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- **Document title:** A Phase 3b, Multicenter, Open-label, Randomized Withdrawal Trial of the Effects of Titrated Oral SAMSCA® (Tolvaptan) on Serum Sodium, Pharmacokinetics, and Safety in Children and Adolescent Subjects Hospitalized With Euvolemic or Hypervolemic Hyponatremia
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Otsuka Pharmaceutical  
Development & Commercialization, Inc.

Investigational Medicinal Product

SAMSCA<sup>®</sup>, Tolvaptan (OPC-41061)

**REVISED CLINICAL PROTOCOL**

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

Protocol No. 156-08-276

IND No. 54,200

NDA No. 22-275

EudraCT No. 2013-002005-59

**CONFIDENTIAL – PROPRIETARY INFORMATION**

Drug Development Phase: 3b

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## Protocol Synopsis

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc.	Protocol No. 156-08-276 IND No. 54,200 NDA No. 22-275 EudraCT No. 2013-002005-59
Name of Product: SAMSCA <sup>®</sup> , Tolvaptan (OPC-41061)	
Protocol Title:	A Phase 3b, Multicenter, Open-label, Randomized Withdrawal Trial of the Effects of Titrated Oral SAMSCA <sup>®</sup> (Tolvaptan) on Serum Sodium, Pharmacokinetics, and Safety in Children and Adolescent Subjects Hospitalized With Euvolemic or Hypervolemic Hyponatremia
Clinical Phase/Trial Type:	Phase 3b, therapeutic confirmatory
Treatment Indication:	Euvolemic or hypervolemic hyponatremia
Objectives:	<p><b>Primary Objective:</b> To demonstrate that tolvaptan effectively and safely increases and maintains serum sodium concentrations in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.</p> <p><b>Secondary Objective:</b> To assess tolvaptan's pharmacokinetics (PK) and its effect on fluid balance in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.</p>
Trial Design:	<p>This is an open-label, multicenter, multiple-dose, randomized withdrawal, parallel-group trial of tolvaptan in children and adolescent subjects hospitalized with euvolemic or hypervolemic hyponatremia.</p> <p>Pediatric and adolescent subjects who are diagnosed with euvolemic or hypervolemic hyponatremia (serum sodium &lt; 130 mEq/L [mmol/L]) that persists despite initial standard background therapy (eg, including fluid restriction) are eligible to be screened for participation in this trial. Subjects who demonstrate prior resistance to vasopressin antagonist therapy will be excluded. All potential subjects must be deemed by the investigator as likely to benefit from a therapy that raises serum sodium levels.</p> <p>Since hyponatremia in this patient population can often be transient and/or may be secondary to hypovolemic states, potential subjects will be screened for hyponatremic histories as well as clinically evaluated to rule out such cases. For the purpose of this protocol, persistent hyponatremia will be defined as serum sodium assessments &lt; 130 mEq/L (mmol/L)</p>

documented as present for at least 48 hours. Specifically, subjects must have at least 2 documented serum sodium assessments < 130 mEq/L (mmol/L) drawn at least 12 hours apart. These values can be documented using historical values previously obtained as per standard of care. A third (immediate [STAT]) serum sodium assessment < 130 mEq/L (mmol/L), which will serve as the baseline value for final trial qualification and clinical management strategy, is to be obtained within 2-4 hours prior to the first dose of tolvaptan. Additional qualification assessments will be performed as per etiology of hyponatremia. The first dose of tolvaptan will be administered upon successful completion of all screening procedures.

Subjects will be required to be in a hospital setting during initiation and titration of tolvaptan.

Overall, in this trial, subjects will undergo treatment (2 to 5 days of tolvaptan among 2 treatment phases) and a post-last dose follow-up phase of 14 days.

### **Treatment Phase A**

After screening, all subjects will initially receive tolvaptan once daily for 2 days. If the desired serum sodium level target improvement is not reached after Day 2 of tolvaptan administration (post 2 doses), a third day (Day 2a) of treatment is required. At the end of Day 2 (or 2a), subjects will be assessed for a serum sodium level change of  $\geq 4$  mEq/L (mmol/L). At that time, subjects who are responders will enter Treatment Phase B, and be randomized to either the Early Withdrawal group or Late Withdrawal group. Responders are defined as those subjects who achieve an increase in serum sodium concentrations of  $\geq 4$  mEq/L (mmol/L); nonresponders are defined as subjects who do not achieve an increase in serum sodium concentration of  $\geq 4$  mEq/L (mmol/L).

### **Treatment Phase B**

#### Responders

Responders from Treatment Phase A will be randomized to either the:

- Late Withdrawal group - subjects continue tolvaptan treatment on Days 3 and 4
- Early Withdrawal group - subjects do not receive additional tolvaptan treatment on Days 3 and 4.

Randomization will include stratification by age [REDACTED]

[REDACTED], serum sodium response [REDACTED]

[REDACTED], and underlying etiology of hyponatremia.

Subjects who are randomized to the Early Withdrawal group will initially be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels. Those subjects whose serum sodium level declines by  $\geq 4$  mEq/L (mmol/L), or whose overall clinical condition requires further treatment to increase serum sodium level, will be treated per the investigator's preferred standard of care. Any intervention intended to raise serum sodium level during the first 48 hours of the Early Withdrawal phase (including fluid restriction) will be defined as rescue therapy. Subjects who receive rescue therapy will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.

#### Nonresponders

If the subject remains a nonresponder at the end of Day 2a, the investigator decides to either (a) continue tolvaptan for 2 additional days, or (b) discontinue tolvaptan and treat the subject per the investigator's preferred standard of care during Days 3 and 4. Subjects will continue to follow scheduled assessments regardless of treatment.

#### All Subjects

All subjects will have serum sodium levels measured at 8, 12, and 24 hours post-first dose and thereafter every 12 ( $\pm 4$ ) hours through completion of Treatment Phase B. In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment will be obtained on Day 1 at 4 to 6 (-1 to + 0.25) hours postdose and at 18 ( $\pm 1$ ) hours postdose. This sodium safety assessment will be repeated at 6 (-1 to + 0.25) and 18 ( $\pm 1$ ) hours postdose each day for the remainder of titration.

#### **Follow-up Phase C**

All subjects will have an additional serum sodium assessment at 72 ( $\pm 4$ ) hours post-last dose and 7 (+ 1) days post-last dose. A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-last dose.

#### **Pharmacokinetic Sampling**

Blood samples for PK analysis will be obtained at 2 and 8 hours post-first dose, and at trough (24 [ $\pm 4$ ] hours post-previous

<p>dose) on Days 1, 2, 3, and 4 for all subjects dosed with tolvaptan on Days 1, 2, 3, and 4, respectively, regardless of responder status. Pharmacokinetic profiles will be evaluated on an ongoing basis to determine variability among subjects. Based on the findings, PK sampling will continue for as long as necessary to establish suitable estimates of clearance with a 90% confidence interval (CI), similar to that observed in adult subject populations. Once these estimates are achieved, sampling will be discontinued in subsequent subjects in order to minimize blood draws in this pediatric population.</p>	
Subject Population:	<p>This trial will enroll approximately 100 male and female subjects to get approximately 70 randomized subjects aged <math>\geq</math> 4 weeks (or <math>\geq</math> 44 weeks adjusted gestational age) to &lt; 18 years who have been diagnosed with euvolemic or hypervolemic hyponatremia (<math>&lt; 130</math> mEq/L [mmol/L]) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). Age groups will be enrolled such that at least 50% of these subjects will be &lt; 10 years old and at least 25% of subjects &lt; 6 years old.</p> <p>Subjects with acute hyponatremia or hyponatremia expected to resolve spontaneously will be excluded from the trial. Children with an impaired ability to sense or communicate their thirst will either be required per protocol to undergo closer in-hospital observation, laboratory and urine output monitoring, or will be excluded from the trial if this is not possible.</p> <p>The protocol entry criteria have been designed to ensure careful selection of subjects with chronic (<math>\geq</math> 48 hours) dilutional hyponatremia (euvolemic or hypervolemic) associated with heart failure, hepatocellular disease (including cirrhosis), or syndrome of inappropriate secretion of antidiuretic hormone/other, who may benefit from treatment with tolvaptan, while excluding those who have acute or transient hyponatremia, have overt symptoms of hyponatremia requiring immediate intervention, or who are at increased risk for developing hyponatremic encephalopathy or osmotic demyelination.</p>
Inclusion/Exclusion Criteria:	<p><u>Key inclusion criteria:</u></p> <ul style="list-style-type: none"> <li>• Male and female subjects <math>\geq</math> 4 weeks (or <math>\geq</math> 44 weeks adjusted gestational age) to &lt; 18 years old</li> <li>• Subjects hospitalized with euvolemic or hypervolemic hyponatremia resistant to initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist) and who are deemed by the</li> </ul>

investigator as likely to benefit from a therapy that raises serum sodium levels

- Persistent euvolemic or hypervolemic hyponatremia defined as being documented as present for at least 48 hours, evidenced by at least 2 serum sodium assessments  $< 130 \text{ mEq/L (mmol/L)}$  drawn at least 12 hours apart (these values can be documented using historical values previously obtained per standard of care); a third (STAT) serum sodium assessment  $< 130 \text{ mEq/L (mmol/L)}$ , which will serve as the baseline value for final trial qualification and clinical management strategy, is to be obtained within 2-4 hours prior to the first dose of tolvaptan

Key exclusion criteria:

- Has evidence of hypovolemia or intravascular volume depletion (eg, hypotension, clinical evidence of volume depletion, response to saline challenge); if the subject has systolic blood pressure or heart rate outside of the normal range for that age, then volume status should be specifically clinically assessed to rule out volume depletion
- Has serum sodium level  $< 120 \text{ mEq/L (mmol/L)}$ , with or without associated neurologic impairment (ie, symptoms such as apathy, confusion, or seizures)
- Current use or expected use during the trial of potent cytochrome P450 (CYP) 3A4 inhibitors in subjects  $< 12 \text{ kg}$  or moderate CYP3A4 inhibitors in subjects  $< 6 \text{ kg}$
- Has estimated glomerular filtration rate (eGFR)  $< 30 \text{ mL/min}/1.73 \text{ m}^2$
- Has acute kidney injury defined as:
  - Increase in serum creatinine by  $\geq 0.3 \text{ mg/dL}$  ( $\geq 26.5 \text{ } \mu\text{mol/L}$ ) within 48 hours; or
  - Increase in serum creatinine to  $\geq 1.5$  times baseline, which is known or presumed to have occurred within the prior 7 days; or
  - Urine volume  $< 0.5 \text{ mL/kg/h}$  for 6 hours
- Has had treatment for hyponatremia with:
  - Hypertonic saline (including normal saline challenge) within 8 hours of qualifying serum sodium assessments
  - Urea, lithium, demeclocycline, conivaptan, or tolvaptan within 4 days of qualifying serum sodium assessments
  - Other treatment for the purpose of increasing serum sodium concurrent with dosing of trial medication
- Has uncontrolled diabetes mellitus defined as fasting

	<p>glucose &gt; 300 mg/dL (16.7 mEq/L [mmol/L])</p> <ul style="list-style-type: none"> <li>Has screening liver function values &gt; 3 × the upper limit of normal (ULN)</li> <li>Subjects who have cirrhosis and meet any of the following conditions: a major gastrointestinal (GI) bleed within the past 6 months, evidence of active bleeding (eg, epistaxis, petechiae/purpura, hematuria, or hematochezia), platelet count &lt; 50,000/<math>\mu</math>L, or use of concomitant medications known to increase bleeding risk</li> </ul>
Trial Sites:	The trial will be conducted at approximately 60 centers globally.
Investigational Medicinal Product, Dose, Formulation, Mode of Administration:	<p>Tolvaptan will be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets and, where approved, as a 1 mg/mL (0.1% w/v) suspension.</p> <p>Tolvaptan tablets will be administered once daily, orally with a dose proportional amount of water. Doses of <math>\geq</math> 15 mg tolvaptan will be given with 240 mL of water, 7.5 mg tolvaptan will be given with 120 mL of water, and 3.75 mg of tolvaptan will be given with 60 mL of water. The treatment duration will be up to 5 days.</p> <p>Tolvaptan suspension will be administered once daily, orally using the provided, appropriately-sized syringe (3 mL or 10 mL) to measure the volume. The lowest volume that can be administered is 0.3 mL (0.3 mg).</p> <p>Any initiation or titration of tolvaptan must occur in a hospital setting.</p> <p>The investigator has the option of performing a swallow test and providing coaching on swallowing techniques using placebo tablets if it is unknown if the subject is able to swallow tablets. Placebo tablets will be provided for use in performing this test at screening.</p> <p>Subjects will be administered tolvaptan on an age- and weight-based scale. Up-titration of tolvaptan doses will be based on serum sodium levels at <math>&gt;</math> 20 hours following initiation of therapy and at <math>&gt;</math> 20 hours following each additional dose; a change in serum sodium <math>\leq</math> 4 mEq/L (mmol/L) from baseline should warrant up-titration, which is limited to no more than twice the previous dose.</p> <ul style="list-style-type: none"> <li>Subjects <math>\geq</math> 4 weeks (or <math>\geq</math> 44 weeks adjusted gestational age)</li> </ul>

to < 2 years of age and weighing  $\geq 3$  kg to < 6 kg will receive 0.1 mg/kg of the suspension on Day 1 with possible up-titration to 0.2 mg/kg and 0.4 mg/kg doses.

- Subjects  $\geq 4$  weeks (or  $\geq 44$  weeks adjusted gestational age) to < 2 years of age and weighing  $\geq 6$  kg to < 12 kg will receive 0.1 mg/kg of the suspension on Day 1 with possible up-titration to 0.2 mg/kg and 0.4 mg/kg doses.
- Subjects  $\geq 2$  to  $\leq 6$  years of age, weighing  $\leq 30$  kg will receive a 0.15 mg/kg dose of the suspension on Day 1 with possible up-titration to 0.3 mg/kg and 0.6 mg/kg doses.
- Subjects  $> 6$  years of age, weighing  $\leq 30$  kg and who cannot safely swallow a tablet, will receive a 0.15 mg/kg dose of the suspension on Day 1 with possible up-titration to 0.3 mg/kg and 0.6 mg/kg doses.
- Subjects  $> 6$  years of age and weighing 20 to 50 kg, inclusive, will receive a 7.5 mg tablet on Day 1 with possible up-titration to 15-mg and 30-mg doses.
- Subjects  $> 6$  years of age and weighing  $> 50$  kg, will receive a 15 mg tablet on Day 1 with possible up-titration to 30-mg and 60-mg doses.

The subjects will continue dosing according to a titration scheme targeting a final serum sodium concentration between 135 and 140 mEq/L (mmol/L). Titration will ideally achieve a change in serum sodium concentration of at least 4 to 8 mEq/L (mmol/L)/24 hours but not exceeding

[REDACTED]

<p>Trial Assessments:</p>	<p><u>Efficacy:</u></p> <ul style="list-style-type: none"> <li>• Serum sodium concentrations</li> </ul> <p><u>Pharmacokinetic/pharmacodynamic:</u></p> <ul style="list-style-type: none"> <li>• Blood sampling for tolvaptan and metabolite plasma concentrations</li> <li>• Fluid intake</li> <li>• Urine output</li> <li>• Urine chemistry</li> </ul> <p><u>Safety:</u></p> <ul style="list-style-type: none"> <li>• Adverse event (AE) reporting</li> <li>• Vital signs</li> <li>• Clinical laboratory tests (hematology, coagulation, chemistry, urinalysis)</li> <li>• Physical examinations, including body weight and neurological examinations</li> </ul>
<p>Criteria for Evaluation:</p>	<p><b>Primary Efficacy Endpoint</b></p> <ul style="list-style-type: none"> <li>• For subjects with serum sodium level increases of <math>\geq 4</math> mEq/L (mmol/L) (ie, responders), change in serum sodium concentration from Day 2 (or 2a) at the end of Treatment Phase A to the end of Treatment Phase B for Early compared to Late Withdrawal groups.</li> </ul> <p><b>Key Secondary Efficacy Endpoint</b></p> <ul style="list-style-type: none"> <li>• For all subjects, the key secondary endpoint is the change in serum sodium concentration at the end of Day 2 (or 2a) in Treatment Phase A from baseline.</li> </ul> <p><b>Other Secondary Endpoints</b></p> <p><u>Safety:</u></p> <ul style="list-style-type: none"> <li>• Percentage of subjects with overly rapid increase in serum sodium level [REDACTED]</li> <li>• Change in serum sodium level from 24 hours post-last dose to 7 days post-last dose</li> <li>• Percentage of subjects requiring rescue therapy (other than fluid restriction) during Treatment Phase A and Treatment Phase B</li> <li>• Percentage of subjects requiring fluid restriction during Treatment Phase A and Treatment Phase B</li> <li>• Vital signs, blood pressure, clinical laboratory tests,</li> </ul>

body weight, and neurological examinations

Pharmacokinetic:

- On Day 1 in Treatment Phase A, tolvaptan maximum (peak) plasma concentration ( $C_{max}$ ), time to maximum (peak) plasma concentration ( $t_{max}$ ), and area under the concentration-time curve from time zero to 24 hours ( $AUC_{0-24h}$ )

Pharmacodynamic:

- Fluid intake, urine output, and fluid balance (intake minus output) every 6 hours on Days 1 and 2 in Treatment Phase A

**Exploratory Endpoints**

- Efficacy will be assessed in nonresponders continuing on tolvaptan therapy by change from baseline in serum sodium concentration at the end of Treatment Phase B compared to the end of Treatment Phase A.
- In all subjects, 24-hour excretion of sodium, creatinine, and osmolality on Days 1 and 2
- 24-hour sodium clearance on Day 1
- Quality of life (QoL) assessments

Statistical Methods:	The primary analysis will use a mixed-model repeated measures analysis based on the observed cases dataset. The key secondary analysis will be analyzed using a paired Student's t-test. Other secondary analyses will use a paired Student's t-test, descriptive statistics, and/or 2-sided 95% CIs.
Trial Duration:	Overall trial duration of enrollment is expected to be approximately 3 years with an enrollment rate of approximately 33 subjects per year. Nominal trial duration for each subject is up to 21 days. Treatment duration is up to 5 days with ongoing monitoring of serum sodium levels. A serum sodium assessment and AE follow-up visit will be performed 7 (+ 1) days post-last dose. A final safety follow-up telephone contact or visit will be performed 14 (+ 2) days post-last dose.

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## List of Abbreviations and Definitions of Terms

<b><u>Abbreviation</u></b>	<b><u>Definition</u></b>
7DFU	7-day follow-up
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
AKI	Acute kidney injury
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
AUC <sub>0-24h</sub>	Area under the concentration-time curve from time zero to 24 hours
AUC <sub>t</sub>	Area under the concentration-time curve calculated to the last observable concentration at time t
AUC <sub>τ</sub>	Area under the concentration-time curve during the dosing interval at steady state
AVP	Arginine vasopressin
BUN	Blood urea nitrogen
BW	Body weight
CHF	Congestive heart failure
CI	Confidence interval
CL/F	Apparent clearance of drug from plasma after extravascular administration
C <sub>max</sub>	Maximum (peak) plasma concentration
CV	Coefficient of variation
CYP	Cytochrome P450
DDAVP	1-deamino-8-D-arginine vasopressin
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
ED <sub>3</sub>	Dose required to triple the urine output
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ET	Early termination
FDA	Food and Drug Administration
FENa	Fractional excretion of sodium
FE urea	Fractional excretion of urea
GCP	Good Clinical Practice
GI	Gastrointestinal
HF	Heart failure
HFI	Hereditary fructose intolerance
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IDMC	Independent data monitoring committee
IEC	Independent ethics committee

IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IRE	Immediately reportable event
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web response system
$K_i$	Inhibition constant
LOCF	Last observation carried forward
LS	Least squares
MHRA	Medicines and Healthcare Products Regulatory
MMRM	Mixed-model repeated measures
OAPI-EQC	Otsuka America Pharmaceutical, Inc.-Ethics, Quality and Compliance
OC	Observed cases
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PI	Principal investigator
PK	Pharmacokinetic(s)
PO	By mouth
PQC	Product quality complaint
PREA	Pediatric Research Equity Act
QoL	Quality of life
RBC	Red blood cell
SAE	Serious adverse event
SALT	<u>S</u> tudy of <u>A</u> scending <u>L</u> evels of <u>T</u> olvaptan in <u>H</u> yponatremia
SALTWATER	<u>S</u> afety and sodium <u>A</u> sessment of <u>L</u> ong-term <u>Tolvaptan <u>W</u>ith <u>h</u>yponatremia: <u>A</u> year-long, open-label <u>Trial to gain <u>E</u>xperience under <u>R</u>eal-world conditions</u></u>
SAP	Statistical analysis plan
SD	Standard deviation
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
STAT	Immediate
$t_{1/2,z}$	Terminal-phase elimination half-life
TEAE	Treatment-emergent adverse event
$t_{max}$	Time to maximum (peak) plasma concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential

## 1 Introduction

Sodium is the major extracellular electrolyte and is a key factor in maintaining extracellular osmolality and transmembrane electrical and chemical potentials. Serum sodium concentration is maintained within a narrow range (normally 135 to 145 mEq/L [mmol/L]) to facilitate optimal cellular hydration and neuromuscular function. Sodium concentration is normally balanced through integrated actions of the cardiovascular, renal, endocrine, gastrointestinal (GI), and nervous systems.

Hyponatremia is a disease seen in all age groups, including pediatrics, and across a wide range of patients “from asymptomatic to the critically ill.”<sup>1</sup> It is characterized by a subnormal concentration of sodium in the blood (serum sodium < 135 mEq/L [mmol/L]) and is manifest by a range of neurological symptoms which, left untreated, can lead to seizure, obtundation, hypoxia, and death. Hyponatremia is rarely seen in isolation and typically is found in association with disorders, behaviors, or circumstances which promote an imbalance of fluid/sodium homeostasis. Children, in particular those hospitalized and receiving parenteral fluids (eg, post-operative maintenance and hydration with hypotonic fluid), are at risk for developing hyponatremia.<sup>2,3</sup>

Both forms of hyponatremia, dilutional and depletion, impair normal neurological function and therefore represent a disease state. Furthermore, there is evidence suggesting that, in both children and adults, hyponatremia has more serious consequences than previously believed.<sup>4</sup> Various clinical and nonclinical experiments and case studies have documented the role of sodium in maintaining extracellular osmolality and transmembrane electrical and chemical potentials. Sudden decreases in the concentration of extracellular sodium lead to influx of water into cells, often resulting in cerebral edema, irreversible neurological damage, respiratory arrest, brainstem herniation, and death if not treated quickly and appropriately.<sup>5</sup> When hyponatremia persists, osmotic adjustments can occur over hours to days through metabolic elimination of electrolytes and then osmotically-active organic compounds from the cells. While these compensatory mechanisms can prevent acute brain herniation, chronic symptoms of hyponatremia may arise from electrochemical imbalances in cations that are important for nerve conduction and/or imbalances in amino acids and neurotransmitters dependent on sodium for transport. Disturbances in these physiological processes lead to symptoms and outcomes which depend on a number of factors, including rapidity of onset, severity of hyponatremia, persistence of underlying disease, and clinical context (age, gender, baseline neurological function). In many cases, morbidity and mortality associated with

hyponatremia can be shown to be prevented or reversed with appropriate and timely correction of serum sodium concentration.

In the adult population, hyponatremia occurs in 7% to 8% of elderly, ambulatory patients<sup>6</sup> and 15% to 20% of hospitalized patients<sup>6,7,8,9</sup> making it the most common serum electrolyte abnormality that physicians encounter, and a prevalent problem for those hospitalized for a wide variety of critical illnesses. A similar situation exists for children in which approximately 25% of hospitalized children were found to have mild hyponatremia (serum sodium < 135 mEq/L [mmol/L]) and approximately 1% were found to have moderate hyponatremia (serum sodium < 130 mEq/L [mmol/L]).<sup>4</sup> Hyponatremia is associated with significant additional hospital morbidity and cost.<sup>10</sup>

Children, especially infants, are particularly vulnerable to sodium and other electrolyte imbalances due to their relatively immature renal function, increased insensible water loss, and their limited ability to communicate thirst. Hence, hyponatremia is not uncommon in hospitalized children and pediatric patients presenting at the Emergency Department. Hyponatremia in children is most often caused by gastroenteritis and water intoxication, the former leading to hypovolemic volume state and requiring fluid administration. Other underlying diseases that can be accompanied by either euvolemic or hypervolemic hyponatremia are CHF, liver diseases, adrenal insufficiency, and renal disorders. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is often associated with central nervous system or pulmonary conditions and also malignancies.<sup>11</sup> An excess of arginine vasopressin (AVP) excretion with impaired free water excretion can lead to hyponatremia in febrile children and approximately 30% of these hospitalized children have SIADH.<sup>12</sup> In addition, several drugs such as thiazide diuretics, antidepressants, anticonvulsants, and chemotherapeutics have been associated with SIADH.

The United States (US) Food and Drug Administration (FDA) has required pediatric trials be conducted for tolvaptan for the indication of hyponatremia. This trial will assess the short-term safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of tolvaptan in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.

## 1.1 Nonclinical Data

Tolvaptan is a vasopressin antagonist that blocks the binding of AVP at the V<sub>2</sub> receptors of the distal portions of the nephron, thereby inducing water diuresis (aquaresis) without depletion of electrolytes. In vitro binding studies demonstrated that tolvaptan has affinity

for the human vasopressin V<sub>2</sub> and V<sub>1a</sub> receptors but not V<sub>1b</sub> receptors. The receptor selectivity potential of tolvaptan for human V<sub>2</sub> receptors (inhibition constant [K<sub>i</sub>] = 0.43 nmol/L) is approximately 30 times that for human V<sub>1a</sub> receptors (K<sub>i</sub> = 12.3 nmol/L) and at concentrations not achieved clinically. Several tolvaptan metabolites (DM-4110, DM-4111, and MOP-21826) have affinity for the human V<sub>2</sub> or V<sub>1a</sub> receptors but to a lesser degree than tolvaptan. None of the metabolites appear to have affinity for V<sub>1b</sub> receptors. Tolvaptan is 1.8 times more potent in binding activity than native AVP.

In vivo pharmacology experiments using water loaded, alcohol-anesthetized rats indicated that tolvaptan at 3 to 30 µg/kg intravenous (IV) dose-dependently antagonized the antidiuretic action of exogenous vasopressin. In conscious mice, rats, and dogs, tolvaptan at 0.3, 1, 3, and 10 mg/kg by mouth (PO) caused dose-dependent water diuresis (aquaresis), ie, an increase in urine volume and a decrease in urine osmolality. The dose required to triple the urine output (ED<sub>3</sub>) within 2 hours post dosing in rats was estimated to be 0.54 mg/kg and the ED<sub>3</sub> after 6 hours in dogs was estimated to be 1.1 mg/kg PO. In the rat model of acute progressive hyponatremia, tolvaptan (0, 1, 3, and 10 mg/kg PO) produced a clear dose-dependent aquaresis over the dosing duration, which resulted in a gradual increase in plasma sodium concentration and a decrease in the mortality rate. In severe hyponatremia, mortality rate decreased from 47% in 1-deamino-8-D-arginine vasopressin (DDAVP) and water loaded rats to 38% in the 1 mg/kg dose group, and no deaths were seen in the 3 and 10 mg/kg dose groups of tolvaptan-treated rats. In the rat model of chronic hyponatremia induced by DDAVP infusion (1 ng/h subcutaneous) and liquid diet, plasma sodium concentration was reduced to about 110 mEq/L and maintained at that level without any deaths. Oral dose titration of tolvaptan from 0.25 to 8 mg/kg gradually increased plasma sodium concentration to the normal levels, and improved the wet weight of kidney and water content in the brain and heart, which were increased by sustained hyponatremia. <sup>13,14</sup>

In a dog model of pacing-induced congestive heart failure (CHF), tolvaptan alone exerted aquaretic effects without activation of sympathetic and renin-angiotensin-aldosterone systems and produced a significant decrease in cardiac preload without affecting cardiac afterload or renal functions. Tolvaptan did not affect the human ether-a-go-go-related gene channel current at the tested concentration up to  $2 \times 10^{-6}$  mol/L, which was the solubility limit for the external solution. In conscious dogs, tolvaptan at doses of up to 1,000 mg/kg PO showed no significant changes in the ST segment, QRS width, QT interval, and QTc interval when compared to the control group. In an action potential

duration study in the guinea pig ventricular papillary muscle, tolvaptan did not affect any of the parameters studied (resting membrane potential, action potential amplitude, maximum aortic velocity, action potential duration at 30%, 60%, and 90% repolarization) at tested concentrations of up to  $3 \times 10^{-5}$  mol/L, which was about 30-fold higher than the maximum serum concentrations in humans at an oral clinical dose of 60 mg of the spray-dried formulation.

Based on results from single-dose toxicity studies, the approximate lethal dose of tolvaptan is higher than 2,000 mg/kg in rats and dogs. The nontoxic dose of the compound is estimated to be 1,000 mg/kg/day in the males, and 100 mg/kg/day in the females in a 26-week repeated oral dose study in rats and 100 mg/kg/day in both males and females in a 52-week repeated oral dose study in dogs. The exposures in animals at these nontoxic dose levels are 4.0 to 13.1 times higher than that in humans following administration of the compound at a dose of 60 mg/day.

