor.

- A period of at least 2 years after the date on which approval to market the IMP is obtained; or, a period of at least 3 years after the data on which the sponsor notifies the trial site that development of the IMP is discontinued or that the final report of this trial will not be submitted in the registration application for the IMP;
- A period of at least 3 years after the trial is discontinued or completed.

The trial site must not dispose of any records that are relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to collect such records. 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 any data clarification forms 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 GCP: Consolidated Guideline (E6), and applicable regulatory requirements and local laws. 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, subinvestigators, and trial site staff members 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. Audits will include, but are not limited to IMP supply, presence of essential documents, the informed consent process, and comparison of CRFs with source documents. The investigator should agree 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: Consolidated Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to regional requirements, and provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling CRFs, the investigator, subinvestigator and their staff members will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number or subject ID will be used to identify each subject. Financial aspects, subject insurance and the publication policy for the trial results 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(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy all of the 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 ID in CRFs. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials according to local regulations.

13 Amendment Policy

The investigator will not make any changes 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 "nonsubstantial" amendments, investigators or subinvestigators will have to wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s) or amendment(s). Administrative amendments are defined as changes that have no effects on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately and reported to the IRB within the local applicable timeline. The sponsor will submit protocol amendments to the applicable regulatory agencies according to local applicable timelines.

When the IRB, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to subjects, the currently approved ICFs and written information for subjects will be amended, as well. In such cases, after approval/favorable opinion of the new ICF and written information for subjects by the IRB, repeat written informed consent will be obtained from subjects enrolled in the trial 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 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 subjects 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

1 Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med. 2007;120(11A): S1-S21.

2 Shoji M, Ota K, Kimura T. Treatment of SIADH. Clin Endocrinol. 1995;43: 1021-8.

3 Ishikawa S. SIADH. In: Orita Y (ed) Vasopressin and its Receptor Antagonism. Basic Principles and Clinical Applications. Osaka: Medical Review. 2011;141-9.

4 Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med. 2006;355:2099-112.

5 Verbalis JG, Adler S, Schrier RW, Berl T, Zhao Q, Czerwiec FS. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. Eur J Endocrinol. 2011;164:725-32.

6 Peri A, Giuliani C. Management of euvolemic hyponatremia attributed to SIADH in the hospital setting. Minerva Endocrinol. 2014;39:33-41.

7 Laville M, Burst V, Peri A. Hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH): therapeutic decision-making in real-life cases. Clin Kidney J. 2013;6(Suppl 1):1-20.

8 Otsuka Pharmaceutical Europe Ltd. A multi-centre multi-national observational post-authorisation safety study to document the drug utilisation of Samsca® and to collect information on the safety of Samsca® when used in routine medical practice. Post Authorisation Safety Study (PASS) Report for Protocol 156-09-101, issued 5 Nov 2014.

9 Otsuka Pharmaceutical Development & Commercialization, Inc. A phase 1b, multicenter, pilot, randomized, double-blind trial to determine the pharmacokinetics and pharmacodynamics of orally administered Tolvaptan 3.75, 7.5, and 15 mg tablets in subjects with syndrome of inappropriate antidiuretic hormone secretion. Clinical Study Report for Protocol 156-12-203, issued 26 Oct 2015.

10 International Conference on Harmonization (ICH) [Internet]. E6: Good Clinical Practice: Consolidated Guideline [finalized 1996 May, corrected 1996 Jun 1996; cited 2014 Dec 5]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

[11] Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, Japanese translation, Japan Clinical Oncology Group (JCOG) (CTCAE v4.0-JCOG for short) [CTCAE v4.03/MedDRA v12.0 [MedDRA/J v19.0 in Japanese], March 10, 2016 version]

[12] Ohta T, Waga S, Handa H, et al. New grading of level of consciousness in acute stage.In: Proceedings of the Third Conference of Surgical Treatment of Stroke. 1975;61-9.