No deleterious changes in copulation or fertility were seen in the fertility studies in rats. No male-factor effects were exhibited in offspring of treated male rats. No increases in fetal mortality or malformation were seen in embryo-fetal development studies in pregnant female rats at up to 1,000 mg/kg and in pregnant female rabbits at up to 100 mg/kg. However, an additional embryo-fetal development study in pregnant female rabbits showed high fetal mortality and a marginal increase in malformations at 1,000 mg/kg/day. A prenatal and postnatal development study in rats showed increased perinatal death and body weight suppression during the lactation period and after weaning in the offspring at 1,000 mg/kg/day. Drug exposure in the rabbits based on area under the concentration-time curve (AUC) values of 3.882 and 16.924  $\mu\text{g}\cdot\text{h}/\text{mL}$  at doses of 100 and 1,000 mg/kg/day, respectively, was approximately 1.2- and 5.2-fold higher than the AUC value of 3.2376  $\mu\text{g}\cdot\text{h}/\text{mL}$  seen in man receiving a 60-mg/day dose. No genotoxicity of the compound was observed and no antigenicity was evident in guinea pigs. No increases in mortality and tumor incidence were seen in the 2-year carcinogenicity study in male mice at doses up to 60 mg/kg/day, in female mice at doses up to 100 mg/kg/day, and in rats at doses up to 1,000 mg/kg/day.

Exposure to metabolites present in humans (including DM-4103, which, while inactive at the AVP receptors, has the highest human exposure) was adequate in animal models for estimation of effects on toxicity, reproduction, and carcinogenicity. No evidence of long-term pharmacologic or toxicologic effects was seen.

Toxicology data suggested that tolvaptan may be safe in humans. No male-factor effects were seen; however, appropriate precautions should be implemented for the inclusion of women of childbearing potential in clinical trials. Additional information relating to

nonclinical studies conducted with tolvaptan can be found in the current version of the Investigator's Brochure (IB).<sup>14</sup>

### **1.1.1 Juvenile Animal Toxicity Data**

Six-week repeated oral dose toxicity study of tolvaptan was conducted in juvenile Sprague-Dawley rats (Crl:CD[SD], 25 days of age at the start of administration, 10 animals of each sex for 30 and 100 mg/kg groups, and 15 animals of each sex for the control and 1,000 mg/kg groups) at daily dose levels of 0 (1% [w/v] hypromellose solution), 30, 100, or 1,000 mg/kg. The reversibility of any effects was also assessed following a 4-week untreated recovery period using 5 animals of each sex in the control and 1,000 mg/kg groups. In addition, serum concentrations of tolvaptan and its 2 metabolites (DM-4103 and DM-4107) were determined after dosing on the first day (Day 1) and last day (Day 42) of administration. No deaths occurred during the administration or recovery period. No test article-related effects were noted in clinical observation, detailed clinical observation, sensory functional examination, or necropsy. Based on the above results, the no observed adverse effect level was judged to be 100 mg/kg/day for both males and females.<sup>14</sup>

A 1-week dose range-finding study was conducted in rat pups at 4 or 7 days of age and results showed tolvaptan to be lethal at 1000 mg/kg/day and tolerable at 100 mg/kg/day and lower.

In another study, male and female rat pups at 4 days of age were orally administered tolvaptan for 9 weeks at doses of 10, 30, and 100 mg/kg/day. Similar to the above study, pharmacologically mediated changes were noted in urine volume, water consumption, and urine electrolytes at all doses. Dilated renal pelvis considered to be attributable to increased urine volume during very early infancy was noted in males at 30 mg/kg/day and higher and females at 100 mg/kg/day. Toxicities were noted at 100 mg/kg/day, including death in one male, suppressed body weight gain and food consumption in males and females, and delayed balanopreputial separation and prolonged prothrombin time in males. Except for prolonged prothrombin time, all changes noted during the administration period showed reversibility after a 4-week recovery period. The no observed adverse effect level in both males and females was judged to be 30 mg/kg/day.<sup>14</sup>

### **1.2 Clinical Data**

Tolvaptan was approved by the United States (US) Food and Drug Administration (FDA) on 19 May 2009, by the European Medicines Agency (EMA) on 03 Aug 2009, and

subsequently in 10 other countries for the treatment of specific forms of hyponatremia. Tolvaptan was approved by the Japanese Ministry of Health, Labour, and Welfare on 27 Oct 2010 for the adjunct treatment of volume overload in HF when adequate response is not obtained with other diuretics; in September 2013 for body fluid retention in hepatic cirrhosis when adequate response is not obtained with other diuretics; and in March 2014 for suppression of progression of autosomal dominant polycystic kidney disease (ADPKD) with increased kidney volume and a rapid rate of increase. Phase 3 development for hepatic edema has been completed in China. Tolvaptan is also being developed for the treatment of ADPKD in the US and multinationally; for the adjunct treatment of chronic renal failure treated with peritoneal dialysis and hemodialysis or hemodiafiltration, for carcinomatous edema in Japan, and for cardiac edema in China and Taiwan. Tolvaptan, under the brand name Jinarc<sup>®</sup>, is approved to treat ADPKD in Canada and the European Union. As of 31 Mar 2015, the tolvaptan clinical development program consists of 105 trials; 97 trials had been completed worldwide, 4 trials were terminated because of slow enrollment, and 8 trials were ongoing. More information is available in the IB.<sup>14</sup>

### **1.2.1 Pharmacokinetics**

Since inception of the program, a total of 53 clinical pharmacology trials have been completed with tolvaptan (as of 31 Mar 2015) in healthy subjects or special populations in Japan, the United Kingdom, China, Korea, Argentina, and the US.

In healthy subjects, following IV dosing, the terminal-phase elimination half-life ( $t_{1/2,z}$ ) of tolvaptan is about 3 hours. Following single oral tablet doses, the  $t_{1/2,z}$  of tolvaptan increases with increasing dose with mean values around 3 hours for a 15-mg dose and 12 hours for 120- to 480-mg doses. Tolvaptan is very insoluble, with solubility being 0.00005 w/v% at 25°C and is pH independent. At lower doses, tolvaptan is mostly absorbed from the upper GI tract so the decline of the terminal portion of the concentration curve reflects elimination process only. With increasing dose, there is continued absorption of tolvaptan from the GI tract such that the rate of decline of the terminal portion of the concentration curve is reflective of both absorption and elimination processes.<sup>14</sup>

The limited early absorption of tolvaptan is exemplified by the fact that the maximum (peak) plasma concentration ( $C_{max}$ ) values show less than dose proportional increases from 30 to 240 mg and then a plateau at doses from 240 to 480 mg. Despite the changes in tolvaptan absorption, tolvaptan AUC values increase proportionally with increasing

dose and apparent clearance of drug from plasma after extravascular administration (CL/F) values are unchanged for single doses of 30 to 480 mg.<sup>14</sup>

Tolvaptan concentrations do not accumulate following once daily dosing. Following 300-mg doses,  $C_{max}$  and AUC during the dosing interval at steady state ( $AUC_{\tau}$ ) were only 4.2- and 6.4-fold higher, respectively, when compared with the 30-mg dose. This indicates bioavailability decreases with increasing dose. Mean (range) absolute bioavailability of tolvaptan when administered as a 30-mg tablet was 56% (42% to 80%).

In healthy subjects, tolvaptan pharmacokinetics following a 15 mg dose as a 1 mg/mL suspension shows a more rapid absorption (the median  $t_{max}$  is shorter, 1.00 versus 2.00 hours respectively), when compared to a 15 mg tablet. The geometric mean ratio (90% CI), for suspension over the tablet, for  $C_{max}$  is 1.614 (1.484 to 1.754) but AUC is unchanged.<sup>14</sup>

Trials in subjects with hyponatremia secondary to liver disease showed that following a single oral dose, tolvaptan concentrations increase dose proportionally from 5 to 60 mg. The clearance following single oral doses of tolvaptan was independent of the dose and similar to clearance in healthy subjects. Following multiple oral doses, tolvaptan concentrations accumulated 2-fold and clearance was decreased about 50%.<sup>14</sup>

Once a day dosage regimen trials in CHF subjects with extracellular volume expansion showed that tolvaptan concentrations increased less than proportionally with dose upon multiple dosing regimens (10, 15, 30, 60, 90, and 120 mg once daily for 13 days) in this subject population. The  $t_{1/2,z}$  and CL/F were unchanged across dose groups. Compared to healthy subjects, the disposition of tolvaptan is slower with longer  $t_{1/2,z}$  (7.8 to 11.1 hours) and smaller CL/F (0.9 to 3.3 mL/min/kg). The  $C_{max}$  was 2- to 2.5-fold greater than that of healthy subjects (at 60- and 90-mg doses). The median volume of distribution following extravascular administration of tolvaptan ranged from 1 to 2.5 L/kg and was not different from healthy subjects.

Tolvaptan is a sensitive substrate for cytochrome P450 (CYP) 3A4 and has no inhibitory activity at CYP3A4. Tolvaptan administration does not produce clinically significant changes in amiodarone, warfarin (or its 7-hydroxy and 10-hydroxy metabolites), lovastatin, furosemide, or hydrochlorothiazide plasma concentrations. Steady state digoxin concentrations were increased approximately 20% (as determined by  $AUC_{\tau}$ ).

When administered with the potent CYP3A4 inhibitor ketoconazole, the ketoconazole + tolvaptan/tolvaptan alone ratio for tolvaptan mean  $C_{max}$  and AUC from

time zero to infinity values were 3.48 and 5.40, respectively. Therefore, a 4-fold reduction in tolvaptan dose is recommended when initiating tolvaptan therapy in subjects using potent CYP3A4 inhibitors and a 2-fold reduction in tolvaptan dose is recommended for subjects using moderate CYP3A4 inhibitors. Lovastatin increases tolvaptan  $C_{max}$  by approximately 20% but CL/F is unchanged. Tolvaptan  $C_{max}$  and AUC calculated to the last observable concentration at time t (AUC<sub>t</sub>) are increased 1.9- and 1.6-fold, respectively, when tolvaptan is coadministered with grapefruit juice. Following coadministration with 600 mg once daily rifampin at steady state, tolvaptan  $C_{max}$  and AUC<sub>t</sub> are decreased 83% and 87%, respectively.

When 30- or 60-mg tablet doses were given following a standard high-fat, high-calorie meal, no clinically significant differences in urine output were observed.<sup>15</sup>

Following multiple oral doses, the tolvaptan metabolite DM-4103 was found to accumulate. This metabolite has no pharmacological activity and has shown an acceptable toxicity profile. The metabolite has not been shown to accumulate in nonclinical toxicokinetic studies; however, in a 26-week study in rats, DM-4103 plasma concentrations greater than those expected at the dose used in this trial revealed no evidence of time-dependent toxicological effects.<sup>14</sup>

### **1.2.2 Pharmacodynamics**

Tolvaptan increases urine excretion rate at concentrations around 20 ng/mL and maximal urine excretion rates are reached between 100 and 150 ng/mL. A single oral dose trial in healthy subjects using doses from 60 to 240 mg showed that there were 1) no further increases in urine excretion rate with doses beyond 180 mg; 2) no further increases in zero to 24 hour urine excretion with doses beyond 180 mg; and 3) as dose was increased, increases in urine excretion were sustained over time. Tolvaptan elevated electrolyte-free water clearance to a positive value, increased serum sodium and serum osmolality, and increased plasma AVP concentrations and renin activity, but no dose-related increases were observed for any other parameter.

When compared to a 15-mg spray-dried tablet, the pharmacodynamic profiles of urine excretion rate, cumulative urine volume, free water clearance, urine osmolality, and serum sodium were not different for 15-mg of the suspension.<sup>14</sup>

Details of the currently available PK/PD data for the compound are available in the IB.<sup>14</sup>

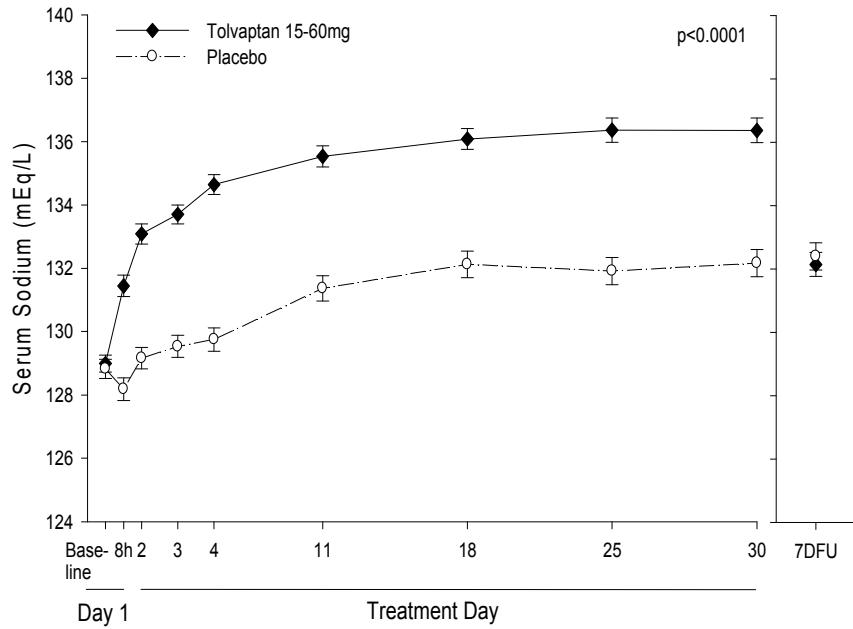
### 1.2.3 Clinical Efficacy

Thirteen trials involving either exclusive evaluation of adult subjects with hyponatremia (10 trials in which all subjects have hyponatremia and a long-term extension trial) or substantial subpopulations of subjects with hyponatremia (3 CHF trials - not all subjects in these trials had hyponatremia) have been conducted.

Briefly, in clinical trials, tolvaptan has consistently been shown to improve or normalize serum sodium concentrations in hyponatremic subjects, regardless of etiology. In clinical trials in subjects with volume overload and hyponatremia, the effect of tolvaptan on serum sodium is combined with a reduction in fluid overload, as shown by greater decreases in body weight compared to placebo. Additionally, subjects with liver disease responded to higher doses of tolvaptan with reductions in body weight.<sup>14</sup>

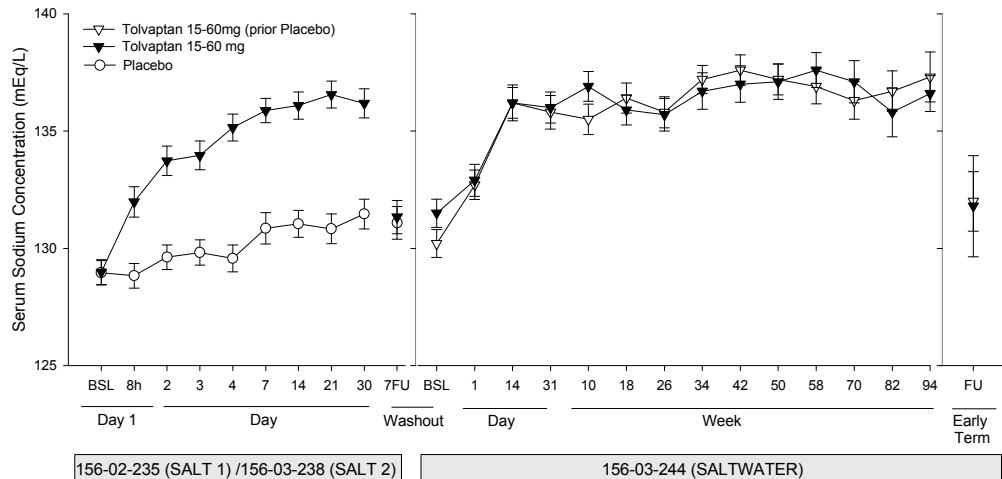
Data from two phase 3, multicenter, randomized, double-blind, placebo-controlled trials evaluating tolvaptan in euvolemic and hypervolemic hyponatremia subjects (Study of Ascending Levels of Tolvaptan in Hyponatremia [SALT] 1 and 2 trials) served as the basis for approval in the US and Europe. A total of 448 subjects were randomized in these trials (oral placebo n = 223 and tolvaptan n = 225) for a 30-day treatment period. The first single daily dose (15 mg) was monitored in-hospital with optional fluid restriction. Subjects were discharged and fluid intake and tolvaptan (30 or 60 mg) were titrated as clinically indicated.

The primary efficacy endpoints for the SALT 1 and 2 trials were the average daily AUC of change from baseline in serum sodium concentration up to Day 4 and up to Day 30. For both primary endpoints, the difference between the treatment groups were highly statistically significant ( $p < 0.0001$ ), and demonstrated that serum sodium concentrations increased more with tolvaptan than placebo over the first 4 days and the entire 30 days. Significance was seen in both mild and severe hyponatremia subgroups ( $p < 0.001$ ). When tolvaptan therapy was stopped, serum sodium concentrations fell to the level of placebo concentrations ([Figure 1.2.3-1](#)), but recovered upon resumption of tolvaptan therapy ([Figure 1.2.3-2](#)).



**Figure 1.2.3-1 Mean (Standard Error) Changes From Baseline in Serum Sodium Concentration Following Tolvaptan or Placebo Treatment for 30 Days and at 7 Days Following Withdrawal of Therapy (Trials 156-02-235 and 156-03-238 [SALT 1 and 2] Combined)**

7DFU = 7-day follow-up.



BSL = Baseline, 7FU = 7-day follow-up, FU = follow-up; SALTWATER = Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions.

**Figure 1.2.3-2**

**Mean (Standard Error) Serum Sodium Concentration Over Time From the Parent Trials (156-02-235 and 156-03-238 [SALT 1 and 2]) to the Open-label Extension Trial (156-03-244 [SALTWATER]); All Subjects (Observed Case)**

Details of the currently available efficacy data for tolvaptan are available in the IB.<sup>14</sup>

### 1.3 Known and Potential Risks and Benefits

As of 31 Mar 2015, pooled exposure data are available from 93 trials, including 7373 subjects worldwide who were exposed to oral doses of tolvaptan. The extent of exposure to oral tolvaptan by dose in the pooled database (N = 7373) comprises 3115 subjects in trials for heart failure (HF), 511 subjects in trials for hyponatremia, 961 subjects in the pivotal long-term ADPKD trial, 270 subjects in short-term trials for ADPKD or renal impairment, 437 subjects in trials for cardiac edema, 855 subjects in trials for hepatic edema 43 subjects in trials for chronic renal failure, 43 subjects in a trial for carcinomatous edema, 37 subjects with renal impairment in a phase 1 trial, and 1101 healthy subjects in clinical pharmacology trials. As of 31 Mar 2014, additionally, 14 healthy adult subjects were also exposed to the tolvaptan suspension formulation.<sup>14</sup>

The most commonly reported treatment-emergent adverse events (TEAEs; by > 10% incidence and greater than placebo) in healthy subjects treated with tolvaptan were thirst, pollakiuria, and headache. Headache was the most commonly reported TEAE in the placebo subjects.

The hyponatremia program comprised 835 subjects from 12 short-term trials involving either exclusive evaluation of subjects with hyponatremia (9 trials) or substantial subpopulations of subjects with hyponatremia (3 CHF trials). The 511 subjects in the hyponatremia trials were exposed to oral tolvaptan doses ranging from 5 to 60 mg, for a total of 8339 days of exposure. In the 9 hyponatremia trials, the most commonly reported TEAEs (> 5% incidence) in the tolvaptan subjects were thirst, dry mouth, peripheral oedema, nausea, dizziness, fatigue, constipation, headache, ascites, diarrhoea, pollakiuria, asthenia, hypotension, pyrexia, and hypokalaemia. The most commonly reported TEAE (> 5% incidence) in the placebo subjects were peripheral oedema, diarrhoea, headache, ascites, vomiting, dyspnoea, nausea, and hypotension. The IB provides a review of the adverse events (AEs) experienced with the spray-dried tablet and suspension formulation of tolvaptan during clinical trials.<sup>14</sup>

There is the potential for osmotic diarrhea due to the sorbitol content in the suspension. D-Sorbitol is a hexahydric sugar alcohol that naturally occurs in fruits and animal tissue. The daily per capita consumption of sorbitol as a food ingredient is approximately 200 mg. The compound is about 35-60% as sweet as sugar, and has been the impetus as a substitute for sugar to reduce caloric intake and prophylactic measures against the formation of dental caries. Absorption of sorbitol by humans is limited by its rate of diffusion from the GI tract and by laxation that may occur after ingestion of high doses. Typically, 25-50 g in adults may cause osmotic diarrhea. The corresponding dose in children is thought to be 10 g and higher, but is dependent on body weight and types of foods ingested. Similar findings are also observed with other sugar alcohols, eg, xylitol.<sup>16</sup>

Following a single 15 mg tolvaptan dose of the suspension, containing 8 g of sorbitol, in healthy adults, no diarrhea was reported.<sup>14</sup>

Therefore, in this trial, suspension dosing is limited to subjects who weigh  $\leq$  30 kg; the maximum dose of sorbitol is expected to be approximately 9.6 grams in a 0.6 mg/kg dose for a subject who weighs 30 kg. Subjects will be started on the lowest dose for their weight and titrated to higher doses as appropriate for their clinical condition. Subjects will be in a hospital setting during titration and will be closely monitored for rate of sodium correction and signs of dehydration including diarrhea.

Analyses of the completed 3-year pivotal Trial 156-04-251 (double-blind, placebo-controlled trial to determine long-term safety and efficacy of oral tolvaptan in adult subjects with ADPKD) have revealed new and important safety information. In this trial, a new signal for imbalanced elevations of liver transaminases in ADPKD subjects

receiving tolvaptan compared with placebo was detected and formally adjudicated by an expert panel blinded to treatment.

Based on the analyses of combined central and local laboratory data, a total of 3 tolvaptan subjects in the ADPKD program (2 in Trial 156-04-251 and one in the ongoing extension Trial 156-08-271) were identified as meeting Hy's Law laboratory criteria (ie, alanine transaminase [ALT] or aspartate transaminase [AST] > 3 times the upper limit of normal [ULN] accompanied by total bilirubin > 2 × ULN with the elevated total bilirubin occurring within 30 days after the transaminase elevation). Based on review of the data from the adjudicated subjects, the transaminase elevations associated with tolvaptan treatment were reversible (ie, returned to ≤ 3 × ULN typically within 1 to 4 months), and were not associated with fulminant liver failure, or permanent liver injury or dysfunction.

No association with tolvaptan dose or exposure was found. The results do not appear to suggest an association between tolvaptan and age or gender with respect to an increased risk of potential liver injury.

Retrospective evaluation of data from the hyponatremia and HF clinical development programs did not reveal an imbalance of subjects with elevated ALT between tolvaptan and placebo groups. In addition, no signal of tolvaptan-induced hepatotoxicity has been detected in the review of the postmarketing experience to date for any non-ADPKD indication. However, these data are not adequate to exclude the possibility that subjects treated with tolvaptan are at a potential increased risk for liver injury. Further details regarding this issue can be found in the IB.<sup>14</sup>

In clinical trials, tolvaptan consistently has shown a beneficial effect in hyponatremic subjects by improving serum sodium concentrations, in many cases to normalization. In subjects with HF, tolvaptan has consistently shown a beneficial effect by improving fluid balance through the induction of increased urine volume. In subjects with volume overload and hyponatremia receiving optimal standard HF therapy, the effect of tolvaptan on serum sodium is combined with a reduction in fluid overload, as shown by greater decreases in body weight as compared with placebo. In subjects hospitalized with worsening HF and symptoms of fluid overload, tolvaptan treatment, in addition to continued conventional therapy including diuretics, increased weight reduction, improved subject-assessed dyspnea and pedal edema, normalized serum sodium concentrations in subjects with hyponatremia, and maintained renal function in comparison to placebo.

Additional safety information can be found in the IB.<sup>14</sup> To date, no clinical trials in children have been completed with tolvaptan.

## 2 Trial Rationale and Objectives

### 2.1 Trial Rationale

The purpose of this trial is to establish the effects of tolvaptan on serum sodium concentration as well as the safety of use of tolvaptan in children and adolescents with euvolemic or hypervolemic hyponatremia secondary to [REDACTED] [REDACTED]. In addition, blood samples will be taken to determine tolvaptan PK specific to a pediatric population, as the absorption, distribution, metabolism, and elimination of drugs in children and adolescents can vary from that of adults. These differences can be due to differences in physiology based on maturity status (eg, GI transit times are faster, the ratio of total body water to body fat is shifting, and the expression of drug metabolizing enzymes change) or based on underlying disease state.<sup>17</sup> Hyponatremia alone does not appear to affect tolvaptan PK; however, tolvaptan exposure is 2-fold greater in adult subjects with CHF compared to healthy adult subjects and clearance appears to decrease about 50% in subjects with moderate to severe hepatic failure (Child-Pugh score > 6). As the primary pharmacodynamic effect of tolvaptan is to produce an increase in urine output (aquaresis), urine output and fluid intake will be determined as PD endpoints.<sup>14</sup>

The proposed population size of 100 subjects is expected to yield 70 subjects who respond to tolvaptan (henceforth termed “responders”), which has adequate power (> 90%) to test for statistical significance in the primary endpoint. Enrollment is expected to take approximately 3 years using approximately 60 sites globally. Additional blood sampling will be included across populations to provide PK information.

Even with a limited size, recruitment for such a trial is expected to be challenging due to the low frequency of AVP-mediated hyponatremia in children. Therefore, the trial will be organized at major pediatric referral centers to access the largest patient population.

It is recognized that the pediatric population is a vulnerable subgroup and there are risks in conducting a clinical trial in the pediatric population. However, given the possible serious and life-threatening consequences of untreated hyponatremia, it is necessary to study hyponatremia treatment in children. Children have different physiology and metabolisms from adults and, therefore, it is not sufficient to study hyponatremia treatment in the adult population to determine the proper course of treatment for hyponatremia in the pediatric population. A clear understanding of exposure-response in adults that can be applied to pediatrics (or from one pediatric group to another) has not yet been established, furthering the need for this trial.<sup>18</sup>

Every effort will be made to anticipate and reduce known risks. This trial was designed to minimize the number of participants and the number of procedures, consistent with good study design.<sup>19</sup> Children will be continuously monitored for signs of distress during this trial. The risk threshold for subjects will be constantly monitored by the investigator. A detailed list and description of the safety monitoring to be conducted during this trial can be found in Section 3.7.4.

### 2.1.1 Dosing Rationale

Enrolled subjects will be dosed based on formulation type, age, weight, and the use of CYP3A4 inhibitors.

In the pivotal hyponatremia trials<sup>14,20,21</sup> the starting 15-mg dose was administered to adult subjects weighing 34.0 to 164.7 kg; in terms of mg/kg, the starting dose of tolvaptan ranged from 0.09 to 0.44 mg/kg. The weight cutoffs for use of tolvaptan tablets in this trial were selected to produce mg/kg doses of tolvaptan within the range observed for the adult trials. Table 2.1.1-1 outlines the mg/kg dose ranges for tolvaptan tablet doses and body weights of 10, 20, 50, 70 (standard adult man), and 100 kg.

**Table 2.1.1-1 Starting Tolvaptan Tablet Doses as mg/kg of Body Weight**

Tolvaptan Tablets	Tolvaptan Doses as mg/kg				
	BW of 10 kg	BW of 20 kg	BW of 50 kg	BW of 70 kg	BW of 100 kg
3.75 mg	0.375	0.19	-	-	-
7.5 mg	-	0.375	0.15	-	-
15 mg	-	-	0.30	0.21	0.15

BW = body weight.

Tolvaptan is metabolized by the CYP3A isozyme. At birth, the amount of CYP3A per gram of liver is less than in an adult, but adult levels of CYP3A are reached by 2 years of age. A physiologically-based pharmacokinetic model of adult tolvaptan concentrations was modified to estimate tolvaptan concentrations in subjects from  $\geq 4$  weeks (or  $\geq 44$  weeks of adjusted gestational age) to  $< 2$  years of age and in subjects  $\geq 2$  to  $< 4$  years of age.<sup>22</sup> It was estimated that doses of 0.1 mg/kg and 0.15 mg/kg, respectively, of the suspension would produce peak tolvaptan concentrations similar to those produced by a 15 mg tablet in an adult subject. However, overall exposure for the suspension as determined by AUC would be 33% and 13% lower, respectively, for subjects  $< 2$  years of age and subjects  $\geq 2$  to  $< 4$  years of age when compared to a 15 mg tablet in an adult. It is expected that a 0.15 mg/kg starting dose of tolvaptan suspension would also be suitable for children  $> 4$  years of age, as CYP3A expression would be the same as for children  $\geq 2$  to 4 years of age. Suspension will only be administered to

children who weigh 30 kg or less to limit the amount of sorbitol administered; a 30 kg child titrated to a 0.6 mg/kg dose of tolvaptan suspension would receive 18 mL of tolvaptan suspension, containing approximately 9.6 g of sorbitol.

Tolvaptan is a sensitive CYP3A4 substrate; plasma concentrations increased approximately 4-fold when tolvaptan was administered with the potent CYP3A4 inhibitor ketoconazole.<sup>14,23</sup> Where appropriate dose reductions are possible, tolvaptan doses may be coadministered with potent or moderate CYP3A4 inhibitors. [Table 3.2.3-1](#) outlines starting dose adjustments when tolvaptan is administered concurrently with potent or moderate CYP3A4 inhibitors.

## **2.2 Trial Objectives**

### **2.2.1 Primary Objective**

The primary objective is to demonstrate that tolvaptan effectively and safely increases and maintains serum sodium concentrations in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.

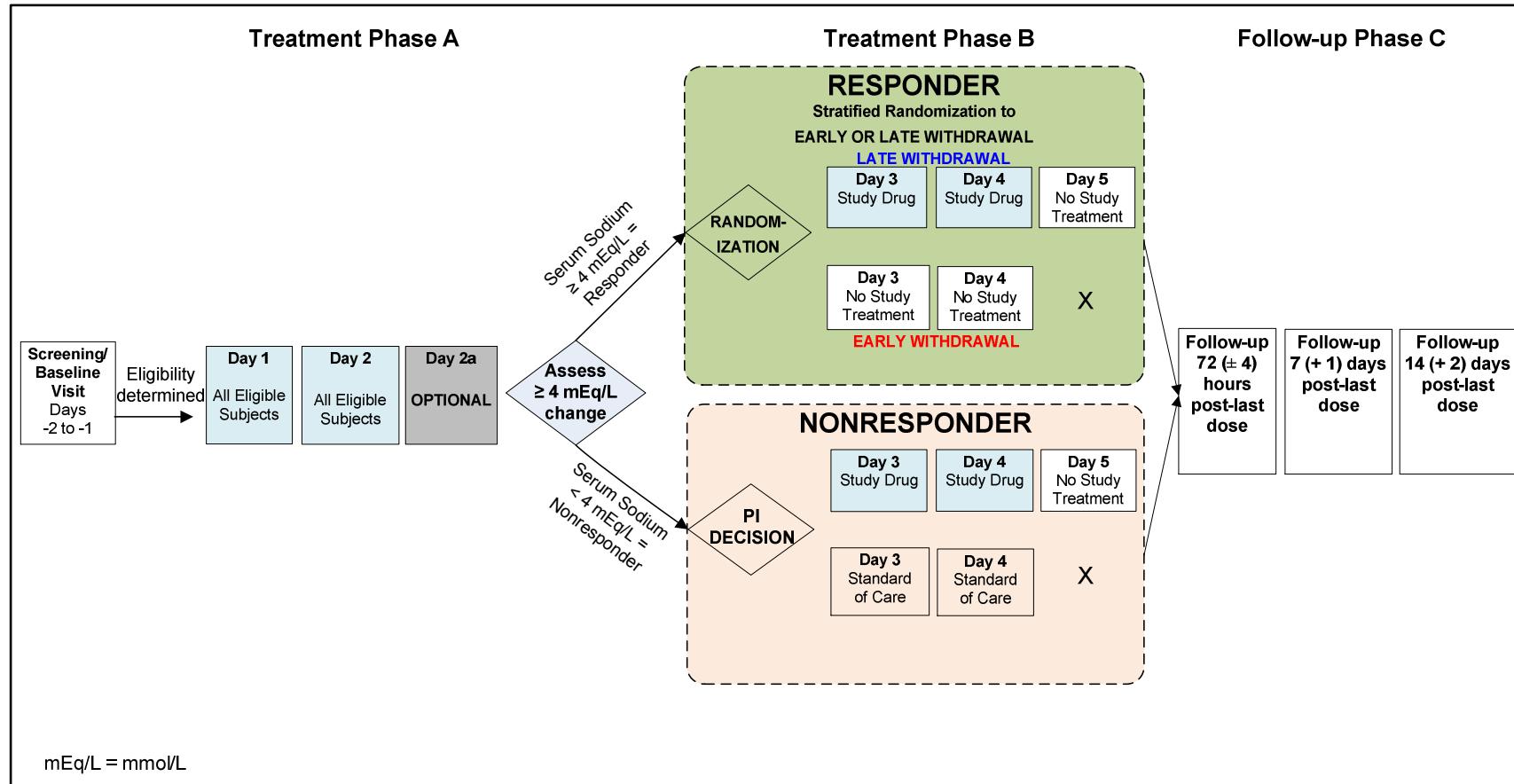
### **2.2.2 Secondary Objectives**

The key secondary objective is to assess the PK of tolvaptan and the effect on fluid balance in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.

## **3 Trial Design**

### **3.1 Type/Design of Trial**

This is an open-label, multicenter, multiple-dose, randomized withdrawal, parallel-group trial of tolvaptan in children and adolescents hospitalized with chronic euvolemic or hypervolemic hyponatremia (serum sodium < 130 mEq/L [mmol/L]) persisting despite initial standard therapy. A schematic of the trial design is provided in [Figure 3.1-1](#).



**PI = Principal investigator.**

### Figure 3.1-1 Trial Design Schematic

### **3.1.1 Trial Phases**

Screening should be performed on Days -2 to -1 to confirm eligibility, followed by the 3 trial phases described in [Section 3.7.1](#).

#### **3.1.1.1 Treatment Phase A**

All subjects will initially receive tolvaptan once daily on Days 1 and 2. If a subject's serum sodium level has not increased by at least 4 mEq/L (mmol/L) by Day 2, an additional day of treatment is required and is referred to as Day 2a. If subjects do not achieve an increase in serum sodium concentration of  $\geq 4$  mEq/L (mmol/L) on Day 2a, they will be defined as nonresponders. If subjects achieve an increase in serum sodium concentration of  $\geq 4$  mEq/L (mmol/L) on Day 2 (or 2a) they will be defined as responders.

#### **3.1.1.2 Treatment Phase B**

On Day 3 responders will be randomized ([Section 3.1.1.2.1](#)) to either the Early Withdrawal group or the Late Withdrawal group. Nonresponders will not be randomized.

For nonresponders from Treatment Phase A, the investigator will determine if the subject is to either:

- Continue treatment with study drug or
- Prescribe treatment per local standard of care for Days 3 and 4.

#### **3.1.1.2.1 Randomization**

Responders will be randomized to either:

- Late Withdrawal group - subjects continue tolvaptan treatment on Days 3 and 4
- Early Withdrawal group - subjects do not receive additional tolvaptan treatment on Days 3 and 4.

Randomization will be stratified by age [REDACTED] [REDACTED], serum sodium response [REDACTED], and underlying hyponatremia etiology [REDACTED].

Subjects randomized to the Early Withdrawal group will be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels. Subjects whose serum sodium declines by  $\geq 4$  mEq/L (mmol/L) or whose overall clinical condition requires further treatment to raise serum sodium levels should be treated per local standard of care. Any intervention intended to raise serum sodium concentration during the first 48 hours of the Early Withdrawal phase (including fluid restriction) will be defined as rescue therapy. Subjects receiving rescue therapy will be considered to

have reached their clinical endpoint, and their data will be censored from that time forward.

### **3.1.1.3 Follow-up Phase C**

All subjects will have an additional serum sodium measurement at 72 ( $\pm$  4) hours post-last dose and 7 (+ 1) days post-last dose. A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-last dose.

## **3.2 Trial Treatments**

### **3.2.1 Tablet Formulation**

Tolvaptan tablets will be administered orally once daily, preferably in the morning hours, with a dose proportional amount of water, as follows:

- Doses of  $\geq$  15 mg tolvaptan will be given with 240 mL of water.
- Doses of 7.5 mg tolvaptan will be given with 120 mL of water.
- Doses of 3.75 mg of tolvaptan will be given with 60 mL of water.

The treatment duration will be up to 5 days. Any initiation or titration of tolvaptan must occur in a hospital setting.

The maximum starting doses, by weight, age, and CYP3A inhibitor, for subjects are shown in [Table 3.2.3-1](#) and are within the range previously used in trials involving adult hyponatremic subjects.

The investigator has the option of performing a swallow test and providing coaching on swallowing techniques using placebo tablets if it is unknown if the subject is able to swallow tablets. Placebo tablets will be provided for use in performing this test during screening.

### **3.2.2 Suspension Formulation**

Tolvaptan suspension, 1 mg/mL (0.1% w/v), will be administered orally once daily, preferably in the morning hours. The treatment duration will be up to 5 days. Any initiation or titration of tolvaptan must occur in a hospital setting.

The maximum starting doses for subjects, by weight, age, and CYP3A inhibitor are shown in [Table 3.2.3-1](#).

### **3.2.3 Dosing Guidelines**

Subjects will be administered tolvaptan on a formulation, age- and weight-based scale.

**Table 3.2.3-1** outlines starting tolvaptan doses and adjustments when tolvaptan is administered concurrently with potent or moderate CYP3A inhibitors. Tolvaptan doses will be reduced 75% and 50% if a potent or moderate inhibitor, respectively, is being concurrently administered. As the smallest volume of suspension that can be administered is 0.3 mL (0.3 mg), subjects weighing < 3 kg, < 6 kg and taking a moderate or a potent CYP3A4 inhibitor, or weighing < 12 kg and taking a potent CYP3A4 inhibitor may not be enrolled. Suspension should be administered with the syringes provided.

<b>Table 3.2.3-1 Starting Tolvaptan Doses With or Without Potent or Moderate CYP3A Inhibitors</b>				
<b>Age/Weight</b>	<b>Can subject swallow a tablet?</b>	<b>Starting Dose: <u>No</u> CYP Inhibitor</b>	<b>Starting Dose: Moderate CYP Inhibitor</b>	<b>Starting Dose: Potent CYP Inhibitor</b>
≥ 4 wk (or ≥ 44 wk adjusted gestational age) to < 2 y AND ≥ 3 kg to < 6 kg <sup>c</sup>	N/A	0.1 mg/kg suspension <sup>a,b</sup>	Not eligible for treatment	Not eligible for treatment
≥ 4 wk (or ≥ 44 wk adjusted gestational age) to < 2 y AND ≥ 6 to < 12 kg <sup>c</sup>	N/A	0.1 mg/kg suspension <sup>a,b</sup>	0.05 mg/kg suspension	Not eligible for treatment
≥ 2 y to ≤ 6 y AND ≤ 30 kg <sup>c</sup>	N/A	0.15 mg/kg suspension	0.08 mg/kg suspension	0.04 mg/kg suspension
> 6 y AND ≤ 30 kg	No	0.15 mg/kg suspension	0.08 mg/kg suspension	0.04 mg/kg suspension
> 6 y AND 20 to 50 kg	Yes	7.5 mg tablet	3.75 mg tablet	1.90 mL suspension
> 6 y AND > 50 kg	Yes	15 mg tablet	7.5 mg tablet	3.75 mg tablet

<sup>a</sup> The smallest volume of suspension that may be administered is 0.3 mL (0.3 mg), therefore dose reductions cannot be accommodated for children < 6 kg taking moderate inhibitors and for children < 12 kg taking potent inhibitors.

<sup>b</sup> Tolvaptan suspension is provided in a concentration of 1 mg/mL.

<sup>c</sup> Suspension required (pediatric subjects ≤ 6 years of age and ≤ 30 kg body weight).

Titration of tolvaptan doses can occur once daily and will be based on serum sodium levels assessed at > 20 hours following initiation of therapy and each subsequent dose; titration may not occur within 24 (± 4) hours of the previous dose. Up-titration is limited to no more than twice the previous dose.

- Subjects ≥ 4 weeks (or ≥ 44 weeks adjusted gestational age) to < 2 years of age and weighing ≥ 3 kg to < 6 kg will receive 0.1 mg/kg of the suspension on Day 1 with possible up-titration to 0.2 mg/kg and 0.4 mg/kg doses.
- Subjects ≥ 4 weeks (or ≥ 44 weeks adjusted gestational age) to < 2 years of age and weighing ≥ 6 kg to < 12 kg will receive 0.1 mg/kg of the suspension on Day 1 with possible up-titration to 0.2 mg/kg and 0.4 mg/kg doses.

- Subjects  $\geq 2$  to  $\leq 6$  years of age, weighing  $\leq 30$  kg will receive a 0.15 mg/kg dose of the suspension on Day 1 with possible up-titration to 0.3 mg/kg and 0.6 mg/kg doses.
- Subjects  $> 6$  years of age, weighing  $\leq 30$  kg and who cannot safely swallow a tablet, will receive a 0.15 mg/kg dose of the suspension on Day 1 with possible up-titration to 0.3 mg/kg and 0.6 mg/kg doses.
- Subjects  $> 6$  years of age and weighing 20 to 50 kg, inclusive, will receive a 7.5 mg tablet on Day 1 with possible up-titration to 15-mg and 30-mg doses.
- Subjects  $> 6$  years of age and weighing  $> 50$  kg, will receive a 15 mg tablet on Day 1 with possible up-titration to 30-mg and 60-mg doses.

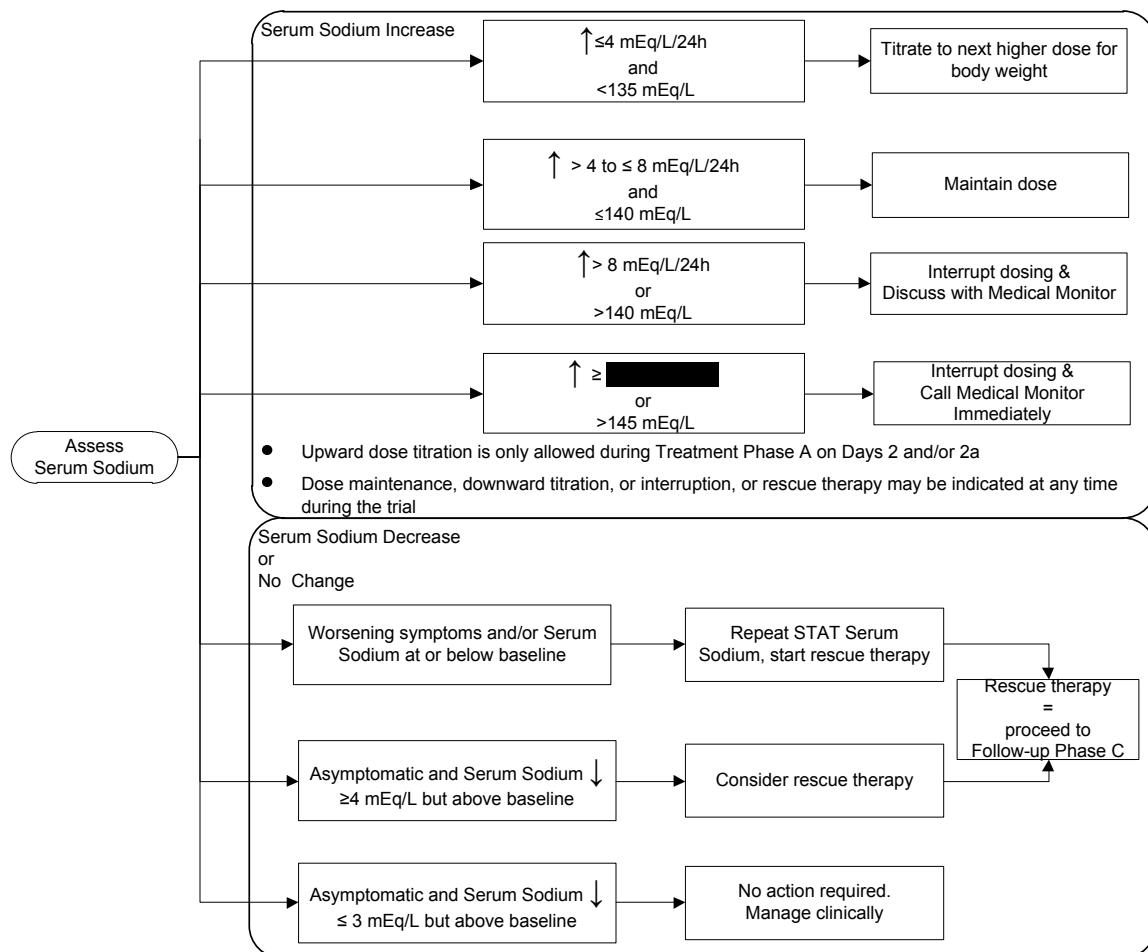
Following their initial tolvaptan dose in the trial, subjects will continue dosing according to the titration scheme (see [Section 3.2.4](#)), targeting a final serum sodium concentration between 135 and 140 mEq/L (mmol/L). Titration guidelines are designed to achieve a change in serum sodium concentration of at least 4 to 8 mEq/L (mmol/L)/24 hours but not [REDACTED].

### **3.2.4 Titration Guidelines and Rescue Therapy**

Initiation and titration of tolvaptan must occur in a hospital setting. Up titration can only take place on Treatment Day 2 (or 2a). Titration (up or down) may not occur within 20 hours of the previous dose. Up-titration is limited to no more than twice the previous dose.

The medical monitor should be contacted at any point if questions arise regarding titration or initiation of rescue therapy. The rationale for any up- or down-titration of tolvaptan must be documented. The evaluation of serum sodium levels, management of tolvaptan titration, and rescue therapy is described in [Figure 3.2.4-1](#).

Figure 3.2.4-1 Titration and Rescue Therapy Scheme



1 mEq/L = 1 mmol/L.

**Figure 3.2.4-1 Titration and Rescue Therapy Scheme**

### 3.2.4.1 Titration

Tolvaptan dose titration (after the initial dose) should be based on changes in serum sodium levels as follows:

- If the serum sodium level increases by  $\leq 4$  mEq/L (mmol/L)/24 hours and the subject is still below the therapeutic target for serum sodium level

(135 mEq/L [mmol/L]), then the tolvaptan dose may be titrated up to the next scheduled dose appropriate for the subject's body weight.

- If the serum sodium level increases  $> 4$  to  $\leq 8$  mEq/L (mmol/L)/24 hours in response to tolvaptan treatment and the serum sodium is  $\leq 140$  mEq/L (mmol/L), then the dose of tolvaptan should remain the same for the subsequent day.
- If the serum sodium level increases  $> 8$  mEq/L (mmol/L)/24 hours or reaches a concentration of  $> 140$  mEq/L (mmol/L), then the next dose of tolvaptan should not be given and the medical monitor should be contacted to consider options (ie, down-titration, tolvaptan interruption, concomitant medication adjustment, fluid supplementation and/or withdrawal).
- If serum sodium level increases by [REDACTED] following dosing, or, at any time after dosing, the serum sodium level is  $> 145$  mEq/L (mmol/L), the next dose of tolvaptan should not be given and the medical monitor should be contacted immediately to consider options.

### **3.2.4.2      Rescue Therapy**

Rescue therapy is defined as any treatment, eg, hypertonic saline, isotonic saline (with or without diuretic for purpose of increasing the serum sodium level), plasmapheresis/dialysis, demeclocycline, urea, lithium, or commercially available vaptans intended to raise the level of serum sodium during the trial. Subjects who develop worsening hyponatremia symptoms may receive rescue therapy at any time during the trial.

If at any point during the trial serum sodium levels or hyponatremia symptoms worsen or fail to improve adequately and definitive therapy (eg, isotonic or hypertonic saline) is required, the subject will be withdrawn from trial treatment to receive rescue therapy. Please see Section 4.2 for further details. These subjects will continue to Follow-up Phase C for collection of safety information.

Additional guidelines for rescue therapy concerning hyponatremia symptoms and decreasing serum sodium level:

- If a subject has worsening symptoms and/or has a serum sodium level at or below the baseline value, repeat serum sodium [STAT] to confirm level, and begin rescue therapy.
- If a subject is asymptomatic and serum sodium has decreased by  $\geq 4$  mEq/L (mmol/L), but is still above the baseline value, consider need for rescue therapy according to local standard of care.
- If a subject is asymptomatic and serum sodium has decreased by  $\leq 3$  mEq/L (mmol/L), but is still above the baseline value, no action is required.

Subjects who are randomized to the Early Withdrawal group will initially be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels. For those subjects whose serum sodium declines by  $\geq 4$  mEq/L (mmol/L) or whose overall clinical condition requires further treatment to increase serum sodium, the investigator may consider rescue therapy per local standard of care. Any intervention intended to raise serum sodium level during the first 48 hours in the responder Early Withdrawal group (including fluid restriction) will be defined as rescue therapy. These subjects will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.

Subjects randomized to the Late Withdrawal group who receive rescue therapy will be considered treatment failures. A subject requiring rescue therapy at any time after starting tolvaptan will be discontinued from trial treatment and will proceed to Follow-up Phase C.

### **3.2.4.3 Fluid Restriction Considerations**

In subjects with chronic hyponatremia, fluid restriction coadministered with initiation of treatment with a vaptan has the potential to accentuate the rate of sodium correction and to cause overly rapid correction or over correction of hyponatremia. Therefore, during treatment, subjects must have access to water and maintain fluid intake levels per institutional guidelines. Fluid restriction at any time during the trial including during the first 48 hours after discontinuation of tolvaptan will be considered rescue therapy.

## **3.3 Trial Population**

This trial will include approximately 100 male and female subjects aged  $\geq 4$  weeks (or  $\geq 44$  weeks adjusted gestational age) to  $< 18$  years who have been diagnosed with euvolemic or hypervolemic hyponatremia ( $< 130$  mEq/L [mmol/L]) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). Age groups will be enrolled such that at least 50% of these subjects will be  $< 10$  years old and at least 25% of subjects  $< 6$  years old. Subjects who are defined as responders will be further stratified by the magnitude of serum sodium response to tolvaptan ( $\leq 7$  and  $> 7$  mEq/L [mmol/L]), age, and underlying etiology of hyponatremia.

### Hyponatremia Etiology in Children and Adolescents

Children with Factor V Leiden or Factor VII abnormalities may be eligible for treatment only if the benefit is judged to outweigh any risk. Tolvaptan may be administered to children with hepatocellular disease (including cirrhosis) who have platelet counts

between 50,000 and 100,000/ $\mu$ L if the need to treat is felt to outweigh the increased risk of GI bleeding.

Children can develop symptomatic hyponatremia more frequently than adults and at less severe levels of hyponatremia because of the large brain volumes in relatively small skulls. The most serious consequence of hyponatremia is hyponatremic encephalopathy, which occurs in over 50% of children with serum sodium < 125 mmol/L.<sup>24</sup>

Hyponatremic encephalopathy is seen in hospitalized children and adolescents in association with SIADH or in the postoperative period. Hyponatremic encephalopathy is a medical emergency that requires immediate intervention;<sup>25,26,27</sup> thus, subjects with known risk factors for developing hyponatremic encephalopathy may be ineligible for tolvaptan treatment (eg, hypoxia, infection, brain injury, neurosurgery, uncontrolled seizure disorders, cerebritis, encephalopathy, central nervous system disorders such as cytotoxic and vasogenic cerebral edema, unstable space-occupying brain lesion, or elevated AVP levels).

Symptoms include headache, nausea and vomiting, weakness, confusion, altered consciousness, and lethargy and may progress to more advanced symptoms, including seizures, coma, and death, if untreated. Subjects with overt symptoms of hyponatremia that require immediate intervention to raise serum sodium acutely will be ineligible for tolvaptan treatment; this syndrome is rapidly reversible with hypertonic saline administration.

Additionally, those subjects who are at risk of developing cerebral demyelination will be ineligible for tolvaptan treatment, including subjects who have severe hyponatremia  $\leq$  120 mEq/L (mmol/L), hypernatremia, hypoxemia, severe liver disease, alcoholism, severe burns, severe malnutrition, hypokalemia, diabetes, or renal failure.<sup>24,25</sup>

Subjects eligible for treatment with tolvaptan will be identified based on serum sodium concentrations that persist at levels  $<$  130 mEq/L (mmol/L). Upon determination of eligibility, each subject's serum sodium will be reassessed just before tolvaptan administration to confirm it remains below this threshold prior to intended treatment initiation.

If any serum sodium value obtained during the pretreatment baseline period for tolvaptan treatment is  $\geq$  130 mEq/L (mmol/L), the subject will be ineligible for tolvaptan administration at that time.

Sorbitol is metabolized to fructose.<sup>28</sup> Subjects who have hereditary fructose intolerance (HFI) who continue to ingest fructose containing products can develop hepatic and renal

dysfunction.<sup>29</sup> The tolvaptan suspension formulation contains sorbitol. Therefore, children who have HFI should not take the tolvaptan suspension formulation.

Hereditary fructose intolerance is typically diagnosed in young children upon the introduction of solid foods containing fructose, sucrose and/or sorbitol (eg, fruits and vegetables). It is not commonly diagnosed in children who are fed exclusively on breast milk. Clinical symptoms can include vomiting, nausea, restlessness, pallor, sweating, lethargy, coagulation disturbances and in some cases, apathy, coma, and convulsions. Laboratory abnormalities may include signs of acute liver failure (eg, elevated serum transaminases, hyperbilirubinemia, abnormal blood clotting factors) or renal failure (eg, proteinuria, generalized hyperaminoaciduria, metabolic acidosis). Continued exposure to fructose can result in hypoglycemia, hepatomegaly, jaundice, steatosis, coagulation disturbances, edema, ascites and signs of proximal renal tubular dysfunction. If HFI is suspected, a thorough history that emphasizes nutritional complaints including the timing of the introduction of fruits and vegetables to the diet should be obtained as well as the appropriate laboratory assessment for confirmation of diagnosis.<sup>29</sup>

For children aged > 2 years, a detailed history with regard to HFI symptoms has to be taken prior to trial entry.

### **3.3.1 Subject Eligibility by Hyponatremia Etiology**

#### **3.3.1.1 General Guidelines**

Investigators should assess subjects' appropriateness to receive tolvaptan. Investigators should ultimately use their medical judgment to make the final determination. It remains the responsibility of the investigator to determine the etiology of hyponatremia and to assess the volume status for each subject using diagnostic tests (eg, fractional excretion of sodium [FENa], fractional excretion of urea [FE urea], urine osmolality, serum osmolality) employed in the usual clinical course of care.

#### **3.3.1.2 Specific Guidelines by Etiology**

- Subjects diagnosed with hyponatremia secondary to SIADH will be evaluated specifically to ensure appropriate volume status. Hypovolemic states are not compatible with tolvaptan administration. Plasma and urine sodium, potassium, creatinine, and urea should be assessed in order to calculate and evaluate FENa and FE urea prior to dosing to ensure safety of tolvaptan administration.
- For hyponatremia due to hepatocellular disease (including cirrhosis), in addition to the above guidelines, the underlying etiology of hepatocellular disease must be documented.
- For hyponatremia due to HF:
  - 1) A definitive diagnosis of HF by a cardiologist must be documented.

2) Loop diuretic use should be assessed and minimized where possible. Steady doses of diuretics are acceptable. Thiazide diuretics must be stopped before tolvaptan administration; the time that these medications must be stopped prior to the first tolvaptan dose depends on the half-life of the diuretic. At least 1 day or a minimum of 3 half-lives are required for washout.

The medical monitor should be contacted if there are questions. The guidelines listed in [Table 3.3.1.2-1](#) are to help guide the medical judgment of the investigator.

<b>Table 3.3.1.2-1      Screening Algorithms by Hyponatremia Etiology</b>	
<b>Etiology</b>	<b>Instruction</b>
All etiologies	Two documented serum sodium assessments of < 130 mEq/L (mmol/L) at least 12 hours apart
	One serum sodium assessment of < 130 mEq/L (mmol/L) within 2-4 hours prior to tolvaptan administration
	Screen subjects for AKI criteria per exclusion criteria
	Collect labs <sup>a</sup>
	Calculate serum osmolality, FENa, and FE urea at pretreatment baseline only
HF	Cardiologist documented diagnosis of HF
	Discontinue or stabilize diuretic use prior to tolvaptan administration
Hepatocellular disease (including cirrhosis)	The underlying etiology of hepatocellular disease must be documented

AKI = acute kidney injury.

<sup>a</sup>Refer to [Table 3.7.4.2.3-1](#) for complete lists of laboratory assessments.

## 3.4      Eligibility Criteria

### 3.4.1      Informed Consent/Accent

Written informed consent and assent, as appropriate, will be freely obtained from the subject's parent/legal guardian or legally acceptable representative, as applicable for local laws, in accordance with requirements of the trial center's institutional review board/independent ethics committee (IRB/IEC). The subject, as required by the trial center's IRB/IEC, must provide informed assent at screening and as such must be able to understand that he or she can withdraw from the trial at any time.

Age-appropriate assent documents will be created and subjects who are able will be required to reconsent or assent as appropriate if they matriculate from one age group to another. Subjects who became legal adults during the trial will be required to provide written informed consent as soon as they reach legal age.

Consent and assent will be documented on a written informed consent form (ICF). The ICF will be approved by the same IRB/IEC that approves this protocol. Each ICF will comply with the International Conference on Harmonisation (ICH) Good Clinical

Practice (GCP) Guideline<sup>30</sup> and local regulatory requirements. The investigator will review any written ICF/assent used in the trial, prior to submission to the IRB/IEC.