Appendix 1 Diagnostic and Treatment Manual of the Hypersecretion of Vasopressin (SIADH), Revised in 2011

Diagnostic and Treatment Manual for the Hypersecretion of Vasopressin (SIADH), Revised in 2011

A. Diagnosis of Hypersecretion of Vasopressin (SIADH)

I. Predominant symptoms

1. Has no symptoms of dehydration
2. May have symptoms of hyponatremia, such as malaise, appetite impaired, and consciousness disturbed

II. Laboratory tests

1. Hyponatremia: Serum sodium <135 mEq/L
2. Plasma vasopressin: Measurable, when serum sodium is <135 mEq/L
3. Blood hyposmosis: Plasma osmolality <280 mOsm/kg
4. Hypersthenuria: Urine osmolality >300 mOsm/kg
5. Persistent natriuresis: Urine sodium ≥20 mEq/L
6. Normal renal function: Serum creatinine ≤1.2 mg/dL
7. Normal adrenocortical function: Fasting morning serum cortisol ≥6 μg/dL

III. Relevant findings

1. The established diagnosis of the etiology of SIADH (Table 1) is helpful in the diagnosis of SIADH.
2. Plasma renin activity is usually ≤5 ng/mL/h.
3. Serum uric acid is usually ≤5 mg/dL.
4. Fluid intake restriction improves hyponatremia, without aggravating dehydration.

[Diagnostic Criteria]

Patients with confirmed SIADH: Among the above criteria, I. 1 and II. 1 to 7 are met.

[Differential diagnosis]

The following conditions resulting in hyponatremia should be excluded.

1. Hyponatremia with excess extracellular fluid volume: Heart failure, ascites associated with hepatic cirrhosis, nephrotic syndrome
2. Hyponatremia with substantial sodium transudation: Renal sodium loss, diarrhoea, vomiting

Table 1. Etiology of Hypersecretion of Vasopressin (SIADH)

1. Central nervous system disorders:	Meningitis Trauma Subarachnoid hemorrhage Brain tumor Cerebral infarction/intracranial hemorrhage Guillain-Barre syndrome Encephalitis
2. Lung diseases:	Pneumonia Lung tumors (excluding ectopic vasopressin producing tumors) Pulmonary tuberculosis Pulmonary aspergillosis Bronchial asthma Positive-pressure respiration
3. Ectopic vasopressin producing tumors:	Small cell lung cancer Pancreatic cancer
4. Drugs:	Vincristine Clofibrate Carbamazepine Amitriptyline Imipramine

B. Treatment of Hypersecretion of Vasopressin (SIADH)

Any of the following therapies (alone or combination) should be selected.

1. Treat the underlying disease.
2. Restrict daily fluid intake to 15 to 20 mL per kg of body weight.
3. Administer salt (≥200 mEq/day) orally or parenterally.
4. In patients who require acute treatment [eg, those with severe hyponatremia (≤120 mEq/L) accompanied by a central nervous system disorder], administer furosemide as an intravenous dose of 10 to 20 mg, as needed, in combination with an amount of 3% saline equivalent to the urinary sodium excretion. To prevent central pontine myelinolysis, the daily increase in serum sodium should not exceed 10 mEq/L.
5. In adult patients with SIADH secondary to ectopic vasopressin producing tumors who have displayed an inadequate response to other existing therapies, mozavaptan hydrochloride (one 30 mg tablet) may be orally administered once daily after a meal. If therapeutic effects are observed during the first 3 days, treatment may be continued for up to 7 days.
6. Administer demeclocycline as an oral dose of 600 to 1200 mg/day.

Health and Labour Sciences Research Grants, Research Project for Overcoming Intractable Diseases, Investigative Research Group for Diencephalon-Pituitary Dysfunction, Fiscal Year 2010 General Partial Research Report
* Revised on 31 Mar 2011

Appendix 2 Handling and Shipment of Pharmacokinetic Blood Samples

Pharmacokinetic blood samples will be handled and shipped according to the procedure outlined below.

1) Blood Sampling and Processing

At each sampling timepoint, an approximately 2 mL blood sample must be taken by venipuncture using a heparin sodium-containing test tube, and the date and time of sampling will be recorded in the source document. The collected blood is to be mixed by slowly turning the test tube upside-down several times, and immediately (within 45 minutes after sampling) centrifuged at approximately 1710 × g for approximately 10 minutes at 4°C. The obtained plasma is to be separated equally and placed in 2 sample stock tubes, to which sample labels containing the protocol number, subject identification number, timepoint of sampling, and other information are to be affixed. The plasma samples will be stored below −15°C.