Investigators may discuss trial availability and the possibility for entry with a potential subject and his/her family without first obtaining consent and assent, as applicable. However, informed consent/assent (as applicable) must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Once appropriate essential information has been provided and fully explained in layman's language to the subject and his/her parent/legal guardian or legally acceptable representative by the investigator (or a qualified designee), the IRB/IEC-approved written ICF will be signed and dated by both the subject's parent/legal guardian or legally acceptable representative and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. In addition, the subject, as required by the trial center's IRB/IEC, must provide informed assent by signing the appropriate form for their age group. The subject's parent/legal guardian or legally acceptable representative will receive a copy of the signed ICF and assent form (as applicable); the originals shall be kept on file by the investigator.

Subjects' parents/legal guardian(s) or legally acceptable representative(s) may be asked to sign additional ICFs if the protocol is amended to significantly add or change procedures. Subjects who are able may be asked to re-assent as appropriate if the protocol is amended to significantly add or change procedures.

### 3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in [Table 3.4.2-1](#).

<b>Table 3.4.2-1 Inclusion Criteria</b>	
1.	Male and female subjects $\geq$ 4 weeks (or $\geq$ 44 weeks adjusted gestational age) to $<$ 18 years old
2.	Subjects hospitalized with euvolemic or hypervolemic hyponatremia resistant to initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist) and who are deemed by the investigator as likely to benefit from a therapy that raises serum sodium levels
3.	Persistent euvolemic or hypervolemic hyponatremia defined as being documented as present for at least 48 hours, evidenced by at least 2 serum sodium assessments $<$ 130 mEq/L (mmol/L) drawn at least 12 hours apart (these values can be documented using historical values previously obtained per standard of care); a third (STAT) serum sodium assessment $<$ 130 mEq/L (mmol/L), which will serve as the baseline value for final trial qualification and clinical management strategy, is to be obtained within 2-4 hours prior to the first dose of tolvaptan
4.	Ability to take oral medication
5.	Ability to maintain adequate fluid intake whether orally or via IV support with adequate monitoring
6.	Ability to comply with all requirements of the trial
7.	Trial-specific written informed consent/assent obtained from a parent/legal guardian or legally acceptable representative, as applicable per age of subject or local laws, prior to the initiation of any protocol-required procedures. In addition, the subject as required by local laws must provide informed assent at Screening and must be able to understand that he or she can withdraw from the trial at any time. All informed consent/assent procedures must be in accordance with the trial center's IRB/IEC and local regulatory requirements
8.	Ability to commit to remain fully abstinent (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] or withdrawal are not acceptable methods of contraception) or practice double-barrier birth control during the trial and for 30 days following the last dose of IMP for sexually active females of childbearing potential

IMP = investigational medicinal product.

### 3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in [Table 3.4.3-1](#).

<b>Table 3.4.3-1 Exclusion Criteria</b>	
1.	Has evidence of hypovolemia or intravascular volume depletion (eg, hypotension, clinical evidence of volume depletion, response to saline challenge); if the subject has systolic blood pressure or heart rate outside of the normal range for that age volume status should be specifically clinically assessed to rule out volume depletion.
2.	Has serum sodium $<$ 120 mEq/L (mmol/L), with or without associated neurologic impairment (ie, symptoms such as apathy, confusion, or seizures)
3.	Current use or expected use during the trial of a potent CYP3A4 inhibitor in subjects weighing $<$ 12 kg or a moderate CYP3A4 inhibitor in subjects weighing $<$ 6 kg
4.	Lacks free access to water (inability to respond to thirst) or without ICU-level fluid monitoring and management
5.	Has a history or current diagnosis of nephrotic syndrome
6.	Has transient hyponatremia likely to resolve (eg, head trauma or post-operative state)
7.	Has hyperkalemia defined as serum potassium above the ULN for the appropriate pediatric age range

**Table 3.4.3-1      Exclusion Criteria**

<b>Table 3.4.3-1</b> <b>Exclusion Criteria</b>	
8.	Has eGFR < 30 mL/min/1.73 m <sup>2</sup> calculated by the following equation: eGFR (mL/min/1.73 m <sup>2</sup> ) = 0.413 × height (cm)/serum creatinine (mg/dL)
9.	Has AKI defined as: <ul style="list-style-type: none"> <li>• Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours; or</li> <li>• Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or</li> <li>• Urine volume &lt; 0.5 mL/kg/h for 6 hours</li> </ul>
10.	Has severe or acute neurological symptoms requiring other intervention (eg, hyperemesis, obtundation, seizures)
11.	Has had treatment for hyponatremia with: <ul style="list-style-type: none"> <li>• Hypertonic saline (including normal saline challenge) within 8 hours of qualifying serum sodium assessments;</li> <li>• Urea, lithium, demeclocycline, conivaptan, or tolvaptan within 4 days of qualifying serum sodium assessments;</li> <li>• Other treatment for the purpose of increasing serum sodium concurrent with dosing of trial medication</li> </ul>
12.	Has anuria or urinary outflow obstruction, unless the subject is, or can be, catheterized during the trial
13.	Has a history of drug or medication abuse within 3 months prior to Screening or current alcohol abuse
14.	Has a history of hypersensitivity and/or idiosyncratic reaction to benzazepine or benzazepine derivatives (such as benazepril)
15.	Has psychogenic polydipsia (subjects with other psychiatric illness may be included per medical monitor approval)
16.	Has uncontrolled diabetes mellitus, defined as fasting glucose > 300 mg/dL (16.7 mEq/L [mmol/L])
17.	Has screening liver function values > 3 × ULN
18.	Subjects who have cirrhosis and meet any of the following conditions: a major GI bleed within the past 6 months, evidence of active bleeding (eg, epistaxis, petechiae/purpura, hematuria, or hematochezia), platelet count < 50,000/µL, or use of concomitant medications known to increase bleeding risk
19.	Has hyponatremia due to the result of any medication that can safely be withdrawn (eg, thiazide diuretics)
20.	Has hyponatremia (eg, hyponatremia in the setting of adrenal insufficiency, untreated hypothyroidism, or hypotonic fluid administration) that is most appropriately corrected by alternative therapies
21.	Is currently pregnant or breastfeeding
22.	Has any medical condition that, in the opinion of the investigator, could interfere with evaluation of the trial objectives or safety of the subjects.
23.	Is deemed unsuitable for trial participation in the opinion of the investigator
24.	Participation in another investigational drug trial within the past 30 days, without prior approval from the sponsor medical monitor
25.	Subjects who weigh < 3 kg
26.	Unable to swallow tablets if the suspension formulation is unavailable
27.	Subjects who require the suspension formulation and have Hereditary Fructose Intolerance

eGFR = estimated glomerular filtration rate; ICU = intensive care unit.

Use of the suspension formulation is at the discretion of the local regulatory authorities and IRB/IECs.

### **3.5      Outcome Variables**

#### **3.5.1      Primary Efficacy Outcome Variable**

For subjects with serum sodium level increases of  $\geq 4$  mEq/L (mmol/L) (ie, responders), change in serum sodium concentration from Day 2 (or 2a) at the end of Treatment Phase A to the end of Treatment Phase B for Early compared to Late Withdrawal groups.

#### **3.5.2      Key Secondary Efficacy Outcome Variable**

For all subjects, the key secondary endpoint is the change in serum sodium concentration at the end of Day 2 (or 2a) in Treatment Phase A from baseline.

#### **3.5.3      Other Secondary Outcome Variables**

##### **3.5.3.1      Safety Variables**

The safety endpoints for all subjects include:

- Percentage of subjects with overly rapid increase in serum sodium level  
[REDACTED])
- Change in serum sodium level from 24 hours post-last dose to 7 days post-last dose
- Percentage of subjects requiring rescue therapy (other than fluid restriction) during Treatment Phase A and Treatment Phase B
- Percentage of subjects requiring fluid restriction during Treatment Phase A and Treatment Phase B
- Vital signs, blood pressure, clinical laboratory tests, body weight, and neurological examinations

##### **3.5.3.2      Pharmacokinetic Variables**

Pharmacokinetic endpoints are tolvaptan  $C_{max}$ , time to maximum (peak) plasma concentration ( $t_{max}$ ), and AUC from time zero to 24 hours ( $AUC_{0-24h}$ ) on Day 1.

##### **3.5.3.3      Pharmacodynamic Variables**

Pharmacodynamic endpoints are fluid intake, urine output, and fluid balance (intake minus output) every 6 hours on Days 1 and 2 in Treatment Phase A.

#### **3.5.4      Exploratory Variables**

- Efficacy will be assessed in nonresponders continuing on tolvaptan therapy by change from baseline in serum sodium concentration at the end of Treatment Phase B compared to the end of Treatment Phase A

- In all subjects, 24-hour excretion of sodium, creatinine, and urine osmolality on Days 1 and 2
- 24-hour sodium clearance on Day 1
- Quality of life (QoL) assessments

### **3.6 Measures to Minimize/Avoid Bias**

This is an open-label trial. Subjects defined as responders from Treatment Phase A will be randomized to either the Early Withdrawal group or the Late Withdrawal group in Treatment Phase B. Treatment assignments for Treatment Phase B will be based on a computer-generated randomization code provided by Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) Biometrics Department.

### **3.7 Trial Procedures**

Treatment in this trial will last up to 5 days. Any initiation or titration of tolvaptan must occur in a hospital setting. Parent(s)/legal guardian(s) or legally acceptable representative(s) must provide informed consent and subjects must provide informed assent (as appropriate) and be screened 1 or 2 days prior to dosing.

In Treatment Phase A, subjects who meet the inclusion and exclusion criteria will be enrolled and will be administered tolvaptan doses based on age, weight, ability to swallow a tablet, and the use of CYP3A4 inhibitors. At the end of Day 2 (or 2a) in Treatment Phase A, subjects who are responders will be randomized to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early Withdrawal).

In Treatment Phase B, subjects who are nonresponders may continue on tolvaptan therapy for 2 additional days or may be withdrawn from tolvaptan to be treated per the investigator's preferred standard of care. During Treatment Phase B, subjects in the Late Withdrawal group and nonresponders continuing treatment will continue to receive tolvaptan for 2 additional days and all subjects will have serum sodium levels measured at 12 ( $\pm$  4) hours postdose and at trough (24 [ $\pm$  4] hours post-previous dose) each day. Subjects in the Early Withdrawal group should be monitored for the first 48 hours post-last dose.

In Follow-up Phase C, all subjects will be monitored and will have an additional serum sodium measurement at 72 ( $\pm$  4) hours post-last dose as well as at 7 (+ 1) days post-last dose. A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-last dose.

Trial assessment time points are summarized in [Table 3.7-1](#). [Section 3.7.1](#) provides a flow overview that describes the sequence of assessments during a visit. [Section 3.7.2](#) provides details around efficacy assessments, [Section 3.7.3](#) provides details around pharmacokinetic/pharmacodynamic assessments and [Section 3.7.4](#) provides details around safety assessments.

Pharmacokinetic samples will be obtained for all subjects on Day 1 at 2 and 8 hours post-first dose and at trough (24 [ $\pm$  4] hours post-previous dose) on Days 1, 2, 3, and 4 for all subjects dosed with tolvaptan on Days 1, 2, 3, and 4, respectively, regardless of responder status. Once adequate PK data are obtained, PK sampling will be discontinued for all subjects.

Subjects will be required to be in a hospital setting during initiation or titration of tolvaptan. A subject is allowed to be discharged, if they:

- 1) Continue to come to the clinic for daily study assessments and
- 2) Are either:
  - a) A nonresponder on standard of care or
  - b) On a stable dose of study drug, or
  - c) In the early withdrawal group without study treatment.

Follow-up for all subjects may occur in the hospital if the subject has not been discharged or the subject may return for outpatient visits if the subject has been discharged from the hospital.

Procedures	Screening	Treatment Phase A			Treatment Phase B			Follow-up Phase C			
	Day -2 to -1	Day 1	Day 2	Day 2a (optional)	Day 3	Day 4	Day 5 <sup>a</sup>	72 ( $\pm 4$ ) h post last dose	7 (+1) days post-last dose	14 (+2) days post-last dose	Early Termination (ET)
Informed Consent/Assent	X										
Inclusion/exclusion criteria <sup>b</sup>	X	X									
Demographic information	X										
Medical and hyponatremia history	X										
Vital signs <sup>c</sup>	X	X	X	X	X	X	X	X	X		X
12-lead ECG	X										
Height <sup>d</sup>	X										
Body weight <sup>d,e</sup>	X	X	X	X	X	X	X	X	X		X
Physical examination <sup>f</sup>	X	X	X	X	X	X		X	X		X
Tanner staging	X										
Neurological examination	X	X <sup>g</sup>	X		X	X		X	X		X
Clinical status <sup>h</sup> assessment	X	X	X	X	X	X		X	X		X
Quality of life assessment	X					X			X		
Alcohol/drug screen <sup>i</sup>	X										
Pregnancy test (if applicable) <sup>j</sup>	X								X		
Fluid intake <sup>k</sup>		X	X								
Urine volume <sup>l</sup>		X	X								
Urinalysis	X							X			X
Urine chemistry <sup>k,l</sup>	X	X	X								
Serum sodium <sup>m</sup>	X	X	X	X	X	X		X	X		X

Procedures	Screening	Treatment Phase A			Treatment Phase B			Follow-up Phase C			
	Day -2 to -1	Day 1	Day 2	Day 2a (optional)	Day 3	Day 4	Day 5 <sup>a</sup>	72 ( $\pm 4$ ) h post last dose	7 (+1) days post-last dose	14 (+2) days post-last dose	Early Termination (ET)
Hematology, coagulation, and serum chemistry <sup>n</sup>	X							X			X
Serum osmolality, FENa, and FE urea	X										
TSH and cortisol <sup>o</sup>	X										
PK plasma samples <sup>p</sup>		X	X		X	X					X
Tolvaptan dosing <sup>q</sup>		X	X	X	X	X					
Swallow test	X <sup>r</sup>										
Assessment for response to tolvaptan			X	X							
Palatability and acceptability assessment			X								
Randomization					X						
Follow-up phone call or visit										X	
Vital status <sup>s</sup>											X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

ECG = electrocardiogram; eCRF = electronic case report form; TSH = thyroid-stimulating hormone.

<sup>a</sup>The Day 5 visit is only for Late Withdrawal subjects and nonresponders continuing on tolvaptan treatment.

<sup>b</sup>Inclusion/exclusion criteria will be checked at screening and predose on Day 1.

<sup>c</sup>Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for  $\geq 3$  minutes and prior to any blood draws. Vital signs are to be assessed at 4 hours and 8 hours postdose on Day 1 and, on Days 2 through 4, at trough (24 [ $\pm 4$ ] hours post-previous dose, but prior to the next dose).

<sup>d</sup>Record growth percentiles at screening only.

<sup>e</sup>Weight will be taken predose.

<sup>f</sup>The initial physical examination should be a full physical. Subsequent physical examinations can be directed physical examinations that are focused on hyponatremia-related signs and symptoms as well as any major changes from baseline. A physical examination should include a fontanelle assessment as age appropriate.

<sup>g</sup>A neurological examination will be performed predose and at 8 hours post-first dose.

<sup>h</sup>Clinical status assessment must be performed predose on Day 1. It is preferred that clinical status assessments be performed predose during subsequent visits. Clinical status assessments will be performed per inpatient standard of care, ie, review subject chart entries (including hyponatremia assessment notes and laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate overall subject eligibility in terms of hyponatremia state. Volume status will be assessed every 6 hours prior to trial entry and every 6 hours during Treatment Phase A.

<sup>i</sup>Alcohol/drug screen is performed per clinical judgment and institutional guidelines.

<sup>j</sup>A serum or urine pregnancy test will be performed on female subjects  $\geq$  12 years of age and all female subjects  $<$  12 years of age if menstruation has started. In the case of a positive urine pregnancy test result, a serum pregnancy test will be performed as confirmatory.

<sup>k</sup>Intervals starting immediately after dosing at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).

<sup>l</sup>Samples within a collection interval are to be refrigerated and pooled. An aliquot for urine chemistry tests will be taken for each collection interval. Urine urea is to be measured at screening only.

<sup>m</sup>Serum sodium assessments are closely tied to dosing time points and PK blood draws.

- Screening: 2 assessments should be taken, at least 12 hours apart (may be part of medical history). One assessment can be combined with the serum chemistry panel.
- Treatment Phase A: Baseline (STAT) assessment will be within 2-4 hours prior to first dose. Post-first dose assessments: 8 (-1 to + 0.25) hours and trough (24 [ $\pm$  4] hours postdose [STAT assessment]). Then every 12 ( $\pm$  4) hours thereafter (alternating 12 hours postdose and at trough [24 ( $\pm$  4) hours postdose; STAT assessment])
- Treatment Phase B: Assessments to be taken every 12 ( $\pm$  4) hours (alternating 12 hours postdose and at trough [24 ( $\pm$  4) hours postdose; STAT assessment])
- Treatment Phase C: Assessments to be taken at 72 ( $\pm$  4) hours post-last dose (can be combined with the serum chemistry panel) and at the 7 (+1) days post-last dose visit.

In addition to serum sodium samples obtained for trial qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point of care sodium assessment unit, where available, on Day 1 at 4 to 6 hours postdose and at 18 ( $\pm$  1) hours postdose, and on Day 2 (and Day 2a, if applicable) at 6 (-1 to + 0.25) hours postdose as well as at 18 ( $\pm$  1) hours postdose. A point of care assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs).

<sup>n</sup>Serum chemistry panel includes serum sodium and assessments can be combined for visits where both assessments are indicated.

<sup>o</sup>Results of these tests will further characterize hyponatremia etiology for the Hyponatremia History eCRF and are not required to determine eligibility. Subjects who have clinically relevant TSH or cortisol levels may not respond properly to tolvaptan and will be withdrawn from the trial.

<sup>p</sup>PK samples are closely tied to dosing time points and serum sodium assessments. An early termination (ET) sample will be taken for any subject who is receiving tolvaptan.

- In Treatment Phase A, PK samples should be collected on Day 1 at 2 hours ( $\pm$  5 minutes) and 8 hours post-first dose and assessed at trough (24 [ $\pm$  4] hours post-first dose). A PK sample should be assessed on Day 2 at trough (24 [ $\pm$  4] hours post-previous dose, but prior to the next dose). On Day 2a no PK samples are taken.
- In Treatment Phase B, PK will be assessed in subjects continuing treatment with tolvaptan (Late Withdrawal group and nonresponders continuing on tolvaptan) at trough (24 [ $\pm$  4] hours post-previous dose, but prior to the next dose) on Days 3 and 4.

If there are restrictions in the allowable total daily blood volumes per local guidelines and subject age, the PK assessment schedule should be the following:

- Day 1 at 2 hours postdose ( $\pm$  5 minutes)
- Day 2 at 8 ( $\pm$  2) hours postdose (may be concurrent with serum sodium or other blood sampling)
- Days 3 and 4 at trough (24 [ $\pm$  4] hours post-previous dose, but prior to the next dose and concurrent with serum sodium sample)

<sup>q</sup>The tolvaptan dose will be titrated based on serum sodium levels as described in [Section 3.2.4](#).

<sup>r</sup>Optional swallow test for subjects for whom it is unknown if they are able to swallow tablets, at the investigator's discretion.

<sup>s</sup>Vital status will be collected at 14 days post-last dose only for subjects who discontinued early and did not withdraw consent.

### **3.7.1 Schedule of Assessments**

#### **3.7.1.1 Screening**

The procedures listed below will be performed during the Screening Visit (Days –2 to –1) to ensure that the subject qualifies for the trial.

- 1) Trial procedures and information regarding the nature of the trial will be reviewed and written informed consent/assent will be obtained prior to any trial-related procedures.
  - a) Informed consent will be obtained from each subject's parent/legal guardian or legally acceptable representative prior to any trial procedures being conducted.
  - b) Each subject who is able will indicate willingness to participate in the trial by signing or marking an assent form (as applicable) supplied for this purpose.
- 2) Inclusion and exclusion criteria will be reviewed.
- 3) Demographic information will be collected.
- 4) Medical and hyponatremia history will be recorded.
  - a) Medical history should include the subject's current list of medical problems that impacts the subject's current hospital stay.
  - b) The hyponatremia medical history should include the etiology of subject's hyponatremia (see [Section 3.3.1](#)) and what treatment was administered prior to trial enrollment. A detailed history specific to etiology of hyponatremia will also be recorded.
  - c) Any observable symptoms of hyponatremia will be assessed and recorded.
- 5) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for  $\geq 3$  minutes. Vital signs should be assessed prior to blood draws.
- 6) A resting 12-lead electrocardiogram (ECG) will be performed after the subject has been supine and at rest  $\geq 10$  minutes.
- 7) Body height and weight will be measured. Growth percentiles will be recorded.
- 8) The initial physical examination should be a full physical. Subsequent physical examinations can be directed physical examinations that are focused on hyponatremia-related signs and symptoms as well as any major changes from baseline.
- 9) Tanner staging will be performed.
- 10) A neurological examination will be performed.
- 11) Quality-of-life (QoL) assessment will be performed, as appropriate by age and where available.
- 12) Clinical status assessments will be performed per inpatient standard of care, eg, subject chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings,

medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.

- 13) Alcohol/drug screen is performed per clinical judgment and institutional guidelines.
- 14) A serum or urine pregnancy test will be performed on all female subjects  $\geq 12$  years of age and all female subjects  $< 12$  years of age if menstruation has started. In the case of a positive urine pregnancy test result, a serum pregnancy test will be performed as confirmatory.
- 15) Urinalysis and urine chemistry laboratory samples will be collected for analysis.
- 16) Two blood samples for serum sodium testing will be collected at least 12 hours apart and can be part of the recent medical history to document chronic hyponatremia. (One of these blood draws can be combined with the serum chemistry panel as appropriate to minimize blood draws.)
- 17) Hematology, coagulation, and serum chemistry laboratory samples will be collected for analysis.
- 18) Serum osmolality, FENa, and FE urea will be calculated.
- 19) Thyroid-stimulating hormone (TSH) and cortisol blood samples will be collected to determine possible need for alternate mode of therapy.
- 20) Concomitant medications will be recorded.
- 21) Adverse events will be recorded.
- 22) Optional swallow test for subjects for whom it is unknown if they are able to swallow tablets, at the investigator's discretion. Placebo tablets will be provided for use in performing this test at screening.

### **3.7.1.2 Treatment Phase A**

During Treatment Phase A every effort should be made to have accurate dosing time points and follow the sequence of assessments specified below as PK/PD assessments and serum sodium blood draws are closely tied to dosing time points.

#### **3.7.1.2.1 Day 1**

The procedures listed below will be performed on Day 1 for all subjects.

##### Predose

- 1) Any observable symptoms of hyponatremia will be assessed within 2 hours prior to first dose to confirm eligibility as part of a clinical status assessment. Clinical status assessments will be performed per inpatient standard of care, eg, subject chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.

- 2) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for  $\geq 3$  minutes. Vital signs should be assessed prior to blood draws.
- 3) A blood sample for STAT serum sodium testing will be collected within 2 to 4 hours prior to dosing.
- 4) Body weight will be measured.
- 5) A directed physical examination will be performed.
- 6) A neurological examination will be performed.
- 7) Inclusion and exclusion criteria will be reviewed and confirmed.

Dosing

- 8) Tolvaptan will be administered.

Postdose

- 9) A blood sample will be collected at 2 hours ( $\pm 5$  minutes) post-first dose for PK analysis of tolvaptan (central laboratory).
- 10) Vital signs will be assessed at 4 and 8 hours post-first dose. Blood pressure, heart rate, respiratory rate, and temperature will be assessed after the subject has been supine for  $\geq 3$  minutes. Vital signs should be assessed prior to blood draws at 8 hours.
- 11) Fluid intake will be recorded at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).
- 12) Urine will be collected at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours). Subjects should be asked to void just prior to the end time of each collection interval, as possible.
  - a) Urine volume will be determined from urine voids made during the 6-hour collection intervals which will be pooled prior to determination of final volume.
  - b) A urine chemistry sample will be collected and assessed from each 6-hour volume interval starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).
- 13) Blood samples will be collected concurrently at 8 hours (-1 to + 0.25) post-first dose for:
  - a) Serum sodium testing
  - b) PK analysis
- 14) A neurological examination will be performed at 8 hours post-first dose.
- 15) In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point of care sodium assessment unit, where available, on Day 1 at 4 to 6 hours postdose and at 18 ( $\pm 1$ ) hours postdose. This sodium safety assessment will be repeated at 6 (-1 to + 0.25) and 18 ( $\pm 1$ ) hours postdose each day for the remainder of titration. A point of care assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs).

- 16) Blood samples will be collected concurrently at trough (24 [ $\pm$  4] hours post-first dose) for:
  - a) A blood sample for STAT serum sodium testing should be taken and the results known prior to subsequent tolvaptan dosing.
  - b) A blood sample for PK analysis.

Throughout the visit

- 17) Concomitant medications will be recorded.
- 18) Adverse events will be assessed.

**3.7.1.2.2 Day 2**

The following procedures will be performed on Day 2 for all subjects.

Trough (24 [ $\pm$  4] hours post-first dose)

- 1) Vital signs will be assessed. Blood pressure, heart rate, respiratory rate, and temperature will be assessed after the subject has been supine for  $\geq$  3 minutes. Vital signs should be performed predose and prior to blood draws.
- 2) Clinical status assessments will be performed per inpatient standard of care, eg, subject chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.
- 3) Complete fluid intake and urine volume collection for specified intervals prior to next dosing with tolvaptan.
- 4) A directed physical examination will be performed.
- 5) Body weight will be measured.
- 6) A neurological examination will be performed.

Dosing

- 7) Tolvaptan will be administered.  
If the subject's serum sodium concentration is  $<$  135 mEq/L (mmol/L) and a  $\leq$  4 mEq/L (mmol/L) increase, tolvaptan dose should be adjusted per the titration guidelines ([Section 3.2.4](#)) for the assigned weight group.

Postdose

- 7) Assess palatability and acceptability of the tolvaptan dose for subjects immediately after dosing and again between 15 to 20 minutes after dosing.
- 8) Fluid intake will be recorded at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).
- 9) Urine will be collected at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours). Subjects should be asked to void just prior to the end time of each collection interval, as possible.

- a) Urine volume will be determined from urine voids made during the 6-hour collection intervals which will be pooled prior to determination of final volume.
- b) A urine chemistry sample will be collected and assessed from each 6-hour volume interval starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).
- 10) A blood sample will be collected for serum sodium testing at 12 ( $\pm 4$ ) hours postdose.
- 12) In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point of care sodium assessment unit, where available, at 6 and 18 hours postdose. A point of care assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs).
- 13) At the end of the Day 2 visit subjects will be assessed for response to tolvaptan treatment. Subjects who are:
  - a) Responders (serum sodium level increase of  $\geq 4$  mEq/L [mmol/L]) will proceed to Treatment Phase B (see [Section 3.7.1.3](#)) for randomization.
  - b) Not responding to tolvaptan treatment (serum sodium level increase of  $< 4$  mEq/L [mmol/L]) will proceed to Day 2a (see [Section 3.7.1.2.3](#)).
- 14) Blood samples will be collected concurrently at trough (24 [ $\pm 4$ ] hours post-previous dose) for:
  - a) STAT serum sodium testing and the results known prior to subsequent tolvaptan dosing.
  - b) PK analysis of tolvaptan.

Throughout the visit

- 15) Concomitant medications will be recorded.
- 16) Adverse events will be assessed.

**3.7.1.2.3 Day 2a (optional)**

The following procedures will be performed on Day 2a for all subjects who are not responsive to tolvaptan treatment at the end of Day 2.

Trough (24 [ $\pm 4$ ] hours post-previous dose)

- 1) Vital signs will be assessed at 24 hours post-previous dose. Blood pressure, heart rate, respiratory rate, and temperature will be assessed after the subject has been supine for  $\geq 3$  minutes. Vital signs should be performed predose and prior to blood draws.
- 2) Clinical status assessments will be performed per inpatient standard of care, eg, subject chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings,

medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.

Predose

- 3) A directed physical examination will be performed.
- 4) Body weight will be measured.

Dosing

- 5) Tolvaptan will be administered. If the subject's serum sodium concentration is  $< 135$  mEq/L (mmol/L) and a  $\leq 4$  mEq/L (mmol/L) increase, tolvaptan dose should be adjusted per the titration guidelines ([Section 3.2.4](#)) for the assigned weight group.

Postdose

- 6) A blood sample will be collected for serum sodium testing at 12 ( $\pm 4$ ) hours postdose.
- 7) In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point of care sodium assessment unit, where available, at 6 and 18 hours postdose. A point of care assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs).
- 8) At the end of the Day 2a visit subjects will be assessed for response to tolvaptan treatment. Subjects who are:
  - a) Responders (serum sodium level increase of  $\geq 4$  mEq/L [mmol/L]) will proceed to Treatment Phase B (see [Section 3.7.1.3](#)) for randomization.
  - b) Nonresponders (serum sodium level increase of  $< 4$  mEq/L [mmol/L]) will continue to Treatment Phase B where they either continue on tolvaptan therapy for 2 additional days or are withdrawn from tolvaptan to be treated per the investigator's preferred standard of care.
- 9) A blood sample will be collected for serum sodium testing at trough (24 [ $\pm 4$ ] hours postdose).

Throughout the visit

- 10) Concomitant medications will be recorded.
- 11) Adverse events will be assessed.