2) Shipment

The trial site is to request for the central laboratory to collect samples. The central laboratory is to collect frozen samples with dry ice, store the samples below −15C°, and ship the samples with dry ice to the bioanalytical laboratory, when appropriate.

3) Reporting and Recording of Results

The bioanalytical laboratory is to measure the plasma concentrations of tolvaptan and its metabolites (DM-4103 and DM-4107) according to the procedures specified by the laboratory, and report the results to the sponsor.

The investigator is to document blood sampling, as well as the date and time in the CRF. Since the results of measurements are to be reported directly to the sponsor by the bioanalytical laboratory, the entry of the results in the CRF is unnecessary.

Appendix 3 Procedure for Readministration with the IMP

If the serum sodium concentration has normalized (≥135 mEq/L) after start of IMP administration, the subject has no subjective symptoms associated with hyponatremia, and the investigator or subinvestigator judges that the serum sodium concentration is unlikely to decrease on withdrawal of the IMP, the treatment may be completed before the duration of treatment reaches 30 days.

If hyponatremia recurs after treatment with the IMP has been completed before the duration of treatment reaches 30 days (except treatment discontinuations as specified in Section 3.8.3.1), and it is judged by the investigator or subinvestigator that readministration with the IMP is necessary, treatment may be resumed within 30 days after the initial IMP administration.

Treatment with the IMP should be resumed according to the procedure outlined below. For matters that are not specified in this appendix, follow the requirements specified by the protocol.

1) Trial Treatment

- Dosage regimen

  The starting dose for readministration is 7.5 mg/day (one 7.5 mg tablet once daily), orally administered according to Section 3.2.1.

  The investigator or subinvestigator is to record the date on which resumption of the trial treatment is decided, and the reason(s) on the source document and CRF.

- Dose titration

  After the start of readministration, the dose of the IMP will be increased as specified in Section 3.2.2, to determine a new maintenance dose for the subject. However, the treatment period will not be extended and will be completed when 30 days have passed since the initial IMP administration even if this occurs before a new maintenance dose is determined.

- Treatment period

  Treatment with the IMP will be continued until either of the following days, whichever comes first.

  – The day on which 30 days have passed since the initial IMP administration
  – The day on which the serum sodium concentration has normalized (≥135 mEq/L), the subject has no subjective symptoms associated with hyponatremia, and the investigator or subinvestigator judges that the serum sodium concentration is unlikely to decrease by terminating the IMP treatment

- Admission to and discharge from the trial site
  The subject is to be admitted to the trial site by the day before the start of retreatment. The subject may be switched to outpatient treatment at the judgement of the investigator or subinvestigator based on serum sodium concentration as specified in Section 3.2.5 on the day after the maintenance dose is determined or later.

2) Readmination procedures

- Day before the start of readministration
  The subject will be admitted to the trial site by the day before the start of readministration, at which time the investigator or subinvestigator will perform the procedures specified in Section 3.7.1.3 except daily urine volume, daily fluid intake, daily fluid balance, urinary sodium excretion, and urine osmolality.

- Day 1 of readministration
  The investigator or subinvestigator is to perform the procedure specified in Section 3.7.1.4 except daily urine volume, daily fluid intake, daily fluid balance, urinary sodium excretion, and urine osmolality. Fluid intake must not be restricted within 24 hours after the IMP administration on Day 1 of readministration.

- From Day 2 of readministration onward
  The investigator or subinvestigator is to perform the procedures specified in Section 3.7.1.5 to Section 3.7.1.13, and Section 3.7.1.15 to Section 3.7.1.18 except daily urine volume, daily fluid intake, daily fluid balance, urinary sodium excretion, and urine osmolality.

- Day after the completion of readministration
  The investigator or subinvestigator is to perform the procedures specified in Section 3.7.1.14.

- At Withdrawal
  The investigator or subinvestigator is to perform the procedures specified in Section 3.7.1.19.

- Follow-up
  The subject is to visit the trial site 3 to 5 days and 7 to 10 days after the completion of readministration, at which time the investigator or subinvestigator is to perform the examinations and investigations specified in Section 3.7.1.20.

- Assessment
  The requirements specified in Section 3.7.2, Section 3.7.3, and Section 3.7.4 should be followed.

3) Withdrawal of individual subjects

The requirements specified in Section 3.8.3 should be followed.