### **3.7.1.3 Treatment Phase B**

#### **3.7.1.3.1 Day 3**

The following procedures will be performed on Day 3. Some assessments are required for all subjects while other assessments only apply to certain subsets of subjects as indicated.

##### **For all subjects**

At trough (24 [ $\pm$  4] hours post-previous dose) the following assessments will be performed:

- 1) Vital signs will be assessed. Blood pressure, heart rate, respiratory rate, and temperature will be assessed after the subject has been supine for  $\geq$  3 minutes. Vital signs should be performed predose and prior to blood draws.
- 2) Clinical status assessments will be performed per inpatient standard of care, eg, subject chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.

##### **For all subjects classified as Responders at the end of Treatment Phase A**

- 1) Randomize the subject to the Early or Late Withdrawal group using the trial's interactive web response system (IWRS).

##### **For subjects receiving tolvaptan (Late Withdrawal group and nonresponders with continuing treatment)**

- 1) Body weight will be measured predose.
- 2) A directed physical examination will be performed predose.
- 3) A neurological examination will be performed.
- 4) Tolvaptan will be administered.
- 5) A blood sample will be collected for serum sodium testing at 12 ( $\pm$  4) hours postdose.
- 6) Blood samples will be collected concurrently at trough (24 [ $\pm$  4] hours post-previous dose) for:
  - a) STAT serum sodium testing and the results known prior to subsequent tolvaptan dosing.
  - b) PK analysis of tolvaptan.
- 8) Concomitant medications will be recorded.
- 9) Adverse events will be assessed.

**For subjects not receiving tolvaptan treatment (Early Withdrawal group and nonresponders treated with standard of care)**

- 1) Early Withdrawal subjects will be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels.
- 2) Nonresponders discontinuing tolvaptan will be treated per the investigator's preferred standard of care.
- 3) A directed physical examination will be performed.
- 4) A neurological examination will be performed.
- 5) A blood sample will be collected for serum sodium testing at 12 ( $\pm$  4) hours post the nominal dosing time.
- 6) A blood sample will be collected for serum sodium testing at 24 ( $\pm$  4) hours post the nominal dosing time.
- 7) Concomitant medications will be recorded.
- 8) Adverse events will be assessed.

**3.7.1.3.2        Day 4**

The following procedures will be performed on Day 4. Some assessments are required for all subjects while other assessments only apply to certain subsets of subjects as indicated.

**For all subjects**

At trough (24 [ $\pm$  4] hours post-previous dose) the following assessments will be performed:

- 1) Vital signs will be assessed. Blood pressure, heart rate, respiratory rate, and temperature will be assessed after the subject has been supine for  $\geq$  3 minutes. Vital signs should be performed predose and prior to blood draws.
- 2) Clinical status assessments will be performed per inpatient standard of care, eg, subject chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.

**For subjects receiving tolvaptan (Late Withdrawal group and nonresponders with continuing treatment)**

- 1) Body weight will be measured predose.
- 2) A directed physical examination will be performed predose.
- 3) A neurological examination will be performed.
- 4) Tolvaptan will be administered.

- 5) A blood sample will be collected for serum sodium testing at 12 ( $\pm 4$ ) hours postdose.
- 6) A QoL assessment will be conducted.
- 7) Blood samples will be collected concurrently at trough (24 [ $\pm 4$ ] hours post-previous dose) for:
  - a) STAT serum sodium testing and the results known prior to subsequent tolvaptan dosing.
  - b) PK analysis of tolvaptan.
- 8) Concomitant medications will be recorded.
- 9) Adverse events will be assessed.

**For subjects not receiving tolvaptan treatment (Early Withdrawal group and nonresponders treated with standard of care)**

- 1) Early Withdrawal subjects will be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels.
- 2) Nonresponders discontinuing tolvaptan will continue to be treated per the investigator's preferred standard of care.
- 3) A directed physical examination will be performed.
- 4) A neurological examination will be performed.
- 5) A blood sample will be collected for serum sodium testing at 12 ( $\pm 4$ ) hours post the nominal dosing time.
- 6) A QoL assessment will be conducted.
- 7) Concomitant medications will be recorded.
- 8) Adverse events will be assessed.

**3.7.1.3.3            Day 5**

The following procedures will be performed on Day 5.

**For subjects receiving tolvaptan (Late Withdrawal group and nonresponders with continuing tolvaptan treatment)**

At trough (24 [ $\pm 4$ ] hours post-previous dose)

- 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for  $\geq 3$  minutes. Vital signs should be performed prior to blood draws.
- 2) Body weight will be measured.

Throughout the visit

- 3) Concomitant medications will be recorded.

- 4) Adverse events will be assessed.

**For subjects not receiving tolvaptan treatment (Early Withdrawal group and nonresponders treated with standard of care)**

- 1) Proceed to Follow-up Phase C, as for these subjects the 72-hour post-last dose time point ([Section 3.7.1.4.1](#)) falls on the morning of Day 5.

**3.7.1.4 Follow-up Phase C**

**3.7.1.4.1 72 Hours Post-last Dose or ET**

The following procedures will be performed for all subjects at 72 ( $\pm$  4) hours post-last dose or at early termination (ET).

- 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for  $\geq$  3 minutes. Vital signs should be performed prior to blood draws.
- 2) Hematology, coagulation, and serum chemistry laboratory samples will be collected.
- 3) For Early Termination only:  
Blood sample for PK analysis of tolvaptan will be collected for all subjects on tolvaptan. The sample is to be taken concurrently with the serum sodium sample (part of the serum chemistry panel).
- 4) A directed physical examination will be performed.
- 5) A neurological examination will be performed.
- 6) Body weight will be measured.
- 7) A urinalysis laboratory sample will be collected.
- 8) Clinical status assessments will be performed per inpatient standard of care, eg, subject chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.
- 9) For Early Termination:  
Subjects will be monitored and treated as clinically warranted per the investigator's preferred standard of care for up to 3 additional days after the last dose of tolvaptan.
- 10) Concomitant medications will be recorded.
- 11) Adverse events will be assessed.
- 12) If a subject terminates early from the trial and agrees to continued telephone contact, the subject or parent/legal guardian or legally acceptable representative will be contacted by telephone at 14 days post-last dose for vital status.

### **3.7.1.4.2 7 Days Post-last Dose**

Subjects will be assessed for maintenance of normal or target serum sodium concentration at 7 (+ 1) days post-last dose. All clinical labs will be performed locally. If the subject was discharged, he/she should return to the clinic for this visit.

- 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for  $\geq$  3 minutes. Vital signs should be performed prior to blood draws.
- 2) A blood sample for serum sodium testing will be collected.
- 3) A serum or urine pregnancy test will be performed on all female subjects  $\geq$  12 years of age and all female subjects < 12 years of age if menstruation has started. In the case of a positive urine pregnancy test result, a serum pregnancy test will be performed as confirmatory.
- 4) A QoL assessment will be conducted.
- 5) A directed physical examination will be performed.
- 6) A neurological examination will be performed.
- 7) Clinical status assessments will be performed per inpatient standard of care, eg, subject chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.
- 8) Body weight will be measured.
- 9) Concomitant medications will be recorded.
- 10) Adverse events will be assessed.

### **3.7.1.4.3 14 Days Post-last Dose**

Subjects or their parent(s)/legal guardian(s) or legally acceptable representative(s) will be contacted via telephone or will be asked to come back to the clinic for a visit at 14 (+ 2) days post-last dose to assess any new or ongoing AEs and to collect information on any medications administered since the last visit. Ongoing follow-up may be required after a subject's trial completion for health status before the analysis of all trial results is completed.

## **3.7.2 Efficacy Assessments**

Efficacy will be assessed through determination of overall serum sodium concentrations and clinical status assessments.

### 3.7.2.1 Serum Sodium Concentrations

Monitoring frequency of serum sodium is at the discretion of the clinical investigator; however, the minimum sample collection required for all subjects is described in [Section 3.7.1](#) and [Section 3.7.4.2.1](#).

In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point of care sodium assessment unit, where available, on Day 1 at 4 to 6 hours postdose and at 18 hours postdose. This sodium safety assessment will be repeated at 6 and 18 hours postdose each day for the remainder of titration. A point of care assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs).

In order to qualify for this trial, subjects must have documentation of chronic dilutional hyponatremia (serum sodium < 130 mEq/L [mmol/L]) that is present for  $\geq$  48 hours. Specifically, each subject must have 2 blood samples collected at least 12 hours apart over a minimum of 48 hours for assessment of baseline serum sodium level to determine subject eligibility. These can be either part of the recent medical history concerning the current hospital stay or prospectively collected as part of this trial.

On Day 1, a third (STAT) serum sodium sample should be drawn within 2-4 hours prior to dosing; the results must be verified to be < 130 mmol/L prior to the first dose. Serum sodium assessments should be performed at 8 hours post-first dose and at trough (24 [ $\pm$ 4] hours post-first dose; this assessment will fall on Day 2 predose).

On Day 2 (or 2a), Day 3, and Day 4 (through the following morning on Day 5):

- For all subjects receiving tolvaptan (Late Withdrawal and nonresponders continuing on tolvaptan) serum sodium assessments will be performed at trough (24 [ $\pm$ 4] hours post-previous dose) and 12 ( $\pm$  4) hours postdose each day during Treatment Phase A and Treatment Phase B.
- For all subjects not receiving tolvaptan (Early Withdrawal and nonresponders treated with standard of care) serum sodium assessments will be performed every 12 ( $\pm$  4) hours throughout Treatment Phase A and Treatment Phase B.

For all subjects final serum sodium assessments will be taken at 72 ( $\pm$  4) hours post-last dose and 7 days post-last dose.

The serum sodium assessments schedule is presented in [Table 3.7.2.1-1](#).

			Blood Draws for Serum Sodium	
Phase	Visit	Day	Efficacy	Supplemental Safety
Treatment Phase A	Screening	-2 to -1	2 blood samples, at least 12 hours apart	-
			Within 2 to 4 hours prior to dosing (STAT)	-
	Titration	1	8 (-1 to + 0.25) hours post-first dose	4 to 6 hours postdose
			24 ( $\pm$ 4) hours post-first dose (STAT)	18 ( $\pm$ 1) hours postdose
		2	12 ( $\pm$ 4) hours postdose	6 (-1 to + 0.25) and 18 ( $\pm$ 1) hours postdose
			24 ( $\pm$ 4) hours post-previous dose (trough) (STAT)	-
	2a (Optional)	12 ( $\pm$ 4) hours postdose	6 (-1 to + 0.25) and 18 ( $\pm$ 1) hours postdose	-
			24 ( $\pm$ 4) hours post-previous dose (trough) (STAT)	-
Treatment Phase B	Late Withdrawal group and nonresponders with continuing treatment	3	12 ( $\pm$ 4) hours postdose	-
			24 ( $\pm$ 4) hours post-previous dose (trough) (STAT)	-
		4	12 ( $\pm$ 4) hours postdose	-
			24 ( $\pm$ 4) hours post-previous dose (trough)	-
	Early Withdrawal group and nonresponders treated with standard of care	3	12 ( $\pm$ 4) hours post nominal dosing	-
			24 ( $\pm$ 4) hours post nominal dosing	-
		4	12 ( $\pm$ 4) hours post nominal dosing	-
Follow-up Phase C	Follow-up	-	72 ( $\pm$ 4) hours post-last dose	-
		-	7 (+ 1) days post-last dose	-

### **3.7.2.2 Clinical Assessments**

Clinical status assessment must be performed predose on Day 1. It is preferred that clinical status assessments be performed predose during subsequent visits. Clinical assessments will be performed per inpatient standard of care and should include review of subject chart entries, including hyponatremia assessment notes, trial- and nontrial-specific laboratory results, any examination findings, medical problem list changes, and fluid intake and output to evaluate overall subject eligibility in terms of hyponatremia state. The clinical assessment will focus on symptoms and signs which will inform treatment decisions (eg, the need to switch to rescue therapy, or the ability to safely discharge a subject from the hospital). The clinical assessment should be

performed by a trial investigator who will be aware of laboratory and other clinical response data.

### **3.7.2.3      Quality of Life Assessments**

Two patient-reported outcomes instruments (acute versions with 7 day recall period) will be used to assess subject quality of life: PedsQL Generic Core Scale and PedsQL Multidimensional Fatigue Scale. Both instruments are appropriate for  $\geq 2$  years of age, however availability may be limited for certain ages and languages. The age groups covered by these assessments are Toddler (2–4 years), Young child (5–7 years), Child (8–12 years), and Adolescent (13–18 years). Depending on the subject's age, the questionnaire may be completed by either the subject, subject and parent/caregiver, or the parent/caregiver, as appropriate.

The PedsQL Generic Core Scale consists of 23 items encompassing physical, emotional, social, and school domains.

The PedsQL Multidimensional Fatigue Scale consists of 18 items in 3 subscales: general fatigue, sleep/rest fatigue, and cognitive fatigue. The instrument focuses on the domains of processing speed, attention/vigilance, visual and working memory.

The assessment time points are at screening, Day 4 and 7 days post-last dose.

## **3.7.3      Pharmacokinetic/Pharmacodynamic Assessments**

### **3.7.3.1      Pharmacokinetic Assessments**

#### **3.7.3.1.1      Blood Collection Times**

Blood samples will be taken so that tolvaptan and metabolite concentrations can be determined. Samples will be taken at the following times:

- On Day 1 at 2 hours ( $\pm 5$  minutes) and 8 hours (concurrent with 8 h serum sodium sample) post-first dose.
- On Days 1, 2, 3, and 4 samples will be taken at trough ( $24 [\pm 4]$  hours post-previous dose) (prior to the subsequent dose), concurrent with serum sodium samples, for subjects dosed with tolvaptan on Days 1, 2, 3, and 4, respectively, regardless of status as responder/nonresponder.
- An early termination (ET) sample will be taken for any subject who is receiving tolvaptan.

On Day 2a no PK samples are taken.

For each PK blood sample collected volumes are not expected to exceed 1.2 mL. Total volume per sample may be lower depending on finalization of blood collection supplies.

Serum sodium assessments and other clinically necessary blood samples take priority; therefore, due to restrictions in allowable total daily blood volumes based on local guidelines and subject age, it may not be possible to take more than one PK sample per day. If so, the PK sampling should be changed to:

- Day 1: 2 hours postdose ( $\pm$  5 minutes)
- Day 2: 8 ( $\pm$  2) hours postdose (may be concurrent with serum sodium or other blood sampling)
- Day 3 at trough, ie, predose/24 hours post prior dose (concurrent with serum sodium sample)
- Day 4 at trough, ie, predose/24 hours post prior dose (concurrent with serum sodium sample)

The PK profiles will be evaluated on an ongoing basis to determine the variability between subjects. Based on the findings, PK sampling will continue for as long as necessary to establish suitable estimates of clearance with a 90% CI similar to that observed in the adult populations. Once these estimates are achieved, sampling will be discontinued in subsequent subjects.

For each subject all samples will be collected according to local guidelines and best practices for pediatric care. If a sample is missing due to limitations in allowable blood volumes based on local regulations or local practice this will not count as a protocol deviation.

### **3.7.3.1.2      Sample Handling and Processing**

All blood samples will be shipped to the testing facility for analysis. Detailed handling and shipping instructions are provided in [Appendix 3](#).

### **3.7.3.2      Pharmacodynamic Assessments**

#### **3.7.3.2.1      Fluid Intake**

Fluid intake (both oral and IV) will be measured at the times presented in the schedule of assessments ([Section 3.7.1](#)). The fluid content of foods with significant water content (eg, soup) should be added to the total fluid intake. Fluid intake will be monitored per institutional guidelines.

#### **3.7.3.2.2      Urine Volume**

Urine volume will be determined in urine samples that will be collected at the intervals presented in the schedule of assessments, [Section 3.7.1](#). All urine voids within a collection interval should be kept refrigerated and pooled according to the size of

available collection containers. At the end of the collection interval all samples should be pooled and the urine volume determined.

### **3.7.3.2.3 Urine Chemistry**

Urine chemistry will be determined from pooled urine samples collected for the intervals presented in the schedule of assessments, [Section 3.7.1](#). An aliquot will be taken for each collection interval according to the procedures of the local clinical chemistry laboratory. The list of urine chemistry tests to be conducted is presented in [Table 3.7.4.2.3-1](#).

### **3.7.3.2.4 Palatability and Acceptability Assessment**

A questionnaire will be administered immediately after dosing to assess palatability to rate flavor/taste, smell, sweetness, and overall liking of the study medication. Subjects will also be asked about the ease of swallowing the study medication. Between 15 to 20 minutes after dosing, a questionnaire will be administered to subjects again to assess overall liking of the study medication. This assessment will only be done in subjects aged 3 years to 18 years.

## **3.7.4 Safety Assessments**

Safety will be assessed through the monitoring of AEs, clinical laboratory tests, vital signs, body weight, directed physical examinations, neurological examinations, rescue therapy, and fluid restriction.

The monitoring frequency of safety assessments is at the discretion of the clinical investigator; however, the trial requires the minimum sample collection for all subjects noted in [Section 3.7.1](#) and [Section 3.7.4.2.1](#).

### **3.7.4.1 Adverse Events**

Refer to [Section 5](#), Reporting of Adverse Events.

In addition, active monitoring is required for:

- Absolute serum sodium level  $\geq 145$  mEq/L (mmol/L) or an overly rapid rise in serum sodium level (an increase in serum sodium of  $> 8$  mEq/L [mmol/L] over a 10-hour period,  $\geq 12$  mEq/L [mmol/L] over a 24-hour period, or a rate of increase in serum sodium concentration that the investigator deems too rapid), neurological symptoms, or other signs or symptoms suggestive of osmotic demyelination (see [Section 0](#) for more details).
- Elevations in AST or ALT that are  $\geq 2 \times$  ULN or levels that increase  $\geq 2$  times their previously observed level. If this occurs, a total bilirubin level should also be evaluated. See [Section 3.7.4](#) for more information and [Section 5.4.1](#) for detailed instructions on how this type of event should be captured.
- Worsening symptoms of hyponatremia
- Hypovolemia or hypotension requiring intervention

### **3.7.4.2 Clinical Laboratory Assessments**

#### **3.7.4.2.1 Serum Sodium**

In addition to serum sodium samples obtained for trial qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point of care sodium assessment unit, where available, on Day 1 at 4 to 6 (-1 to + 0.25) hours postdose and at 18 ( $\pm 1$ ) hours postdose. This sodium safety assessment will be repeated at 6 (-1 to + 0.25) and 18 ( $\pm 1$ ) hours postdose each day for the remainder of Treatment Phase A. A point of care assessment unit is preferred since it is expected to reduce overall daily blood volume needed for assessments (expected 0.5 mL for regular blood draws versus up to several drops for a point of care assessment, depending on the device used); however, regular blood draws may be used (especially if they can be combined with standard of care labs).

Additional unscheduled serum sodium assessments may be performed at the discretion of the clinical investigator and other physicians of record, depending on the local standards and subject's clinical condition. All unscheduled serum sodium concentrations collected as part of standard of care will be reported as unscheduled sodium assessments in the electronic case report form (eCRF) through the follow-up sodium assessments.

#### **3.7.4.2.2 Serum Osmolality**

Serum osmolality will be calculated to help guide dosing. Local site personnel will determine serum osmolality using one of the following equations:

- Where Na, glucose, and blood urea nitrogen (BUN) are measured in mg/dL:

$$\text{Serum Osmolality (mOsm/kg)} = 2 \text{ Na} + \text{BUN} / 2.8 + (\text{glucose} / 18)$$

b) Where Na, glucose, and urea are measured in mmol/L:

$$\text{Serum Osmolality (mOsm/kg)} = 2 \text{ Na} + \text{glucose} + \text{urea}$$

### **3.7.4.2.3 Clinical Lab Tests**

[Table 3.7.4.2.3-1](#) presents required clinical laboratory assessments (serum chemistry, hematology, coagulation, urinalysis, and urine chemistry). All clinical laboratory tests will be performed by local laboratories. Serum cortisol and TSH will be measured during screening using the remaining blood sample obtained for serum chemistry. If these results are obtained as part of the standard of care for the subject, a trial-specific sample should be obtained and sent to the local laboratory for analysis per the schedule of assessments ([Section 3.7.1](#)). Urine urea will be measured during screening for calculation of FE urea.

It is recognized that there may be limitations based on age and weight of children for the amount of blood that can be drawn at a single time point, per day, and the overall conduct of the trial. Wherever possible, it is encouraged to combine standard of care samples that would be taken regardless of trial participation with those samples required for the trial.

In case of limited blood or urine volume availability, the bolded assessments in [Table 3.7.4.2.3-1](#) take priority. Serum sodium and liver function tests are essential to the conduct of the trial.

**Table 3.7.4.2.3-1 Clinical Laboratory Tests to be Performed Locally**

<u>Hematology:</u> WBC count with differential RBC count Hematocrit Hemoglobin Mean corpuscular volume Mean corpuscular hemoglobin concentration Platelet count RBC volume distribution width <u>Additional Tests:</u> <b>TSH</b> <b>Serum cortisol</b> <u>Coagulation:</u> International normalized ratio <u>Platelets</u> Prothrombin time Activated partial thromboplastin time	<u>Serum Chemistry:</u> <b>ALT</b> <b>Alkaline phosphatase</b> <b>AST</b> Bicarbonate (or carbon dioxide) <b>Bilirubin, total</b> <b>Urea or Blood urea nitrogen (BUN)</b> Calcium Chloride Cholesterol, total <b>Creatinine</b> Gamma glutamyl transferase <b>Glucose</b> Lactic dehydrogenase <b>Potassium</b> Protein, total Triglycerides Uric acid <u>Efficacy:</u> <b>Serum sodium</b>
<u>Urinalysis:</u> <b>Color</b> <b>Appearance</b> <b>Bilirubin</b> <b>Glucose</b> <b>Ketones</b> <b>Leukocytes</b> <b>Nitrites</b> <b>Occult blood</b> <b>Protein</b> Urobilinogen <b>Microscopic analysis of RBC/WBC (per high powered field)</b> <u>Urine Chemistry:</u> <b>Osmolality</b> <b>Sodium</b> <b>Potassium</b> <b>Creatinine</b> <b>Urea</b> <u>Additional Test:</u> <b>Serum or urine pregnancy test (if applicable)</b>	<u>Drug Screen (all items in urine):</u> <b>Alcohol</b> <b>Amphetamines</b> <b>Barbiturates</b> <b>Benzodiazepines</b> <b>Cannabinoids</b> <b>Cocaine</b> <b>Methadone</b> <b>Opiates</b> <b>Phencyclidine</b> <u>Additional Drug Screen Test:</u> Alcohol (breath)

WBC = white blood cell; RBC = red blood cell.

In case of limited blood or urine volume availability the **bolded** assessments take priority. Serum Sodium and liver function tests are essential to the conduct of the trial.

### 3.7.4.2.4 Monitoring of Liver Transaminases

Long-term use of tolvaptan has demonstrated the potential to cause a clinically significant elevation in laboratory tests of liver function. Based on previous research in the adult

polycystic kidney disease population, the expected onset of the elevation, if it occurs, is between 3 and 14 months of chronic treatment with tolvaptan.

For a subject who experiences an elevation in AST or ALT that is  $\geq 2 \times$  ULN or whose levels increase  $\geq 2$  times their previous observed value, a total bilirubin level should also be evaluated. These elevated values should be confirmed by retesting. If total bilirubin is  $\geq 2 \times$  ULN or  $\geq 2$  times their previous observed value, an immediately reportable event (IRE) form with all values listed should be completed and also reported as an AE on the eCRFs. See [Section 5.4.1](#) for detailed instructions on how this type of event should be captured.

### **3.7.4.3 Physical Examination**

Full and directed physical examinations will be performed and documented according to the schedule of assessments ([Section 3.7.1](#)). The initial physical examination should be a full physical. Subsequent physical examinations can be directed physical examinations that are focused on hyponatremia-related signs and symptoms as well as any major changes from baseline.

The principal investigator or his/her appointed designee is primarily responsible to perform the physical examination. If the appointed designee is to perform the physical examination, he/she must be permitted by local regulations. Whenever possible, the same individual should perform all physical examinations for a given subject. Any condition present at the post-treatment directed physical examination that was not present at Screening should be documented as an AE and followed to a satisfactory conclusion.

Full physical examination assessments should include assessments of all major body systems, including but not limited to, ears, nose, and throat, the thorax area, abdomen, urogenital, extremities, and skin and mucosae. Directed physical examinations should be focused on hyponatremia-related signs and symptoms as well as any major changes from baseline. Physical examination will include a fontanelle assessment as age appropriate. Neurological examinations will be performed in an age-appropriate manner per [Section 3.7.4.3.1](#).

Body weight will be measured predose each day throughout Treatment Phase A, Treatment Phase B and at each clinic visit in Follow-up Phase C, as possible. Every effort should be made to ensure that body weight measurements are performed in a reproducible and consistent manner. Body weight measurements should be performed at the clinical site always using the same scale. Subjects should wear the same type of clothes at each measurement, preferably a gown and no shoes. All body weight measurements should be taken post void.

### **3.7.4.3.1      Neurological Examination**

A neurological examination will be performed as part of the directed physical exam per the schedule of assessments ([Section 3.7.1](#)). It will include an evaluation of mental status, cranial nerves, muscle tone, muscle strength/symmetry, reflexes, neonatal primitive reflexes, sensory system, gait, and finger to nose, as age appropriate.

### **3.7.4.4      Tanner Staging**

Tanner Staging must be completed together with the physical examination by the same trial-affiliated clinician in the most inconspicuous manner for the subject as possible.

Tanner Staging could be completed by the trial affiliated pediatrician or family practitioner (additionally physician's assistant or nurse practitioner where licensing permits). Sites should make attempts to have examiners of both sexes. Attempts should be made to have the examination performed by the same sex personnel as the subject. Otherwise, trial-affiliated personnel of the same sex as the subject (ie, nurse) should be in the same examination room as the subject.

Tanner Staging assessment consists of 2 domains (pubic hair and breast development) for girls and 3 domains (pubic hair, penis development, and testes development) for boys.

The Tanner Staging assessment as a reference for the completing clinician is included in [Appendix 4](#). The investigator will arrive at a single score summarizing the domains (not individual domain scores) when evaluating the subject.

### **3.7.4.5      Vital Sign Assessments**

Vital signs (including supine blood pressure, heart rate, respiratory rate, and temperature) will be assessed at time points according to [Section 3.7.1](#) of this protocol. Supine vital signs will be taken when the subject has been lying down (bed positioned < 45 degree angle) for  $\geq$  3 minutes. All assessments for vital signs should be performed around the time of the formal hyponatremia assessment (sodium blood draw) during Screening, Treatment Phase A and Treatment Phase B and anytime during the Follow-up Period consistent with the timing of other trial assessments. All vital sign assessments should be performed predose and prior to the blood draw at the nominal time point.

### **3.7.4.6      Electrocardiogram Assessments**

One ECG will be recorded at screening, prior to any blood draws. Twelve-lead ECGs will be recorded with the subject supine and at rest (for at least 10 minutes). Heart rate, PR interval, QRS duration, and QT interval will be recorded. The principal investigator or designee will review, sign, and date each ECG reading. Any abnormalities should be reported as part of the medical history. Whenever possible, the same reviewer should

evaluate, sign, and date the ECGs. A paper copy of the ECG will be sent for storage to a central ECG storage facility.

#### **3.7.4.7      Hyponatremia History**

Each subject's hyponatremia medical history will be recorded at screening. The hyponatremia history should include the etiology of subject's hyponatremia (including assessments per [Section 3.2.4.2](#)) and what treatment was administered prior to trial enrollment. Symptoms potentially attributable to hyponatremia should be specifically assessed for prior history. The hyponatremia assessment at Screening will consist of documentation of hyponatremia etiology (eg, HF, hepatocellular disease [including cirrhosis], SIADH/other), prior fluid intake and output, and prior hyponatremia treatment, ie, fluid restriction, if applicable. A detailed history specific to etiology of hyponatremia will also be recorded.

#### **3.7.4.8      Volume Status Assessment**

Volume status will be assessed every 6 hours prior to trial entry and every 6 hours during Treatment Phase A.

#### **3.7.4.9      Vital Status**

An assessment of vital status will be conducted on subjects who terminate prior to the last study visit, and do not withdraw consent for continued telephone contact. The telephone contact will be made 14 days post-last dose, and will be conducted with a reliable informant; either the subject and/or the parent/guardian, per investigator discretion. Vital status collected and recorded will be:

- Subject alive
- Subject deceased (date of death, cause of death)

#### **3.7.5      End of Trial**

The End of Trial Date is defined as the last Date of Contact or the Date of Final Contact Attempt from the Post-treatment Follow-up eCRF page for the last subject completing or withdrawing from the trial.

#### **3.7.6      Independent Data Monitoring Committee**

An independent data monitoring committee (IDMC) will be established for this trial. This committee will meet on a regular basis to ensure the safe and ethical treatment of trial subjects, ensure the scientific integrity of the trial, and to ensure the trial is conducted within the bounds of ethical medical practice. It may make recommendations

to the sponsor and trial steering committee to amend or terminate the trial based on grounds of safety, futility, or greater than expected efficacy as defined by the accepted statistical practices and procedures to be detailed in their charter. The specific duties of the IDMC will be detailed in a separate IDMC charter document.

### **3.8      Stopping Rules, Withdrawal Criteria and Procedures**

#### **3.8.1      Entire Trial or Treatment Arm(s)**

If the sponsor terminates or suspends the trial for safety or unanticipated other reasons, prompt notification will be given to investigators, IRBs/IECs, and regulatory authorities in accordance with regulatory requirements.

#### **3.8.2      Individual Site**

The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

#### **3.8.3      Individual Subject Discontinuation**

If a subject discontinues from the trial prematurely, the reason must be fully evaluated and recorded appropriately in source documents and the eCRF. If the subject is being withdrawn because of an AE, that AE should be indicated as the reason for withdrawal.

All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary. In addition, subjects meeting the following criteria following the first dose of tolvaptan must be withdrawn from the trial:

- a) Occurrence of any AE, intercurrent illness, or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial;
- b) Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator;
- c) Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (eg, blood draw requirements); see [Section 3.12](#), Subject Compliance);
- d) At the request of the subject, investigator, OPDC or designee, or regulatory authority;
- e) Subject becomes pregnant; or
- f) Subject is lost to follow-up.

Subjects who have clinically relevant TSH or cortisol levels may not respond properly to tolvaptan and will be withdrawn from the trial.

In addition, subjects meeting the following criteria should have results confirmed with a repeat test (if the result is confirmed, the medical monitor should be contacted to consider options of down-titration, dose interruption, concomitant medication adjustment, fluid supplementation, and/or withdrawal):

- Subject's serum sodium level increases by  $> 8$  mEq/L [mmol/L] in any 10-hour period following dosing on Day 1
- Subject's serum sodium level increases by  $\geq 12$  mEq/L [mmol/L] in the 24-hour period following dosing
- At any time after dosing, the subject's serum sodium is  $\geq 145$  mEq/L [mmol/L]

Subjects who require IV infusion of isotonic or hypertonic saline for hyponatremia or who receive another approved/off-label therapy (rescue therapy) for hyponatremia before completion of the trial will be withdrawn from trial treatment; these subjects should continue to Phase C to be followed. Subjects, who are randomized to the Early Withdrawal group, whose serum sodium level declines by  $\geq 4$  mEq/L (mmol/L), or whose overall clinical condition requires further treatment to increase serum sodium level will be treated per the investigator's preferred standard of care. Any intervention intended to raise serum sodium during the first 48 hours of the Early Withdrawal phase (including fluid restriction) will be defined as rescue therapy. The subject will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.

The sponsor and the medical monitor should be notified promptly when a subject requires treatment other than trial treatment for the purpose of raising serum sodium. Subjects receiving rescue therapy are to continue to be monitored per protocol (to discharge or death). Subjects terminated prior to completion will not be re-enrolled.

The investigator will notify the sponsor promptly when a subject is withdrawn.

When a subject or parent/legal guardian or legally responsible representative decides to withdraw from the trial they will be asked to indicate whether they wish to discontinue from the trial as a whole, or still allow telephone contact. If they agree to continued telephone contact, they will be contacted 14 days after the last study visit for vital status ([Section 3.7.4.9](#)).

### **3.9 Screen Failures**

A screen failure subject is one from whom informed consent/assent (if applicable) has been obtained and is documented in writing (ie, the subject's parent/legal guardian or legally acceptable representative signs an ICF), but who is not enrolled into the trial. If a subject's serum sodium level during the Screening period is  $\geq 130$  mEq/L [mmol/L], that subject will be determined a screen failure. Subjects who are deemed screen failures may be rescreened for possible participation if they have not taken a dose of IMP.

### **3.10 Definition of Completed Subjects**

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the tolvaptan.

For purposes of this trial, subjects who are randomized responders and who complete required trial assessments (including their assigned trial treatment) through the end of the trial will be defined as responder trial completers.

For purposes of this trial, subjects who are nonresponders (not randomized) but who complete required trial assessments through the end of the trial will be defined as nonresponder trial completers.

Subjects who discontinue tolvaptan prior to the end of Treatment Phase B, but who continue in the trial and complete some or all of their required assessments to the end of the trial, will be considered "early" end of treatment (EEOT) completers.

### **3.11 Definition of Lost to Follow-up**

Subjects or subjects' parent(s)/legal guardian(s) or legally acceptable representative(s) who cannot be contacted on or before the final Follow-up Contact at 14 days post-last dose prior to the trial termination date, who do not have a known reason for discontinuation (eg, withdrew consent or AE) and for whom a current health status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Current health status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, or statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact

the subject via certified mail or an alternative similar method, where appropriate, before assigning a “lost to follow-up” status.

### **3.12     Subject Compliance**

All subjects in this trial who deviate from assigned treatment will be considered noncompliant.

Compliance will be ensured by watching the subject take his/her tolvaptan while the subject is hospitalized or during clinical trial site visits. For nonclinical trial site days, compliance will be assessed by the number of tablets remaining when the subject returns the blister cards at the next visit. This information will be recorded on the appropriate eCRF and on the Drug Accountability Forms.

### **3.13     Protocol Deviations**

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

## **4     Restrictions**

### **4.1     Prohibited Medications**

Continuous or short term use of other medications, while not prohibited, may be restricted by the investigator because of their potential for interference with tolvaptan metabolism. Tolvaptan is a sensitive CYP3A4 substrate; plasma concentrations increased approximately 4-fold when tolvaptan was administered with the potent CYP3A4 inhibitor ketoconazole.<sup>14,23</sup> Where appropriate dose reductions are possible, tolvaptan doses may be coadministered with potent or moderate CYP3A4 inhibitors (see [Section 2.1.1](#) and [Table 3.2.3-1](#)).

A partial list of CYP3A4 inhibitors is provided in [Table 4.1-1](#).

<b>Table 4.1-1 List of Cytochrome P450 3A4 Inhibitors (Partial List)</b>	
boceprevir clarithromycin clotrimazole (oral) conivaptan indinavir itraconazole ketoconazole lopinavir mibepradil	nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole

## 4.2 Other Restrictions

The ingestion of pomelo, grapefruit, grapefruit juice, products containing Seville oranges, and St. John's Wort is prohibited from 72 hours prior to dosing until 24 hours post-last dose of IMP. In addition, the use of alcohol within 72 hours prior to dosing and during the trial is prohibited.

Other treatment for the purpose of increasing serum sodium, eg with urea, lithium, demeclocycline, conivaptan or tolvaptan, concurrent with dosing of trial medication or within 4 days of qualifying serum sodium assessments at screening is prohibited.

The use of saline in this population should be closely monitored. The use of hypertonic saline (3% or greater), including normal saline challenge within 8 hours of the qualifying screening serum sodium laboratory assessment is prohibited. The use of hypertonic saline (3% or greater) is prohibited during tolvaptan treatment. Routine use of hypertonic saline, while prohibited, may be considered only if used emergently (ie, with a severe symptomatic episode) and with the understanding that free water clearance may be stimulated if tolvaptan had been administered in the prior 24 hours, based on the medical judgment of the investigator.

The use of normal saline (0.9%) is allowed during screening until the beginning of Treatment Phase A; normal saline use can resume in Phase C. Subjects should no longer be on maintenance fluids containing normal saline during treatment with tolvaptan. Subjects may be administered IV solutions containing hypotonic saline (eg, half-normal [0.45%] saline), if necessary, for fluid management. The medical monitor should be contacted at any point if questions arise regarding the use of saline during the trial.

## 5 Reporting of Adverse Events

### 5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs would not include information recorded as medical history at screening for pre planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction 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. For the purpose of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IMP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

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

Nonserious adverse events 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) case (see [Section 5.4](#)).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication.

**Clinical Laboratory Test Value Changes:** It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator 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 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 (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 eCRF. 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 will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you

felt since yesterday/last time we spoke?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRFs provided by the sponsor. Serious AE collection is to begin after a subject has signed the ICF.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in [Section 5.3](#). Special attention should be paid to recording hospitalization and concomitant medications.

### **5.3      Immediately Reportable Events**

The investigator must immediately report after either the investigator or site personnel become aware of any SAE, DILI, or confirmed pregnancy, by telephone, fax, or e-mail to INC Research as outlined in [Appendix 1](#). An IRE form must be completed and sent by e-mail, fax, or overnight courier to INC Research. (Please note that the IRE form is NOT the AE eCRF.)

Subjects experiencing SAEs should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to INC Research.

#### **5.3.1      Hyponatremia-related Adverse Events**

##### **5.3.1.1      Rapid Correction of Serum Sodium**

When tolvaptan is not administered with adequate fluid intake, overly rapid correction of serum sodium may occur. Rapid correction of serum sodium level may lead to osmotic demyelination syndrome, a condition that can lead to severe brain damage and even death. Age-appropriate neurological examinations will be performed during administration of tolvaptan to monitor changes in health status in addition to serum sodium. This protocol is designed to provide adequate vigilance during the administration of tolvaptan to ensure that over rapid correction does not occur in this pediatric population.

Rapid correction of hyponatremia is defined as any increase in serum sodium [REDACTED] [REDACTED]. If this change is observed during the trial, it should be reported as an IRE following the instructions detailed in [Section 5.3](#) of the protocol.

### **5.3.1.2 Other Hyponatremia-related Adverse Events**

Other events related to hyponatremia should be monitored closely and reported as appropriate depending on their severity:

- Absolute serum sodium level  $\geq 145$  mEq/L
- Any increase in serum sodium  $> 8$  mEq/L [mmol/L] over a 10-hour period
- Neurological symptoms or other signs or symptoms suggestive of osmotic demyelination
- Worsening symptoms of hyponatremia
- Hypovolemia or hypotension requiring intervention
- Signs and symptoms of dehydration

All AEs must be monitored until symptom resolution or until the condition stabilizes.

## **5.4 Potential Drug-induced Liver Injury**

For a subject who experiences an elevation in AST or ALT that is  $\geq 2 \times$  ULN or whose levels increase  $\geq 2$  times their initial baseline value, a total bilirubin level should also be evaluated. Elevated values should be confirmed via retest. If the total bilirubin is  $\geq 2 \times$  ULN or  $\geq 2$  times their baseline value, an IRE form should be completed with all values listed and also should be reported as an AE on the eCRFs.

If hepatic injury is suspected, tolvaptan should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine probable cause. Such an event should be reported and followed until resolution.

### **5.4.1 Liver Transaminase Elevations**

Management of abnormal liver function test results should be based on the investigator's clinical judgment. A liver function test result that is  $2 \times$  ULN is generally accepted as a medically significant occurrence across various medical disciplines.

For a subject that experiences an elevation in AST or ALT that is  $\geq 2 \times$  ULN or whose levels increase  $\geq 2$  times their initial baseline value in subjects with an elevated baseline value, a total bilirubin level should also be evaluated. If the total bilirubin is  $\geq 2 \times$  ULN or  $\geq 2$  times their baseline value in subjects with an elevated baseline value, an IRE form with all values listed should be completed and also reported as an AE on the eCRFs.

The following guideline for repeat testing may be used by investigators as a reference for any subject with an ALT or AST  $\geq 2 \times \text{ULN}$ :

- 1) ALT, AST, alkaline phosphatase, and total bilirubin should be repeated within 48 to 72 hours (needed to confirm abnormalities and determine if they are increasing or decreasing).
- 2) Inquiries should be made about symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and/or rash) and signs like jaundice, yellowish discoloration of sclera, etc.
- 3) If discharged or transferred, the subjects should be retested locally and results given to the investigator immediately, along with that laboratory's normal ranges.
- 4) Close observation is required if symptoms persist or repeat testing shows ALT or AST  $\geq 3 \times \text{ULN}$  for subjects with normal baseline measures OR 2-fold increases above baseline values for subjects with elevated values before drug exposure. If close monitoring is not possible, the drug should be interrupted until such monitoring is possible or the drug should be permanently discontinued.
- 5) All trial subjects with evidence of possible drug-induced liver injury should be followed until all abnormalities return to normal or to the baseline state.

Close observation may involve:

- 1) Repeating liver enzymes and serum bilirubin tests 2 or 3 times weekly.
- 2) Frequency of retesting can decrease to once a week or less if abnormalities stabilize or if the trial drug has been interrupted/discontinued and the subject is asymptomatic.
- 3) Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- 4) Obtaining a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, special diets, and change in diet.
- 5) Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- 6) Obtaining a history of exposure to environmental chemical agents.
- 7) Obtaining additional tests to evaluate liver function, as appropriate (eg, international normalized ratio [INR], direct bilirubin).
- 8) Considering gastroenterology or hepatology consultations.

#### **5.4.1.1 Criteria for Discontinuation Due to Liver Transaminase Elevations**

A subject must be discontinued from the trial on confirmation of any of the following criteria:

- 1) ALT or AST  $\geq 8 \times$  ULN
- 2) ALT or AST  $\geq 5 \times$  ULN for more than 2 weeks
- 3) ALT or AST  $\geq 3 \times$  ULN AND (total bilirubin  $\geq 2 \times$  ULN or INR  $> 1.5$ )
- 4) ALT or AST  $\geq 3 \times$  ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $> 5\%$ ) and signs of jaundice

If there is any question about how to proceed with a particular subject's case, do not hesitate to contact your regional medical monitor to discuss. The FDA has issued a guidance for industry regarding this topic. This guidance is not specific to hyponatremia. Otsuka is integrating many of the recommendations in this guidance into all of its clinical research programs. Links to this guidance and information from the FDA regarding drug-induced liver injury are provided in the references. <sup>31,32</sup>

#### **5.5 Pregnancy**

Women of childbearing potential (WOCBP) are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months).

For WOCBP and for males who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months) or remains fully abstinent (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] or withdrawal are not acceptable methods of contraception), 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, condom with spermicide, or sponge with spermicide. The following 3 contraceptive methods are not allowed in this trial: birth control pills, birth control depot injection, and birth control implant. Any single method of birth control, including vasectomy and tubal ligation, may

fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

Before enrolling WOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all WOCBP. The topics should generally include:

- General information
- ICF/assent form, as applicable
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject or the subject's parent/legal /guardian or legally acceptable representative must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed with the subject and/or the parent/legal guardian or legally acceptable representative.

A urine and/or serum pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening on all WOCBP and female subjects  $\geq$  12 years of age and all female subjects  $<$  12 years of age, if menstruation has started. If a urine test is performed and is positive, the investigator will follow up with a confirmatory serum test.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect 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 tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. (Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with INC Research [see [Appendix 1](#) for contact information].)

The investigator must immediately notify INC Research of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and forward it to INC Research. INC Research will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

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

## **5.6 Procedure for Breaking the Blind**

Not applicable as this is an open-label trial.

## **5.7 Follow-up of Adverse Events**

For this trial, information on AEs will be followed for up to 14 days post-last dose for all subjects or until resolution, whichever is longer.

### **5.7.1 Follow-up of Nonserious Adverse Events**

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status noted. If a subject has an AE or has not recovered from an AE at the last scheduled contact, follow-up contacts will be scheduled at least every 4 weeks until resolution of the AE is confirmed or the condition is considered clinically stable. All nonserious events that are ongoing at the last scheduled contact will be recorded as ongoing on the eCRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

### **5.7.2 Follow-up of Serious Adverse Events**

This trial requires that subjects be actively monitored for SAEs up to 14 days post-last dose or until resolution of the SAE, whichever is longer.

Serious AEs that are **identified or ongoing at the last scheduled contact** must be recorded on the AE eCRF page and reported to INC Research according to the reporting procedures outlined in [Section 5.3](#). This may include **unresolved previously reported SAEs, or new SAEs**. The investigator will follow SAEs until the events are resolved,

stabilized, or the subject is lost to follow-up. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to INC Research up to the point the event has been resolved.

### **5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring After Last Scheduled Contact**

Any new SAEs reported by the subject to the investigator that occur **after the last scheduled contact**, and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to INC Research. This may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined trial period (ie, up to last scheduled contact). The investigator should follow serious related AEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to INC Research up to the point the event has been resolved.

## **6 Pharmacokinetic/Pharmacodynamic Analyses**

### **6.1 Pharmacokinetic Analysis**

Tolvaptan and metabolite plasma concentrations will be summarized using descriptive statistics (n, median, mean, standard deviation [SD], percent coefficient of variation [CV], minimum, and maximum) by dose group and time point. Plasma PK parameters, including tolvaptan  $C_{max}$ ,  $t_{max}$ ,  $AUC_{0-24h}$ , and clearance (dose divided by  $AUC_{0-24h}$ ) on Day 1, and volume of distribution on Day 1, will be summarized using descriptive statistics by dose group and age group (age [REDACTED] | [REDACTED]). These parameters will be analyzed to assess the potential effects of age, sex, race, and disease state on tolvaptan PK.

A population analysis will be performed and reported separately.

### **6.2 Pharmacodynamic Analysis**

Urine volume will be summarized by 6-hour intervals using descriptive statistics. Fluid intake and the calculated value of fluid balance will be summarized for each 6-hour period and for the 24-hour daily interval on Days 1 and 2 in Treatment Phase A using descriptive statistics. A subgroup analysis by the disease etiology of hyponatremia or by

fluid status (euvolemic, hypervolemic) may be conducted if there are sufficient subjects in each category.

Urine osmolality and urine creatinine, potassium, and sodium concentrations will be summarized by collection interval and for zero to 24 hours on Days 1 and 2 in Treatment Phase A using descriptive statistics.

Missing urine concentrations or volumes will not be imputed. All calculations will use nominal times.

If urine volume during a collection interval is zero, then the amount excreted for that interval will be set to missing; values for 24 hours will be determined.

Correlations between urine output or fluid balance and change in serum sodium concentration may be explored graphically.

Correlations between tolvaptan AUC values and urine output on Day 1 may be explored graphically.

## **7 Statistical Analysis**

### **7.1 Sample Size**

#### **7.1.1 Sample Size for Efficacy**

A total of 70 randomized subjects will provide 90% power to detect a treatment difference of 4 mEq/L (mmol/L) in change in serum sodium from Day 2 (or 2a) at the end of Treatment Phase A to the end of Treatment Phase B using a 2-sided alpha of 0.05. An SD of 5 in change of serum sodium was used for the sample size calculation. After the end of Treatment Phase A at Day 2 (or 2a), subjects will be randomized at a ratio of 1:1 to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early Withdrawal). Sample size re-estimation will be conducted when 90% of the subjects finish (complete or discontinue) the trial. The trial must include no fewer than 60 subjects on IMP for the assessment of safety based on regulatory feedback.

#### **7.1.2 Sample Size for Pharmacokinetic Parameters**

Sample size to establish similarity between the CIs for PK parameter estimates between adults and pediatrics is based on PK data of clearance. [REDACTED]

[REDACTED]. To be conservative, it is assumed that the CV of clearance is 0.42. In

order to establish a 95% CI within 60% and 140% of the point estimate for the geometric mean estimate of clearance in an age group (age < 10 or  $\geq$  10 years), under the assumption that the geometric means estimates of clearance are equal between adult and pediatric subjects, CIs of the ratio of geometric means of pediatrics and adults will be constructed. Twenty pediatric subjects and 80 adult subjects are needed to have 90% power to establish a 95% CI of the ratio of geometric means within 0.71 and 1.40. In the actual analysis, all 81 adult subjects' data will be used.

## 7.2 Datasets for Analysis

The following samples are defined for this trial:

- Enrolled Sample consists of all subjects for whom an ICF/assent form was signed for the trial.
- Treatment Phase A Safety Sample consists of all subjects who receive at least one dose of IMP in Treatment Phase A of the trial.
- Treatment Phase B Safety Sample consists of all randomized late withdrawal subjects who receive at least one dose of IMP in Treatment Phase B of the trial and all randomized early withdrawal subjects.
- Treatment Phase A Efficacy Sample consists of all subjects who are in Treatment Phase A Safety Sample and have baseline and at least one post-baseline efficacy evaluation in Treatment Phase A.
- Treatment Phase B Efficacy Sample is based on the intent-to-treat (ITT) principle; the full analysis dataset will be composed of all subjects who are in the Treatment Phase B Safety Sample and have both baseline and at least one post-baseline efficacy evaluation in Treatment Phase B.

Core dataset for efficacy analyses will be based on the ITT population. In order to handle missing data and restrictions imposed by different types of analyses (eg, change from baseline analysis), datasets derived from the ITT dataset will be used for the efficacy analyses.

## 7.3 Handling of Missing Data

For the primary endpoint analysis, missing data will be handled by analysis of mixed-model repeated measures (MMRM) methodology under the assumption of missing at random. The MMRM analysis will be performed based on the observed cases (OC) data. In order to assess sensitivity of results due to missing data, last observation carried forward (LOCF) analysis will be performed as a sensitivity analysis. In contrast to the OC dataset, which will consist of the actual observations recorded at each visit, the LOCF dataset will include data recorded at a scheduled visit (ie, all OC data, or, if no observation is recorded at that visit, data carried forward from the previously scheduled

visit). Baseline data will not be carried forward to impute missing values for the LOCF dataset.

## **7.4 Primary and Secondary Outcome Analysis**

### **7.4.1 Primary Outcome Analysis**

The primary endpoint in this trial is the change in serum sodium level for responders from Day 2 (or 2a) at the end of Treatment Phase A (where all subjects receive tolvaptan) to the end of Treatment Phase B for the Early compared to Late Withdrawal groups. The null hypothesis of this comparison is that there is no difference between the Late and the Early Withdrawal groups in change of serum sodium level from Day 2 (or 2a) at the end of Treatment Phase A to the end of Treatment Phase B. The analysis of the primary endpoint is based on the Treatment Phase B Efficacy Sample. Once a subject is randomized to Treatment Phase B, any additional therapies for the purpose of raising serum sodium, including fluid restriction, will be considered rescue therapy. Upon receipt of rescue therapy, a subject's endpoint data will be collected and then censored thereafter. The primary analysis of this protocol is based on the data collected in this manner.

A sensitivity analysis will be provided to include serum sodium data collected while an Early Withdrawal subject is under fluid restriction for the analysis of the primary endpoint. This sensitivity analysis would become the primary analysis if at least 30% of the Early Withdrawal subjects do not have serum sodium data at 24 and 48 hours post-randomization due to application of fluid restriction in the withdrawal phase of the protocol.

The MMRM analysis with an unstructured variance covariance structure based on the OC dataset will be performed on the primary endpoint. The MMRM model will include fixed effect of treatment, age subgroup [REDACTED], serum sodium response subgroup ([REDACTED]), underlying etiology ([REDACTED] [REDACTED]), visit, treatment visit interaction, and covariate of baseline and baseline visit interaction. Statistical test of the least squares (LS) mean differences between treatment groups at the end of Treatment Phase B of the MMRM analysis will serve as the primary analysis.

As a sensitivity analysis, analysis of covariance with baseline value as covariate and treatment, age subgroup, serum sodium response subgroup, and underlying etiology of hyponatremia as factors will be applied to the LOCF dataset. Treatment comparison between the Late and Early Withdrawal groups will be conducted by comparing LS means.

For the primary endpoint analysis, baseline is the last evaluation of serum sodium level in Treatment Phase A prior to randomization.

## **7.4.2 Secondary Outcome Analyses**

### **7.4.2.1 Secondary Efficacy Outcome Analyses**

For all subjects, the key secondary endpoint is the change in serum sodium concentration at the end of Day 2 (or 2a) at the end of Treatment Phase A. The analysis of the key secondary endpoint will be based on the Treatment Phase A Efficacy Sample.

A paired Student's t-test will be used to analyze the key secondary endpoint.

For the key secondary efficacy analysis, a hierarchical testing procedure will be used to maintain the overall experiment-wise type I error rate at 0.05. Thus, if the primary efficacy analysis yields a statistically significant result at alpha level of 0.05 (2-sided), then the paired t-test will be performed at an alpha level of 0.05 for the key secondary endpoint.

Baseline for the key secondary analysis is the last evaluation prior to first dose of IMP in Treatment Phase A.

### **7.4.2.2 Secondary Safety Outcome Analyses**

Other secondary endpoints include:

- Percentage of subjects with overly rapid increase in serum sodium level [REDACTED].
- Change in serum sodium level from 24 hours post-last dose to 7 days post-last dose.
- Percentage of subjects requiring rescue therapy (other than fluid restriction) during Treatment Phase A and Treatment Phase B.
- Percentage of subjects requiring fluid restriction during Treatment Phase A and Treatment Phase B.
- Other secondary safety outcomes to be assessed are presented in Section 3.5.3.1 (Vital signs, blood pressure, clinical laboratory tests, body weight, and neurological examinations)

Descriptive statistics along with 2-sided 95% CIs will be applied for percentage of subjects with overly rapid increase in serum sodium and percentage of subjects requiring rescue therapy or fluid restriction.

The change in serum sodium level from 24 hours post-last dose to 7 days post-last dose will be summarized using a paired Student's t-test.

#### **7.4.2.3 Pharmacokinetic Parameters**

Previously obtained PK data from 81 adult subjects who received a 30-mg dose of tolvaptan will be included in the analysis to show the similarity for PK parameter estimates between adult and pediatric subjects. An analysis of variance model will be performed on the natural-log transformed PK parameters using the MIXED procedure in SAS, in which only one fixed effect of subject group (pediatric and adult groups) is included in the model. The anti-logs of the difference of LS means and the confidence limits will provide the estimate and 90% CI for the ratio of the geometric means of pediatric group and adult group. Similarity of a PK parameter between pediatrics and adults will be indicated if the 90% CI for the ratio of the population geometric means is contained within the equivalence limits of 0.6 to 1.4.

#### **7.4.3 Exploratory Outcome Analyses**

Details will be provided in the statistical analysis plan.

The change in serum sodium concentration in nonresponders continuing on tolvaptan therapy by change from baseline at the end of Treatment Phase B compared to the end of Treatment Phase A will be analyzed using a paired Student's t-test.

The procedure for the analysis of data for the QoL assessments will be provided in the statistical analysis plan (SAP).

The analysis for the following exploratory PD endpoints is described in [Section 6.2](#):

- In all subjects, 24-hour excretion of sodium, creatinine, and osmolality on Days 1 and 2
- 24-hour sodium clearance on Day 1

#### **7.4.4 Interim Analysis**

It was recommended by the FDA that the sample size should be re-estimated when approximately 90% of the subjects had finished the trial. The sample size re-estimation will assess the variability of change from Day 2 (or 2a) at the end Treatment Phase A to the end of Treatment Phase B in serum sodium level by using the pooled variance of the 2 treatment groups. At the trial planning stage, an SD of 5 was used to detect a treatment difference of 4, resulting in a sample size of 70 with a 2-sided alpha of 0.05 and 90% power. In case the variance ratio (equal to the observed pooled variance divided by 25, the square of 5 as an SD used in the sample size calculation) is  $\leq 1$ , no sample size increase will be made, and the trial will proceed to finish enrollment of 70 randomized subjects. In case the variance ratio is  $> 1$ , the sample size re-estimation will be equal to

70 multiplied by the variance ratio, then rounded up to the nearest even number. [Table 7.4.4-1](#) provides an example of the sample size re-estimation under different variance ratios.

<b>Table 7.4.4-1      Sample Size Re-estimation</b>	
<b>Variance Ratio</b>	<b>Sample Size</b>
1.1	78
1.2	84
1.3	92
1.4	78
1.5	106

## **7.5      Analysis of Demographic and Baseline Characteristics**

Demographic characteristics and medical history at Screening will be summarized by descriptive statistics, eg, proportion, mean, median, SD, minimum, and maximum values. These summary statistics will be reviewed to identify any potential lack of balance between the groups.

## **7.6      Safety Analysis**

Safety analysis will be conducted based on the Safety Samples, which are defined in [Section 7.2](#). Safety variables (in addition to those listed in [Section 7.4.2.2](#)) to be analyzed include AEs, clinical laboratory data, and vital signs. In general, summary statistics will be provided for safety variables based on all available data.

Safety analyses will be performed for Treatment Phase A and Treatment Phase B separately.

### **7.6.1      Adverse Events**

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

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

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

### **7.6.2 Clinical Laboratory Assessment Data**

Summary statistics for changes from baseline in the clinical laboratory measurements will be provided. Potentially clinically significant results in laboratory tests will also be summarized. Shift tables will be produced for assessing changes from baseline in clinical laboratory measurements in low-normal-high scale.

### **7.6.3 Physical Examination and Vital Signs Data**

In general, summary statistics for changes from baseline in vital signs will be provided. Potentially clinically significant results in vital signs will also be summarized. No analysis will be performed on physical examination data. Physical examination data will be listed.

## **8 Management of Investigational Medicinal Product**

### **8.1 Packaging and Labeling**

The IMP will be provided to the investigator(s) by the sponsor (or designated agent). The IMP will be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets in blister packs or as 60 mL bottles containing 1 mg/mL (0.1% w/v) tolvaptan suspension. Each blister pack and suspension bottle used in the dosing period will be labeled to clearly disclose the compound ID, trial number, the sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements, and other information required by local regulatory authorities. Each site will be supplied with bottle(s) containing placebo tablets to use for subject screening purposes. Each placebo bottle will be labeled to clearly disclose the compound ID, trial number, instruction for use, route of administration, appropriate precautionary statement, and other information required by the local regulatory authorities. For dosing suspension, syringes and bottle adaptors will be made available to the sites.