4) Prohibited concomitant medications

The requirements specified in Section 4.1 should be followed.

5) Fluid intake restriction

The requirements specified in Section 4.2 should be followed. Requirements 2) and 3) shall be read, as follows:

2) Within 24 hours after the initial IMP administration on Day 1 of readministration

Fluid intake must not be restricted.

3) After the IMP administration on Day 2 of readministration onwards

Setting the fluid intake volume from immediately before IMP administration on Day 1 of readministration to immediately before IMP administration on Day 2 of readministration as the upper limit of daily fluid intake, subjects will be instructed to restrict fluid intake. Fluid intake is the total volume of liquids taken as beverages (eg, juice, milk, tea), water, and transfusions, not including solid food-derived fluids.

The investigator or subinvestigator should pay attention to an excessive increase in urine volume or rapid increase in serum sodium concentration. If thirst or dehydration, and other unfavorable symptoms develop, the investigator or subinvestigator should instruct the subject to take more fluids, regardless of the upper limit of daily fluid intake, to ensure the safety of the subject.

6) Reporting of adverse events

The requirements specified in Section 5 should be followed.

Appendix 4 Protocol Amendments/Administrative Changes

Amendment Number: 2

Issue Date: 29 Mar 2017

PURPOSE:

Corrected entry omissions, etc.

BACKGROUND:

Since entry omissions were found, the protocol was modified.

MODIFICATIONS TO THE PROTOCOL:

- Measurement of urine sodium concentration (added)
  To Section 3.7.1.1 and Table 3.7-1, the measurement of urine sodium concentration during the screening period was added.
- Urine sample processing (screening period) was added (corrected in association with the above change).
  To Section 3.7.4.2.6, "1) Urine sample processing (screening period)" was added.
- Total volume of blood collected throughout the trial (description edited)
  The description regarding the total volume of blood collected in Section 3.7.3.2 was modified.

ADDITIONAL RISK TO THE SUBJECTS:

No additional risk will be imposed on the trial subjects.

Amendment Number: 3

Issue Date: 23 Jun 2017

PURPOSE:

Corrected to uniformly confirm measured values for eligibility assessment and to edit descriptions

BACKGROUND:

Since the procedure for confirming the results of serum sodium concentration measurement was found to be inconsistent within the protocol, and the correction of a few descriptions was required, the protocol was modified.

MODIFICATIONS TO THE PROTOCOL:

- Section 3.2.1, Section 3.4.2, and Section 3.4.3
  The serum sodium concentrations used in the decisions regarding eligibility for inclusion, exclusion, dose escalation, maintenance dose, and switching to outpatient treatment were changed from "the serum sodium concentrations measured centrally" to "the serum sodium concentrations measured at each trial site."

- Protocol Synopsis, Subject Population
  The descriptions regarding the subject population were changed as follows: From "The sample size will be 16 subjects." to "total of 16 subjects with a central measurement value for serum sodium concentration of <135 mEq/L at predose on Day 1 of the treatment period are to be treated with the investigational medicinal product (IMP)." and from "... of the above subjects treated with the IMP..." to "...of the above subjects...".

- Section 3.3.1
  The description, "The number of subjects treated with the IMP is to be 16." was changed to "The trial population must include 16 subjects who are evaluable for the primary endpoint, the percentage of subjects with normalized serum sodium concentration (ie, subjects whose predose serum sodium concentration centrally measured on Day 1 is <135 mEq/L)." In addition, the description, "...of the above subjects treated with the IMP..." was changed to "...of the above subjects... ."

  [Subjects whose serum sodium concentration at baseline (predose on Day 1) is ≥135 mEq/L will be excluded from the denominator data in calculating the percentage of subjects with normalized serum sodium concentration (the primary endpoint), according the inclusion criterion regarding serum sodium concentration.

The above descriptions were changed to result in the certain acquisition of 16 subjects who are evaluable for the primary endpoint, the percentage of subjects with normalized serum sodium concentration.]

- Section 3.7.3.2
  The description of the volume of blood to be collected for the central measurement of serum sodium concentration, in addition to that for clinical laboratory tests was changed to "Blood samplings for the central measurement of serum sodium concentration for efficacy evaluation."