### **8.2 Storage**

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to the investigators and their designees. Neither investigators nor any designees may provide trial drugs to any subject not participating in this protocol.

The IMP blister packs will be stored at 25°C (77°F) or below, with excursions allowed from 15 to 30°C (59 to 86°F). The IMP suspension bottles will be stored at 2 to 8°C (35.6 to 46.4°F) and protected from light. The clinical site staff or designated personnel will maintain a temperature log in the IMP storage area recording the temperature at least once each working day.

### **8.3 Accountability**

The investigator, or designee, 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 and/or partially used IMP must be returned to OPDC (or a designated contractor).

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

### **8.5 Reporting of Product Quality Complaints**

A product quality complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate, or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness, or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty 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 or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) within 24 hours of becoming aware of the PQC by e-mail or telephone and according to the procedure outlined below.

- Online – Send information required for reporting purposes (listed below) to [OAPI-EQCProductComplaints@Otsuka-us.com](mailto:OAPI-EQCProductComplaints@Otsuka-us.com)
- Phone – Rocky Mountain Call Center at +1-800-438-6055

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

### **8.5.2 Information Required for Reporting Purposes**

Information required for reporting purposes include:

- Description of complaint
- Reporter identification (eg, subject, investigator, site)
- 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, it should be indicated whether the complaint sample is available for return. If the complaint sample is available for return, the sample should be returned in the product retrieval package, which will be provided by Otsuka America Pharmaceutical, Inc.-Ethics, Quality and Compliance (OAPI-EQC).

It should be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to OAPI-EQC for complaint investigation.

### **8.5.4 Assessment/Evaluation**

Assessment and evaluation of PQCs will be handled by OAPI EQC-QM group.

## **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 progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, 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 clinic, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- 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's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of each clinician (or designee) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above. Any changes to information in the trial progress notes and other source documents will be initialled and dated on the day the change is made by a site trial staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the

correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician. If electronic data systems are being utilized, a full audit trail of changes must be maintained.

Information from the trial progress notes and other source documents will be promptly and LEGIBLY transcribed to eCRFs for transmission to the sponsor. Changes will be entered by investigative site personnel directly onto electronic CRFs in the sponsor's electronic data capture (EDC) system. Changes to the data will be captured by an automatic audit trail.

### **9.3 File Management at the Trial Site**

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6<sup>30</sup> and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

### **9.4 Records Retention at the Trial Site**

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following 3 periods:

- A period of at least 2 years following the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities; OR
- Longer, region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator 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 documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

## **10 Quality Control and Quality Assurance**

### **10.1 Monitoring**

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and 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 site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and clinical site personnel 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 be limited to, IMP supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits.

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

## **11 Ethics and Responsibility**

This trial must be conducted in compliance with the protocol, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB or IEC according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB/IEC will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling eCRFs, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

Financial aspects, subject insurance, and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

## **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 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 numbers in eCRFs. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject 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/IEC. 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/IEC, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB/IEC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB/IEC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB/IEC, 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 participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

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<sup>22</sup> [REDACTED]. Physiologically-based pharmacokinetic modeling of tolvaptan for the prediction of syrup suspension doses in pediatric subjects from 4 Weeks to 4 years of age. Otsuka Clinical Study Report for Protocol 156-13-214, issued 27 Feb 2014, amended 13 Mar 2014.

<sup>23</sup> [REDACTED] A Randomized Double-Blind Study to Assess the Safety and Pharmacokinetics of Concomitant Administration of Orally Administered OPC 41061 Tablets and Ketoconazole in Healthy Adult Male and Female Volunteers. Otsuka Clinical Study Report for Protocol 156-98-201, issued 07 Dec 2000, amended 15 Feb 2001, 28 May 2003, and 03 Mar 2004.

<sup>24</sup> Moritz ML, Ayus JC. Preventing neurological complications from dysnatremias in children. *Pediatr Nephrol*. 2005;20:1687-700.

<sup>25</sup> Moritz ML, Ayus JC. New aspects in the pathogenesis, prevention, and treatment of hyponatremic encephalopathy in children [Review]. *Pediatr Nephrol*. 2010;25(7):1225-38.

<sup>26</sup> Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med*. 2007;120(11 Suppl 1):S1-S21.

<sup>27</sup> Karp BI, Laureno R. Pontine and extrapontine myelinolysis; a neurologic disorder following rapid correction of hyponatremia. *Medicine*. 1993;72:359-73.

<sup>28</sup> El-Kabbani O, Darmanin C, Chung RP. Sorbitol dehydrogenase: structure, function and ligand design. *Curr Med Chem*. 2004 Feb;11(4):465-76.

<sup>29</sup> Mayatepek E, Hoffmann B, Meissner T. Inborn errors of carbohydrate metabolism. *Best Practice & Research Clinical Gastroenterology*. 2010;24:607-618.

<sup>30</sup> International Conference on Harmonisation (ICH) [homepage on the Internet]. E6: Good Clinical Practice: Consolidated Guideline [finalized 1996 May, corrected 1996 Jun 1996; cited 2005 Dec 6].

<sup>31</sup> U.S. Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation [report on the Internet]. 2009 Jul [cited 15 Feb 2014].

<sup>32</sup> U.S. Food and Drug Administration. [homepage on the Internet]. Silver Spring: [updated 05 Aug 2015; cited 12 Nov 2015].

## Appendix 1                   Names of Sponsor Personnel

Report Immediately Reportable Events (serious adverse events, potential drug-induced liver injuries, and pregnancies) as follows:

Country	INC Research Safety Fax Numbers	
Belgium		
Canada		(primary) or [REDACTED] (alternative)
Czech Republic		
Germany		
Italy		
Poland		
Romania		
Spain		
Turkey	No toll free number available; please dial [REDACTED] (primary) or [REDACTED] (alternative)	
United Kingdom		
United States	(primary) or [REDACTED]	(alternative)

[REDACTED]:  
 [REDACTED]  
 Phone [REDACTED]; Fax [REDACTED]

[REDACTED]  
 [REDACTED] t  
 Phone [REDACTED]; Fax [REDACTED]

[REDACTED]  
 [REDACTED]  
 Phone [REDACTED]; Fax [REDACTED]

## Appendix 2

## Institutions Concerned With the Trial

Institutions concerned with this trial are:

### Sponsor

Otsuka Pharmaceutical Development & Commercialization, Inc.  
2440 Research Boulevard  
Rockville, Maryland 20850, USA  
Phone: [REDACTED]

### Medical Monitoring

INC Research  
3201 Beechleaf Court, Suite 600  
Raleigh, North Carolina 27604-1547, USA  
Phone: [REDACTED]  
Fax: [REDACTED]

### Medical Monitor:

[REDACTED]  
[REDACTED]  
[REDACTED]  
Phone [REDACTED]; Mobile [REDACTED]  
[REDACTED]  
Fax: [REDACTED]  
E-Mail: [REDACTED]

### Trial Management & Clinical Monitoring

INC Research  
3201 Beechleaf Court, Suite 600  
Raleigh, North Carolina 27604-1547, USA  
Phone: [REDACTED]

### Electronic Data Capture

MediData Solutions  
79 Fifth Avenue, 8th Floor  
New York, New York 10003, USA  
Phone: [REDACTED]  
Fax: [REDACTED]

### Investigational Materials

Fisher Clinical Services  
7554 Schantz Road  
Allentown, Pennsylvania 18106, USA  
Phone: [REDACTED]  
Fax: [REDACTED]

### Study Communications & Patient/Site Support

Matthews Media Group  
700 King Farm Boulevard, Suite 500  
Rockville, MD 20850, USA  
Phone: [REDACTED]

### IRT Systems (treatment randomization)

S-CLINICA  
1500 Market Street  
12th Floor East Tower  
Philadelphia, Pennsylvania 19102, USA  
Phone: [REDACTED]

### Central ECG Storage

eResearch Technology, Inc.  
1818 Market Street  
Philadelphia, Pennsylvania 19103, USA  
Phone: [REDACTED]

### Clinical Laboratory Supplies

Covance Central Laboratory Services  
8211 SciCor Drive  
Indianapolis, Indiana 46214, USA  
Phone: [REDACTED]

### Central Laboratory (PK)

ICON Development Solutions, Inc.  
8282 Halsey Road  
Whitesboro, New York 13492, USA  
Phone: [REDACTED]

**IDMC Support**

Chiltern (formerly Theorem Clinical Research)

1016 West Ninth Avenue

King of Prussia, PA 19406, USA

Phone: [REDACTED]

Fax: [REDACTED]

## Appendix 3 Handling and Shipment of Bioanalytical Samples

All tubes must be labeled such that the protocol number, subject number, date of collection, and time can be verified. The OPDC Bioanalytical Scientist must approve the labels, prior to use. It is important to note the exact time of the blood collection on the eCRF, not the scheduled time for the drawing. The exact time of dosing should also be noted.

## Plasma Samples for Tolvaptan

Blood will be collected into tubes containing lithium heparin anticoagulant. The tubes should be gently inverted 3 to 4 times and then centrifuged at 2,000 to 3,000 rpm for at least 10 to 15 minutes at 4°C. The rpm should be kept at a constant setting throughout the trial. Plasma should be stored in a freezer at -20°C or colder or on dry ice. Samples should be shipped after a subject has completed treatment and the final PK sample has been drawn and processed so as to include the entire set of samples for each subject within one shipment.

## Shipment of Plasma

The label on each tube must correspond to the requisition sheet and must be firmly attached with transparent tape and should include the protocol number, subject number, date of collection, and sample protocol time elapsed postdose. Samples must be neatly packed and retained in an insulated container (place container supplied within a cardboard box) with enough dry ice to last 72 hours (ie, at least 15 to 20 pounds). Boxes should be completely filled with dry ice to avoid air spaces that will allow evaporation of the dry ice. The container should be sealed with tape and placed in a cardboard box. The recipient must be alerted of shipments. Packages will not be shipped on Thursdays, Fridays, Saturdays, or any day prior to a holiday. Shipments will be via an overnight carrier.

**Appendix 4****Tanner Staging****Classification of Sex Maturity Stages in Girls**

<b>Stage</b>	<b>Pubic Hair</b>	<b>Breasts</b>
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; areolar diameter increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant but amount less than adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature; nipple projects, areola part of the general breast contour

**Classification of Sex Maturity Stages in Boys**

<b>Stage</b>	<b>Pubic Hair</b>	<b>Penis</b>	<b>Testes</b>
1	Preadolescent	Preadolescent	Preadolescent
2	Scanty, long, slightly pigmented	Slight enlargement	Enlarged scrotum, pink texture altered
3	Darker, starts to curl, small amount	Longer	Larger
4	Resembles adult type but less in quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

## Appendix 5                    Protocol Amendments

**Amendment Number:**            1

**Issue Date:**                    04 Nov 2013

### **PURPOSE:**

- To update the clinical management representative for this trial
- To remove the serum chemistry assessment at 7 ( $\pm 1$ ) days post-randomization
- To change the sample size from 80 to 70 responders
- To clarify that subjects who cannot safely swallow the tablet are excluded until a liquid formulation is available
- To add neurological exam as an exploratory variable
- To update the dosing rationale based on starting doses (mg/kg) used for hyponatremia trials of tolvaptan in adults
- To change early termination from the 7-day Follow-up Visit to Day 5/6
- To clarify that Phase B (Randomization Phase) applies to all subjects
- To correct the definition of a rapid correction of serum sodium
- To update the interim analysis
- To update the contact list for reporting an IRE

**BACKGROUND:** This protocol is being amended to provide a more developed argument for the dosing rationale. The statistical section has also been updated.

### **MODIFICATIONS TO PROTOCOL:**

- **Bold and underlined text:**    Changed Text
- **~~Bold and strike through text:~~**        Deleted Text
- ***Bold and italicized text:***        Added Text

### COVER PAGE

#### **Added and Changed Text:**

#### **REVISED CLINICAL PROTOCOL**

Clinical Management

[REDACTED] t  
Phone [REDACTED]; Fax [REDACTED]

E-mail: [REDACTED]  
[REDACTED]

Phone [REDACTED]

; Fax [REDACTED]

E-mail: [REDACTED]

***Date of Amendment 1: 04 Nov 2013***

#### FOOTER

##### **Changed Text:**

**Final 03 Jul 2013 Amendment 1: 04 Nov 2013**

#### SYNOPSIS TRIAL DESIGN

##### **Deleted Text:**

Phase C (Follow-up Phase): All subjects will be monitored and treated as clinically warranted per the investigator's preferred standard of care for up to 3 additional days after the last dose of tolvaptan (note: the Early Withdrawal group should be monitored for the first 48 hours post-last dose). All subjects will have an additional serum sodium measurement at 72 ( $\pm$  4) hours post randomization and 7 ( $\pm$  1) days post-randomization. **An additional chemistry panel will also be collected 7 ( $\pm$  1) days post randomization.** A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-last dose.

#### SYNOPSIS SUBJECT POPULATION

##### **Changed Text:**

This trial will include up to 100 male and female subjects aged  $\geq$  4 weeks (or  $\geq$  44 weeks adjusted gestational age for premature births) to  $<$  18 years who have been diagnosed with euvolemic or hypervolemic hyponatremia ( $<$  130 mmol/L) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). It is expected that **80** **70** subjects will have a serum sodium increase of  $\geq$  4 mmol/L (ie, responders).

**Eighty Seventy** randomized subjects will provide 90% power to detect a treatment difference of 4 mmol/L in change in serum sodium from randomization (at the end of Day 2/3 [Phase A]) to the end of Day 4/5 (2 days after randomization [Phase B]). Age groups will be stratified such that half (**40** **35**) of these subjects will be  $<$  10 years old with at least 25% (**20** **17**) of subjects  $<$  6 years old. Subjects who are

defined as responders will be further stratified by the magnitude of serum sodium response to tolvaptan ( $\leq 7$  and  $> 7$  mmol/L) and underlying etiology of hyponatremia.

## SYNOPSIS INVESTIGATIONAL MEDICINAL PRODUCT, DOSE, FORMULATION, MODE OF ADMINISTRATION

### Changed Text:

- Subjects  $< 2$  years of age, ~~or~~ weighing  $< 10$  kg, **or who cannot safely swallow the tablet** will be excluded until the availability of a liquid formulation. Dosing information will be available at that time.

## SYNOPSIS CRITERIA FOR EVALUATION

### Added Text:

#### *Exploratory Endpoints:*

##### Efficacy:

- *In nonresponders continuing on tolvaptan therapy, change in trough serum sodium concentration on Day 6 compared to Day 4*

##### Safety:

- *Neurological examinations*

#### Pharmacodynamic:

- *In all subjects, 24-hour excretion of sodium, creatinine, and osmoles on Days 1 and 2*
- *24-hour sodium clearance*

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

### Added Text:

***BW***      *Body weight*

## Section 2.1 TRIAL RATIONALE

### Changed Text:

The proposed population size of 100 subjects should provide **80** **70** responders, which has adequate power ( $> 90\%$ ) to test for statistical significance in the primary endpoint. Enrollment is expected to take 3 years using up to 50 sites globally. Additional blood sampling will be included across populations to provide PK information.

## Section 2.1.1 DOSING RATIONALE

**Added and Changed Text:**

Enrolled subjects will be dosed based on age, weight, and the use of CYP3A4 inhibitors. Subjects < 2 years of age or < 10 kg will be excluded until the availability of a liquid formulation. Subjects  $\geq$  2 years of age and weighing  $\geq$  10 to < 20 kg will receive an oral once daily dose of tolvaptan starting as a 3.75-mg spray-dried tablet. Subjects weighing 20 to 50 kg, inclusive, will receive an oral once daily dose of tolvaptan starting as a 7.5 mg spray-dried tablet. Subjects weighing > 50 kg will receive an oral once daily dose of tolvaptan starting as a 15-mg spray-dried tablet. For subjects weighing  $\geq$  20 kg and taking moderate inhibitors of CYP3A4, a half dose will be used (3.75 or 7.5 mg, by weight). For subjects weighing > 50 kg and taking potent inhibitors of CYP3A4, a one quarter dose will be used (3.75 mg). Subjects weighing < 20 kg and who are taking any CYP3A4 inhibitors will be excluded from the trial until such time that an alternate dosing formulation is available.

~~It is estimated that subjects 6 years of age weigh approximately 25 kg.<sup>17</sup> A 7.5-mg dose in a subject weighing 25 kg would be 0.3 mg/kg. For a subject weighing 50 kg, a 7.5-mg dose would be a 0.15 mg/kg dose. For a 15-mg dose, the corresponding body weights for 0.3 and 0.15 mg/kg doses would be 50 to 100 kg.~~

In the pivotal hyponatremia trials,<sup>13,18,19</sup> the starting 15-mg dose was administered to adult subjects weighing 34.0 to 164.7 kg; in terms of mg/kg, the starting dose of tolvaptan ranged from 0.09 to 0.44 mg/kg. The weight cutoffs for this trial were selected to produce mg/kg doses of tolvaptan within the range observed for the adult trials. Table 2.1.1-1 outlines the mg/kg dose ranges for tolvaptan tablet doses and body weights of 10, 20, 50, 70 (standard adult man), and 100 kg.

Table 2.1.1-1 Proposed Tolvaptan Doses as mg/kg of Body Weight					
Tolvaptan Tablets	Tolvaptan Doses as mg/kg				
	BW of 10 kg	BW of 20 kg	BW of 50 kg	BW of 70 kg	BW of 100 kg
<u>15 mg</u>	-	-	<u>0.30</u>	<u>0.21</u>	<u>0.15</u>
<u>7.5 mg</u>	-	<u>0.375</u>	<u>0.15</u>	-	-
<u>3.75 mg</u>	<u>0.375</u>	<u>0.19</u>	-	-	-

BW = body weight.

Tolvaptan is a sensitive CYP3A4 substrate; plasma concentrations increased approximately 4-fold when tolvaptan was administered with the potent CYP3A4 inhibitor ketoconazole.<sup>13,20</sup> Where appropriate dose reductions are possible, tolvaptan doses may be coadministered with potent or moderate CYP3A4 inhibitors.

## Section 3.1 TYPE/DESIGN OF TRIAL

### **Deleted Text:**

Phase C (Follow-up Phase): All subjects will be monitored and treated as clinically warranted per the investigator's preferred standard of care for up to 3 additional days after the last dose of tolvaptan (note: the Early Withdrawal group should be monitored for the first 48 hours post-last dose). All subjects will have an additional serum sodium measurement at 72 ( $\pm$  4) hours post randomization and 7 ( $\pm$  1) days post randomization. **An additional chemistry panel will also be collected**

**7 ( $\pm$  1) days post randomization.** A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-last dose.

Figure 3.1-1 TRIAL DESIGN SCHEMATIC

### **Added Text:**

<sup>a</sup>Subjects must be  $\geq$  2 years of age **and weigh  $\geq$  10 kg** until development of a liquid formulation is complete.

## Section 3.2 TREATMENTS

### Added Text:

*Subjects who cannot take an oral tablet are currently excluded due to their inability to safely swallow the spray-dried tablet. Subjects weighing < 10 kg are also excluded as that weight has not been studied in previous PK trials and, therefore, the dose of tolvaptan being delivered is not confirmed. To support the enrollment of these subjects, an age and weight appropriate suspension formulation is being developed. Once available, the protocol will be amended to include the formulation.*

*Consequently, the maximum starting dose for subjects weighing > 50 kg is slightly less than 0.30 mg/kg; starting doses for subjects weighing 20 to 50 kg, inclusive, range from 0.38 to 0.15 mg/kg; starting doses for subjects weighing  $\geq$  10 to < 20 kg range from 0.375 mg/kg to slightly greater than 0.19 mg/kg. Therefore, the maximum starting doses planned for this pediatric trial are in the range previously used in adult hyponatremic subjects.*

### **Deleted Text:**

~~Some very young subjects will not be able to safely swallow the spray-dried tablet. To support the enrollment of these subjects, an age appropriate suspension formulation is being developed. Once available, the protocol will be amended to include the formulation.~~

### Section 3.3 TRIAL POPULATION

#### **Changed Text:**

This trial will include up to 100 male and female subjects aged  $\geq 4$  weeks (or  $\geq 44$  weeks adjusted gestational age for premature births) to  $< 18$  years, who have been diagnosed with euvolemic or hypervolemic hyponatremia ( $< 130$  mmol/L) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). It is expected that ~~80~~ 70 subjects will have a serum sodium increase of  $\geq 4$  mmol/L (ie, responders).

Age groups will be stratified such that half (~~40~~ 35) of these subjects will be age  $< 10$  years with at least 25% (~~20~~ 17) of subjects  $< 6$  years old. Subjects who are defined as responders will be further stratified by the magnitude of serum sodium response to tolvaptan ( $\leq 7$  and  $> 7$  mmol/L) and underlying etiology of hyponatremia.

### Section 3.5.3.2 SAFETY VARIABLE

#### **Added Text:**

##### *3.5.3.2 Safety Variable*

*The other safety variable is neurological examinations.*

### Section 3.7 TRIAL PROCEDURES

#### **Deleted Text:**

Treatment in this trial will be up to 5 days. Any initiation or titration of tolvaptan must occur in a hospital setting. Parents or legal guardians will consent and subjects will assent (as appropriate) and be screened up to 24 hours prior to dosing. Subjects who meet the inclusion and exclusion criteria will be enrolled and will be administered a 3.75-, 7.5-, or 15-mg dose based on age, weight, and the use of CYP3A4 inhibitors. At the end of Treatment Day 2 (optionally Day 3 [Phase A]), subjects who are responders will be randomized to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early Withdrawal). Subjects who are nonresponders may continue on tolvaptan therapy for 2 additional days at their highest dose or may be withdrawn from tolvaptan to be treated per the investigator's preferred standard of care. During Phase B, subjects in the Late Withdrawal group and nonresponders continuing treatment will continue treatment with tolvaptan for 2 additional days and all subjects will have serum sodium measured every 12 ( $\pm 4$ ) hours post-randomization. In Phase C, or Follow-up Phase, subjects will be monitored and treated as clinically warranted per the investigator's preferred standard of care for up to 3 additional days after the last dose of tolvaptan (note: the Early Withdrawal group should be monitored for the first 48 hours post-last dose) and will have an additional serum

sodium concentration measurement at 72 ( $\pm$  4) hours post randomization and 7 ( $\pm$  1) days post-randomization. ~~An additional chemistry panel will also be collected at 7 ( $\pm$  1) days post-randomization.~~ A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-last dose.

Table 3.7-1 SCHEDULE OF ASSESSMENTS

**Changed Text:**

Procedures	Phase A		Phase B	Phase C		
	Screening/ Baseline Visit Days -2 to -1	Initial Treatment Phase Days 1 and 2/3	Randomization Phase Days 3/4 and 4/5	Follow-up Phase Day 5/6 <u>or ET</u>	Follow-up (7 [ $\pm$ 1] days post-random.) <u>or ET</u>	Follow-up Phone Call/Visit (14 [ $\pm$ 2] days post-random.)
Informed consent and assent	X					
Review inclusion/exclusion criteria	X	Day 1: predose				
Demographic information	X					
Medical and hyponatremia history	X					
Alcohol and drug screen	X					
Pregnancy test (if applicable) <sup>a</sup>	X					
Serum chemistry	X			X	X	
Serum osmolality, FeNa, and Fe urate	X					
TSH and cortisol <sup>b</sup>	X					
Hematology and coagulation	X			X		
Urinalysis	X			X		
Urine chemistry	X	Days 1 and 2 only: 6-hour intervals starting at Hour 0				
Serum sodium <sup>c</sup>	2 assessments at least 12 hours apart	Baseline (Hour 0; within 3 [ $\pm$ 1] hours of dosing), 12 hours post-first dose, and 24 ( $\pm$ 4) hours post-previous dose	12, 24, 36, and 48 ( $\pm$ 4) hours post-random.	72 ( $\pm$ 4) hours post-random.	X	

**Table 3.7-1 Schedule of Assessments**

Procedures	Phase A		Phase B	Phase C		
	Screening/ Baseline Visit Days -2 to -1	Initial Treatment Phase Days 1 and 2/3	Randomization Phase Days 3/4 and 4/5	Follow-up Phase Day 5/6 or ET	Follow-up (7 [ $\pm$ 1] days post-random.) or ET	Follow-up Phone Call/Visit (14 [ $\pm$ 2] days post-random.)
Vital signs <sup>d</sup>	X	2, 4, 8, and 24 hours post-first dose and on Day 3, if applicable	X	X	X	
Fluid intake and urine volume		Days 1 and 2 only: 6-hour intervals starting at Hour 0				
PK plasma samples <sup>e</sup>		1, 2, 4, 12, and 24 hours post-first dose	24 and 48 hours post-random.	<b>ET only</b>	<b>ET only</b>	
12-lead ECG	X					
Directed physical examination	X	Baseline (Hour 0), 8 hours post-first dose, and Day 2/3	Daily	X	X	
Neurological examination	X	Baseline (Hour 0), 8 hours post-first dose, and Day 2/3	Daily	X	X	
Body height and weight <sup>f</sup>	X	Daily (predose): weight only	Daily (predose): weight only	Weight only	Weight only	
Clinical assessment <sup>g</sup>	X	End of Day 2/3	Day 4/5	X	X	
Randomization		Responders: End of Day 2 (optionally Day 3)				
Tolvaptan dosing <sup>h</sup>		Once daily	Once daily <sup>i</sup>			
Follow-up phone call						X
Concomitant medications	<----->					
Adverse events	<----->					

## Section 3.7.1.1 PHASE B: RANDOMIZATION PHASE

### **Added Text:**

The following procedures will be performed on Days 3/4 and 4/5 **for all subjects**:

### Section 3.7.1.3.1 FOLLOW-UP (DAY 5/6)/EARLY TERMINATION

### **Added Text:**

#### 3.7.1.3.1 Follow-up (Day 5/6)/***Early Termination***

The following procedures will be performed on Day 5/6 **or at early termination (ET)** for all subjects:

- 4) *A blood sample for PK analysis of tolvaptan will be collected at ET only if ET occurs before the last scheduled PK assessment (ie, 48 hours post-randomization for subjects continuing on tolvaptan).*

### Section 3.7.1.3.2 FOLLOW-UP

### **Deleted Text:**

#### 3.7.1.3.2 Follow-up/***Early Termination***

Subjects will be assessed for maintenance of normal or target serum sodium concentration at 7 ( $\pm$  1) days post-randomization. If the subject was discharged, he/she should return to the clinic for the serum sodium collection. **In addition, the following procedures will be performed for any subjects terminating early:**

- 1) **A serum chemistry laboratory sample will be collected.**
- 2) A blood sample for serum sodium testing will be collected. **(This blood draw can be combined with the chemistry panel as appropriate to minimize blood draws.)**
- 3) **A blood sample for PK analysis of tolvaptan will be collected at early termination (ET) only if ET occurs before the last scheduled PK assessment (ie, 48 hours post randomization for subjects continuing on tolvaptan).**

### Section 3.7.4.1 ADVERSE EVENTS

### **Changed Text:**

In particular, the following AEs must be actively monitored: absolute serum sodium level  $\geq$  145 mmol/L, overly rapid rise in serum sodium defined as an increase in serum sodium of  $> 8$  mmol/L over a 10-hour period,  $> \geq 12$  mmol/L over a 24-hour period, or a rate of increase in serum sodium that the investigator deems too rapid,

neurological symptoms, or other signs or symptoms suggestive of osmotic demyelination (see Section 5.3.1 for more detail).

### Section 3.8.3 INDIVIDUAL SUBJECT

#### **Changed Text:**

- The subject's serum sodium increases by  $\geq 12$  mmol/L in the 24-hour period following dosing

### Section 5.3.1.1 RAPID CORRECTION OF SERUM SODIUM

#### **Changed Text:**

Rapid correction of hyponatremia is defined as any increase in serum sodium  $\geq 12$  mmol/L/24 hours. If this change is observed during the trial, it should be reported as an IRE following the instructions detailed in Section 5.3 of the protocol.

### Section 7.1.1 SAMPLE SIZE FOR EFFICACY

#### **Changed Text:**

A total of **80** **70** randomized subjects will provide 90% power to detect a treatment difference of 4 mmol/L in change in serum sodium from randomization (at the end of Day 2/3 [Phase A]) to the end of Day 4/5 (2 days after randomization [Phase B]) using a 2-sided alpha of 0.05. An SD of 5 in change of serum sodium was used for the sample size calculation. After the end of treatment at Day 2/3, subjects will be randomized at a ratio of 1:1 to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early Withdrawal). Sample size re estimation will be conducted when 90% of the subjects finish (complete or discontinue) the trial.

### Section 7.4.2.3 PHARMACOKINETIC PARAMETERS

#### **Deleted Text:**

The PK data of 81 adult subjects with a 30-mg **tolvaptan**-dose will be included in the analysis to show the similarity for PK parameter estimates between adults and pediatrics.