- Section 4.1
  The period of time during which the use of hypertonic saline is prohibited was changed from "from the pretreatment observation period until the completion of treatment" to "from the time informed consent is obtained until the completion of IMP."

- Section 7.3
  The description, "Missing data will not be imputed." was changed to "Missing data on the day after the final IMP administration will be imputed using the last available data obtained by the day after the final IMP administration."

  (A description about the handling of missing data on the day after the final IMP administration had been omitted.)

- Section 7.4.1 and "Statistical Methods" of Protocol Synopsis
  The description, "in subjects whose serum sodium concentration is <135 mEq/L at baseline (predose on Day 1)" was added.

  (It was clearly stated that subjects whose serum sodium concentration at baseline is ≥135 mEq/L are not included in the denominator data in calculation of the percentage of subjects with normalized serum sodium concentration.)

ADDITIONAL RISK TO THE SUBJECTS:

No additional risk will be imposed on the trial subjects.

Amendment Number: 4

Issue Date: 14 Nov 2017

PURPOSE:

In consideration of the time required for measurement of the serum sodium concentration and determination of the maintenance dose, the allowable time window for the predose examination on or after Day 2 was redefined.

BACKGROUND:

Since some time is required from blood sampling for measurement of the serum sodium concentration to the IMP administration based on the measurement result, the descriptions regarding the allowable time window for the predose examination after Day 2 of treatment period onwards, together with other inappropriate descriptions, were corrected. However, no changes were made to the descriptions on the days of plasma drug concentration measurement.

MODIFICATIONS TO THE PROTOCOL:

- Section 3.7.1.5 to Section 3.7.1.12 (Days 2 to 10, Day 14), Section 3.7.1.15 (Procedure to be performed until the maintenance dose is determined), and Section 3.7.1.17 (When Determining the Possibility of Switching to Outpatient Treatment): common in all of these sections.

  1) Before IMP administration (21 to 24 hours after IMP administration on the day before)

  The timing of the predose examination was changed from "22 to 24 hours after IMP administration on the day before" to "21 to 24 hours after IMP administration on the day before."

- In addition, the following changes were made: the fax number on the title page was deleted; the description regarding the reporting of adverse events, "or maybe facsimile, if e-mail is not available" was changed to "by e-mail, as a rule"; and, the description regarding the reporting of IREs other than pregnancies was changed to "through the IRE form."

ADDITIONAL RISK TO THE SUBJECTS:

No additional risk will be imposed on the trial subjects.

Amendment Number: 5

Issue Date: 15 May 2018

PURPOSE:

The possibility that serum sodium concentration will drop rapidly upon the completion of treatment was considered.

BACKGROUND:

To address the possibility of a rapid drop of serum sodium concentration during the follow-up period, fluid intake restriction after the completion of treatment and measurement of the serum sodium concentration 3 to 5 days after the completion of treatment were specified.

MODIFICATIONS TO THE PROTOCOL:

- Section 3.1, Figure 3.1-1, Figure 3.1-2, and Section 3.7.2.1
  Descriptions were changed due to the additional measurement of serum sodium concentration.
- Table 3.7-1 Schedule of Assessments
  The item field, “Fluid intake restriction” was added.
- Table 3.7-1 Schedule of Assessments (Continued)
  To the follow-up, the two fields, “serum sodium concentration 3 to 5 days after completion” and “fluid intake restriction” were added.
- Section 3.7.1.20
  The section title was changed to “Section 3.7.1.20 Follow-up,” and subsection “Section 3.7.1.20.1 Serum Sodium Concentration (3 to 5 Days After the Final IMP Administration)” was added.
- Total volume of blood collected throughout the trial
  The total volume of blood collected in Section 3.7.3.2 was corrected (due to the additional measurement of serum sodium concentration 3 to 5 days after completion).
- Section 4.2
  The subitem, “4) From the completion of the examination on the day after the final IMP administration to the completion of the follow-up examination” was added.

ADDITIONAL RISK TO THE SUBJECTS:

No additional risk will be imposed on the trial subjects.

Agreement

I, the undersigned principal 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 new drug, tolvaptan (OPC-41061), the concurrent 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 clinical trial facility 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 on CRF by me and 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 research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendments 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 timelines. 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 experiences 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.

_____	_____
Principal Investigator Print Name	Trial Site
_____	_____
Signature	Date

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