### Section 7.4.3 EXPLORATORY OUTCOME ANALYSIS

#### **Added Text:**

##### ***7.4.3 Exploratory Outcome Analysis***

*Details will be provided in the statistical analysis plan.*

Section 7.4.3.1 EFFICACY

**Added Text:**

***7.4.3.1 Efficacy***

*The change in serum sodium concentration on Day 6 compared to Day 4 in nonresponders continuing on tolvaptan therapy will be analyzed using a paired Student's t-test.*

Section 7.4.3.2 SAFETY

**Added Text:**

***7.4.3.2 Safety***

*Neurological examination data will be presented in the data listings.*

Section 7.4.3.3 PHARMACODYNAMIC

**Added Text:**

***7.4.3.3 Pharmacodynamic***

*The exploratory PD endpoints include:*

- *In all subjects, 24-hour excretion of sodium, creatinine, and osmoles on Days 1 and 2*
- *24-hour sodium clearance*

*These endpoints will be analyzed as described in Section 6.2.*

Section 7.4.4 INTERIM ANALYSIS

**Changed Text:**

***7.4.3 7.4.4 Interim Analysis***

It was recommended ~~that an interim analysis should be conducted by the FDA to re-estimate the sample size~~ when about 90% of the subjects had finished the trial, ~~in order to re-evaluate the power of this protocol and provide sample size re-estimation if needed. In this case, this protocol would be a protocol of 2-stage adaptive design, in which the first stage would provide data for sample size re-evaluation and the second stage would include all data collected after the first stage. The final statistical test would combine data collected in both stages to~~

~~conclude the trial. It was further recommended that the weighted Z statistic approach outlined in Cui et al 1999 should be used as the final statistical test, due to its flexibility and being able to maintain the type I error in any cases once the weights are prespecified.~~<sup>23</sup>

~~To identify the need of sample size increase, the conditional power (CP) would be examined under the current trend in the interim analysis. Conditional power under the current trend is defined as the power of the trial of its planned sample size of 80 and the prespecified alpha of 0.05, under the assumption that the current trend observed at the interim analysis will continue to the end of the trial. Under this assumption, there is no need to increase the sample size when the CP is high or low enough, since it is expected the trial would succeed if the CP is high enough and fail if the CP is low enough. For this trial, the window for sample size increase is  $50\% \leq CP < 80\%$ . Furthermore, this window is divided into 3 intervals [ $50\%, 60\%$ ), [ $60\%, 70\%$ ), and [ $70\%, 80$ ), and the sample size increase (or sample size needed in the Stage 2) in these 3 intervals will be determined by the sample size increase when the CP is equal to  $50\%$ ,  $60\%$ , and  $70\%$ , respectively. With a designed sample size of 80, an interim analysis at 70, and the use of the weighted Z statistics proposed in Cui et al 1999,<sup>23</sup> in which nature weights of  $(70/80)^{1/2}$  and  $(10/80)^{1/2}$  are assigned to the Z statistics obtained in Stages 1 and 2, respectively, the estimated sample sizes based on these 3 intervals of CP are shown in Table 7.4.3.1.~~

**Table 7.4.3.1 Condition Power**

Condition Power	Sample Size for Stage 2
$50\% \leq CP < 60\%$	168
$60\% \leq CP < 70\%$	130
$70\% \leq CP < 80\%$	96

~~Since the sample sizes needed for Stage 2 when CP falls in this window for sample size increase are very big and even bigger than the sample size planned for this trial (80), this adaptive design is very inefficient. It would be much more efficient to allow this trial to run through its planned sample size (10 additional subjects) and, if necessary, to use the information collected to design a new trial. Thus, no adaptive sample size re-estimation will be designed in this trial, and no interim analysis in this trial will be conducted for the adaptive design.~~

The sample size re-estimation will assess the variability of change from randomization (end of Phase A) to end of Day 4/5 (Phase B) in serum sodium by using the pooled variance of the 2 treatment groups. At the trial planning stage, an SD of 5 was used to detect a treatment difference of 4, resulting in a sample size of 70 with a 2-sided alpha of 0.05 and 90% power. In case the variance ratio (equal to the observed pooled variance divided by 25, the square of 5 as an SD used in the sample size calculation) is  $\leq 1$ , no sample size increase will be made, and the trial will proceed to finish enrollment of 70 randomized subjects. In case the variance ratio is  $> 1$ , the sample size re-estimation will be equal to 70

**multiplied by the variance ratio, then rounded up to the nearest even number.**  
**Table 7.4.3-1 provides an example of the sample size re-estimation under different variance ratios.**

<b><u>Table 7.4.3-1 Sample Size Re-estimation</u></b>	
<b><u>Variance Ratio</u></b>	<b><u>Sample Size</u></b>
<b><u>1.1</u></b>	<b><u>78</u></b>
<b><u>1.2</u></b>	<b><u>84</u></b>
<b><u>1.3</u></b>	<b><u>92</u></b>
<b><u>1.4</u></b>	<b><u>78</u></b>
<b><u>1.5</u></b>	<b><u>106</u></b>

## Section 7.6.4 NEUROLOGICAL EXAMINATION

**Deleted Text:**

~~Neurological examination data will be presented in the listings.~~

## Section 8.1 PACKAGING AND LABELING

**Added Text:**

The current tolvaptan tablet formulation intended for use in this trial is limited to administration to those who can easily swallow a 3.75-mg tablet (6 mm) ***and weigh  $\geq 10$  kg.*** A suspension formulation is in development that will be suitable for children who cannot swallow tablets (eg,  $< 4$  years) and will also allow dosage adjustment for children with body weight  $< 20$  or  $\leq 50$  kg who are taking moderate or potent inhibitors of CYP3A4, respectively. Once available, the protocol will be amended to include the details of this formulation.

## Section 14 REFERENCES

**Added Text:**

<sup>18</sup> [REDACTED]. *Multicenter, randomized, double-blind, placebo-controlled, efficacy & safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia.* Otsuka CSR for Protocol 156-02-235, issued 07 Aug 2006.

<sup>19</sup> [REDACTED]. *International, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia.* Otsuka CSR for Protocol 156-03-238, issued 25 Jul 2006.

<sup>20</sup> [REDACTED]. *A Randomized Double-Blind Study to Assess the Safety and Pharmacokinetics of Concomitant Administration of Orally Administered OPC-41061 Tablets and Ketoconazole in Healthy Adult Male and Female Volunteers.* Otsuka Clinical Study Report for Protocol 156-98-201, issued 07 Dec 2000, amended 15 Feb 2001, 28 May 2003, and 03 Mar 2004.

**Deleted Text:**

<sup>23</sup> ~~Cui L, Hung HMJ, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999;55:1551-62.~~

## Appendix 1 NAMES OF SPONSOR PERSONNEL

**Replaced table:**

<u>Country</u>	<u>Safety Fax Numbers</u>	
<u>Taiwan</u>		
<u>Philippines</u>		
<u>Malaysia</u>		
<u>Singapore</u>		
<u>Thailand</u>		
<u>Hong Kong</u>		
<u>Australia</u>		
<u>Czech Republic</u>		
<u>Netherlands</u>		
<u>Belgium</u>		
<u>Italy</u>		
<u>Romania</u>		
<u>Spain</u>		
<u>Poland</u>		
<u>Russia</u>		
<u>Ukraine</u>		
<u>Israel</u>		
<u>South Africa</u>		
<u>Germany</u>		
<u>France</u>		
<u>Serbia</u>		
<u>United Kingdom</u>		
<u>Finland</u>		
<u>Peru</u>		
<u>Columbia</u>		
<u>Argentina</u>		
<u>Mexico</u>		
<u>US</u>	(primary) or (alternative)	
<u>Canada</u>	(primary) or (alternative)	

<u>Country</u>	<u>Safety Fax Numbers</u>	
<u>United States</u>	(primary) or	(alternative)
<u>Argentina</u>		
<u>Australia</u>		
<u>Belgium</u>		
<u>Canada</u>	(primary) or	(alternative)
<u>Colombia</u>		
<u>Czech Republic</u>		
<u>Finland</u>		

<u>France</u>		
<u>Georgia</u>	<u>No toll free number available; please dial</u> [REDACTED] <b>(primary)</b> <u>or</u> [REDACTED] <b>(alternative)</b>	
<u>Germany</u>		
<u>Hong Kong</u>		
<u>Israel</u>		
<u>Italy</u>		
<u>Korea</u>		
<u>Latvia</u>		
<u>Malaysia</u>		
<u>Mexico</u>		
<u>Netherlands</u>		
<u>Philippines</u>		
<u>Peru</u>		
<u>Poland</u>		
<u>Romania</u>		
<u>Russia</u>		
<u>Serbia</u>		
<u>Singapore</u>		
<u>South Africa</u>		
<u>Spain</u>		
<u>Taiwan</u>		
<u>Thailand</u>		
<u>Turkey</u>	<u>No toll free number available; please dial</u> [REDACTED] <b>(primary)</b> <u>or</u> [REDACTED] <b>(alternative)</b>	
<u>Ukraine</u>		
<u>United Kingdom</u>		

**Changed Text:**

Phone [REDACTED]; Fax [REDACTED]

**Deleted Text:**

Phone [REDACTED]; Fax [REDACTED]

**ADDITIONAL RISK TO THE SUBJECT:** There is no additional risk to the subjects.

**Amendment Number:** 2**Issue Date:** 19 May 2014**PURPOSE:**

- To increase the consistency of this protocol with other tolvaptan pediatric hyponatremia protocols
- To add neurocognitive and quality-of-life assessments as exploratory endpoints
- To clarify study design, procedures, and assessments
- To better define study phases and associated visits
- To provide greater detail about clinical laboratory tests
- To add Tanner staging to the assessments performed during the physical examination
- To better define completers and stopping rules
- To incorporate newly revised definitions of IMP causality

**BACKGROUND:** As several protocols in the tolvaptan hyponatremia pediatric development program were being conceived through negotiations with both US and European regulatory agencies, it became apparent that they needed to be aligned more closely in order to achieve as much consistency in data collection and to allow for data to be generated that could be synthesized and analyzed across studies.

**SECTIONAL REVISIONS:**

Location:	Old Text:	New Text:
Title Page:	Medical Director: [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] <b>Date of Amendment 2: 19 May 2014</b>
Protocol Synopsis/ Secondary Objective:	To assess the pharmacokinetics (PK) of tolvaptan and the effect on fluid balance in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.	To assess tolvaptan's pharmacokinetics (PK) and its effect on fluid balance in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.
Trial Design:	Subjects will undergo a treatment phase (2 to 5 days of tolvaptan) and a follow-up phase post-randomization of 14 days. <b>Phase A</b> (Treatment Phase): All subjects will initially receive tolvaptan once daily for the first 2 days. If a subject has not reached the desired sodium target improvement per the investigator's judgment (ie, the subject is a nonresponder) after Day 2 of tolvaptan	The trial will be conducted in two stages. The first stage will be conducted using the available tablet formulation of tolvaptan whereas the second stage will expand to the use of a suspension once that formulation becomes available....  Subjects will be required to be in a hospital setting during initiation and titration of

Location:	Old Text:	New Text:
	<p>administration (post 2 doses), a third day of treatment is permitted.</p> <p>At the end of Day 2 (optionally Day 3), subjects who are responders will be randomized to either the Early or Late Withdrawal group. Responders will be defined as those subjects who achieve an increase in serum sodium by <math>\geq 4</math> mmol/L. Early or Late Withdrawal assignment will be stratified by age [REDACTED] [REDACTED], serum sodium response [REDACTED], and underlying etiology of hyponatremia. If the subject remains a nonresponder to tolvaptan at the end of Day 3, the investigator is permitted to continue tolvaptan for 2 additional days at the highest dose or to discontinue tolvaptan and treat the subject per the investigator's preferred standard of care.</p> <p>Phase B (Randomization Phase): Subjects who are randomized to the Late Withdrawal group and nonresponders continuing treatment after Day 3 will continue treatment with tolvaptan for 2 additional days. Subjects who are randomized to the Early Withdrawal group and nonresponders discontinuing treatment after Day 3 will discontinue tolvaptan treatment immediately after randomization.</p> <p>Nonresponders will be treated per the investigator's preferred standard of care during Days 3/4 and 4/5 (treatment day is dependent upon the number of doses that a subject receives during Phase A).</p> <p>Those subjects whose serum sodium declines by <math>\geq 4</math> mmol/L or whose overall clinical condition requires further treatment to increase serum sodium will be treated per the investigator's preferred standard of care. Any intervention intended to raise serum sodium during the first 48 hours of the Early Withdrawal phase (including fluid restriction) will be defined as rescue therapy; the subject will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.</p> <p>All subjects will have serum sodium measured at 12, 24, 36, and 48 (<math>\pm 4</math>) hours</p>	<p>tolvaptan.</p> <p>Overall, in this trial, subjects will undergo treatment (2 to 5 days of tolvaptan among 2 treatment phases) and a post-last dose follow-up phase of 14 days.</p> <p><b>Treatment Phase A</b></p> <p>After screening, all subjects will initially receive tolvaptan once daily for 2 days. If the desired serum sodium level target improvement is not reached after Day 2 of tolvaptan administration (post 2 doses), a third day (Day 2a) of treatment is required. At the end of Day 2 (or 2a), subjects will be assessed for a serum sodium level change of <math>\geq 4</math> mEq/L (mmol/L). At that time, subjects who are responders will be randomized to either the Early Withdrawal group or Late Withdrawal group. Responders are defined as those subjects who achieve an increase in serum sodium concentration of <math>\geq 4</math> mEq/L (mmol/L); nonresponders are defined as subjects who do not achieve an increase in serum sodium concentration of <math>\geq 4</math> mEq/L (mmol/L).</p> <p><b>Treatment Phase B</b></p> <p><u>Responders</u></p> <p>Responders from Treatment Phase A will be randomized to either the:</p> <ul style="list-style-type: none"> <li>• Late Withdrawal group - subjects continue tolvaptan treatment on Days 3 and 4</li> <li>• Early Withdrawal group - subjects do not receive additional tolvaptan treatment on Days 3 and 4.</li> </ul> <p>Randomization will include stratification by age [REDACTED], serum sodium response [REDACTED], [REDACTED], and underlying etiology of hyponatremia.</p> <p>Those subjects whose serum sodium level declines by <math>\geq 4</math> mEq/L (mmol/L), or whose overall clinical condition requires further treatment to increase serum sodium level, will be treated per the investigator's preferred standard of care. Any intervention intended to raise serum sodium level during the first 48 hours of the Early Withdrawal phase (including fluid restriction) will be defined as rescue therapy. Subjects who receive rescue</p>

Location:	Old Text:	New Text:
	<p>post-randomization. Serum sodium assessment time points for nonresponders will follow the same schedule, but the values will be reported separately from the primary efficacy analysis. For analysis purposes, these assessments for nonresponders will be referred to as “post-randomization.”</p> <p>Phase C (Follow-up Phase): All subjects will be monitored and treated as clinically warranted per the investigator’s preferred standard of care for up to 3 additional days after the last dose of tolvaptan (note: the Early Withdrawal group should be monitored for the first 48 hours post-last dose). All subjects will have an additional serum sodium measurement at 72 (<math>\pm</math> 4) hours post-randomization and 7 (<math>\pm</math> 1) days post-randomization. A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-randomization.</p> <p><b>Pharmacokinetic</b> samples will be obtained on Day 1 (Phase A) and, for tolvaptan-treated subjects, at 24 and 48 hours post-randomization in Phase B. The PK profiles will be evaluated on an ongoing basis to determine the variability between subjects. Based on the findings, PK sampling will continue for as long as necessary to establish suitable estimates of clearance with a 90% confidence interval (CI) similar to that observed in the adult populations. Once these estimates are achieved, sampling will be discontinued in subsequent subjects in order to minimize blood draws in this population.</p> <p>Subjects will be required to be in the hospital during initiation or up-titration of administration of tolvaptan. If a subject is in the withdrawal phase or is not expected to receive a higher dose of tolvaptan, continued administration can be done outside of the hospital setting. Follow-up for all subjects may occur in the hospital if the subject has not been discharged or the subject may return for outpatient visits if the subject has been discharged from the hospital.</p>	<p>therapy will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.</p> <p><b>Nonresponders</b> If the subject remains a nonresponder at the end of Day 2 (or 2a), the investigator decides to either (a) continue tolvaptan for 2 additional days, or (b) discontinue tolvaptan and treat the subject per the investigator’s preferred standard of care during Days 3 and 4. Subjects will continue to follow scheduled assessments regardless of treatment.</p> <p><b>All Subjects</b> All subjects will have serum sodium levels measured at 8, 12, and 24 hours post-first dose and thereafter every 12 hours through completion of Treatment Phase B.</p> <p><b>Follow-up Phase C</b> All subjects will have an additional serum sodium assessment at 72 (<math>\pm</math> 4) hours post-last dose and 7 (<math>\pm</math> 1) days post-last dose. A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-last dose.</p> <p><b>Pharmacokinetic Sampling</b> Blood samples for pharmacokinetic (PK) analysis will be obtained at 2 and 8 hours post-first dose, and at trough on Days 2, 3, 4 and 5 for all subjects when dosed with tolvaptan on Days 1, 2, 3, and 4, respectively, regardless of responder status. PK profiles will be evaluated on an ongoing basis to determine variability among subjects. Based on the findings, PK sampling will continue for as long as necessary to establish suitable estimates of clearance with a 90% confidence interval (CI), similar to that observed in adult subject populations. Once these estimates are achieved, sampling will be discontinued in subsequent subjects in order to minimize blood draws in this pediatric population.</p>
<b>Subject Population:</b>	This trial will include up to 100 male and female subjects aged $\geq$ 4 weeks (or $\geq$ 44	This trial will include up to 100 male and female subjects aged $\geq$ 4 weeks (or $\geq$ 44

Location:	Old Text:	New Text:
	<p>weeks adjusted gestational age for premature births) to &lt; 18 years who have been diagnosed with euvolemic or hypervolemic hyponatremia (&lt; 130 mmol/L) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). It is expected that 70 subjects will have a serum sodium increase of <math>\geq 4</math> mmol/L (ie, responders).</p> <p>Subjects with euvolemic or hypervolemic hyponatremia eligible to be screened for participation in this trial include, but are not limited to, those diagnosed and admitted to a hospital for treatment of heart failure, hepatocellular disease (including cirrhosis), or syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Subjects with acute hyponatremia or hyponatremia expected to resolve spontaneously will be excluded from the trial....</p> <p>Seventy randomized subjects will provide 90% power to detect a treatment difference of 4 mmol/L in change in serum sodium from randomization (at the end of Day 2/3 [Phase A]) to the end of Day 4/5 (2 days after randomization [Phase B]).</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Subjects who are defined as responders will be further stratified by the magnitude of serum sodium response to tolvaptan [REDACTED] and underlying etiology of hyponatremia.</p> <p>All subjects will be initially identified based on serum sodium concentrations that persist at levels &lt; 130 mmol/L despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). Upon determination of eligibility, each subject's serum sodium will be reassessed just before tolvaptan administration to confirm that it remains persistent below this threshold prior to intended treatment initiation.</p>	<p>weeks adjusted gestational age) to &lt; 18 years who have been diagnosed with euvolemic or hypervolemic hyponatremia (&lt; 130 mEq/L [mmol/L]) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). Age groups will be enrolled such that 50% of these subjects will be &lt; 10 years old and at least 25% of subjects &lt; 6 years old.</p> <p>Subjects with acute hyponatremia or hyponatremia expected to resolve spontaneously will be excluded from the trial....</p>
<b>Inclusion/Exclusion Criteria:</b>	<p><u>Key inclusion criteria:</u></p> <ul style="list-style-type: none"> <li>• Male and female subjects <math>\geq 4</math> weeks (or <math>\geq 44</math> weeks adjusted gestational age for premature births) to &lt; 18 years old...</li> <li>• Persistent euvolemic or hypervolemic</li> </ul>	<p><u>Key inclusion criteria:</u></p> <ul style="list-style-type: none"> <li>• Male and female subjects <math>\geq 4</math> weeks (or <math>\geq 44</math> weeks adjusted gestational age) to &lt; 18 years old...</li> <li>• Persistent euvolemic or hypervolemic</li> </ul>

Location:	Old Text:	New Text:
	<p>hyponatremia defined as being documented as present for at least 48 hours, evidenced by at least 2 serum sodium assessments &lt; 130 mmol/L drawn at least 12 hours apart (these values can be documented using historical values previously obtained per standard of care); a third (STAT) serum sodium assessment &lt; 130 mmol/L, which will serve as the baseline value for efficacy endpoints, is to be obtained within 3 (<math>\pm</math> 1) hours of the first dose of trial medication</p> <p><u>Key exclusion criteria:</u></p> <ul style="list-style-type: none"> <li>Has evidence of hypovolemia or intravascular volume depletion (eg, hypotension, clinical evidence of volume depletion, response to saline challenge); if the subject has systolic blood pressure &lt; 90 mmHg or pulse &gt; 120 bpm, then volume status should be specifically clinically assessed to rule out volume depletion</li> <li>Has serum sodium &lt; 120 mmol/L, with or without associated neurologic impairment (ie, symptoms such as apathy, confusion, or seizures)</li> <li>Has a history or current diagnosis of nephrotic syndrome</li> <li>Has transient hyponatremia likely to resolve (eg, head trauma or post-operative state)</li> <li>Has hyperkalemia defined as serum potassium above the upper limit of normal (ULN) for the appropriate pediatric age range</li> <li>Has estimated glomerular filtration rate (eGFR) &lt; 30 mL/min/1.73 m<sup>2</sup> calculated by the following equation: eGFR (mL/min/1.73 m<sup>2</sup>) = 0.413 × height (cm)/serum creatinine (mg/dL)</li> <li>Has severe or acute neurological symptoms requiring other intervention (eg, hyperemesis, obtundation, seizures)</li> <li>Has had treatment for hyponatremia with:</li> <li>Has psychogenic polydipsia (subjects with other psychiatric illness may be included per medical monitor approval)</li> <li>Has uncontrolled diabetes mellitus defined as fasting glucose &gt; 300 mg/dL (16.7 mmol/L)</li> <li>Has Screening liver function values &gt; 3 × ULN</li> </ul>	<p>hyponatremia defined as being documented as present for at least 48 hours, evidenced by at least 2 serum sodium assessments &lt; 130 mEq/L (mmol/L) drawn at least 12 hours apart (these values can be documented using historical values previously obtained per standard of care); a third (STAT) serum sodium assessment &lt; 130 mEq/L (mmol/L), which will serve as the baseline value for efficacy endpoints, is to be obtained 2-4 hours prior to the first dose of tolvaptan</p> <p><u>Key exclusion criteria:</u></p> <ul style="list-style-type: none"> <li>Has evidence of hypovolemia or intravascular volume depletion (eg, hypotension, clinical evidence of volume depletion, response to saline challenge); if the subject has systolic blood pressure or heart rate outside of the normal range for that age, then volume status should be specifically clinically assessed to rule out volume depletion</li> <li>Has serum sodium level &lt; 120 mEq/L (mmol/L), with or without associated neurologic impairment (ie, symptoms such as apathy, confusion, or seizures)</li> <li>Has estimated glomerular filtration rate (eGFR) &lt; 30 mL/min/1.73 m<sup>2</sup></li> <li>Has had treatment for hyponatremia with:</li> <li>Uncontrolled diabetes mellitus defined as fasting glucose &gt; 300 mg/dL (16.7 mEq/L [mmol/L])</li> <li>Screening liver function values &gt; 3 × ULN</li> <li>Deficient coagulation (eg, cirrhotic at risk of gastrointestinal [GI] bleed), including subjects who meet any of the following criteria: a major GI bleed within the past 6 months, evidence of active bleeding (eg, epistaxis, petechiae/purpura, hematuria, or hematochezia), platelet count &lt; 50,000/<math>\mu</math>L, or use of medications known to increase bleeding risk</li> </ul>

Location:	Old Text:	New Text:
	<ul style="list-style-type: none"> <li>Has deficient coagulation (eg, cirrhotic at risk of gastrointestinal [GI] bleed), including subjects who meet any of the following criteria: a major GI bleed within the past 6 months, evidence of active bleeding (eg, epistaxis, petechiae/purpura, hematuria, or hematochezia), platelet count &lt; 50,000/<math>\mu</math>L, or use of concomitant medications known to increase bleeding risk</li> <li>Has hyponatremia due to the result of any medication that can safely be withdrawn (eg, thiazide diuretics)</li> </ul> <p>Has hyponatremia (eg, hyponatremia in the setting of adrenal insufficiency, untreated hypothyroidism, or hypotonic fluid administration) that is most appropriately corrected by alternative therapies</p>	
<b>Investigational Medicinal Product, Dose, Formulation, Mode of Administration</b>	<p>...Upon the availability of a liquid formulation, the protocol will be amended to reflect additional dosing options.</p> <p>...Up-titration of tolvaptan doses will be based on serum sodium levels at &gt; 20 hours following initiation of therapy; a change in serum sodium <math>\leq</math> 4 mmol/L from baseline should warrant up-titration, which is limited to no more than twice the previous dose.</p> <ul style="list-style-type: none"> <li>Subjects &lt; 2 years of age, weighing &lt; 10 kg, or who cannot safely swallow the tablet will be excluded until the availability of a liquid formulation. Dosing information will be available at that time.</li> </ul> <p>The subjects will continue dosing according to a titration scheme targeting a final sodium concentration between 135 and 140 mmol/L. Titration will ideally achieve a change in serum sodium concentration of at least 4 to 8 mmol/L/24 hours but not exceeding 12 mmol/L/24 hours.</p> <p>At the end of Day 2 (optionally Day 3 [Phase A]), subjects with a serum sodium increase of <math>\geq</math> 4 mmol/L will be randomized to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early Withdrawal). Early or Late Withdrawal assignment will be stratified by age (██████████, serum</p>	<p>....Upon the availability of an oral suspension formulation, the protocol will be amended to reflect additional dosing options.</p> <p>....Up-titration of tolvaptan doses will be based on serum sodium levels at &gt; 20 hours following initiation of therapy and at &gt; 20 hours following each additional dose; a change in serum sodium <math>\leq</math> 4 mEq/L (mmol/L) from baseline should warrant up-titration, which is limited to no more than twice the previous dose.</p> <ul style="list-style-type: none"> <li>Subjects &lt; 2 years of age, weighing &lt; 10 kg, or who cannot safely swallow the tablet will be excluded until the availability of a suspension formulation.</li> </ul> <p>The subjects will continue dosing according to a titration scheme targeting a final serum sodium concentration between 135 and 140 mEq/L (mmol/L). Titration will ideally achieve a change in serum sodium concentration of at least 4 to 8 mEq/L (mmol/L)/24 hours but not exceeding ██████████.</p>

Location:	Old Text:	New Text:
	<p>sodium response [REDACTED], and underlying etiology of hyponatremia. Nonresponders will be allowed to be treated with tolvaptan for 2 additional days at the highest dose or to discontinue tolvaptan and be treated per the investigator's preferred standard of care.</p>	
<b>Trial Assessments:</b>	<p><u>Pharmacokinetic/pharmacodynamic:</u></p> <ul style="list-style-type: none"> <li>• Blood sampling for tolvaptan plasma concentrations</li> <li>• Fluid balance</li> <li>• Urine output and urine chemistry</li> </ul> <p><u>Safety:</u></p> <ul style="list-style-type: none"> <li>• Physical examinations, including body weight</li> <li>• Neurological examinations</li> </ul> <p><u>Screening/Baseline:</u></p> <ul style="list-style-type: none"> <li>• Clinical laboratory tests (hematology, coagulation, chemistry, urinalysis)</li> <li>• Electrocardiogram</li> <li>• Medical and hyponatremia history</li> <li>• Thyroid-stimulating hormone and cortisol tests</li> <li>• Plasma osmolality, fractional excretion of sodium, and fractional excretion of urate</li> <li>• Alcohol and drug screen</li> <li>• Pregnancy test</li> </ul>	<p><u>Pharmacokinetic/pharmacodynamic:</u></p> <ul style="list-style-type: none"> <li>• Blood sampling for tolvaptan and metabolite plasma concentrations</li> <li>• Fluid intake</li> <li>• Urine output</li> <li>• Urine chemistry</li> </ul> <p><u>Safety:</u></p> <ul style="list-style-type: none"> <li>• Physical examinations, including body weight and neurological examinations</li> </ul>
<b>Criteria for Evaluation:</b>	<p><b>Primary Endpoints:</b></p> <p><b>Efficacy:</b></p> <ul style="list-style-type: none"> <li>• For subjects with serum sodium increases of <math>\geq 4</math> mmol/L (ie, responders), change in serum sodium concentration from randomization (at the end of Day 2/3 [end of Phase A]) to the end of Day 4/5 (Phase B) for Early compared to Late Withdrawal groups</li> </ul> <p><b>Secondary Endpoints:</b></p> <p><b>Efficacy:</b></p> <ul style="list-style-type: none"> <li>• For all subjects, change in serum sodium concentration at the end of Day 2/3 from baseline in Phase A</li> </ul> <p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>• Percentage of subjects with overly rapid increase in serum sodium [REDACTED]</li> <li>• Percentage of subjects requiring rescue medication during Phase A and Phase B of the trial</li> <li>• Change in serum sodium from 24 hours</li> </ul>	<p><b>Primary Efficacy Endpoint</b></p> <ul style="list-style-type: none"> <li>• For subjects with serum sodium level increases of <math>\geq 4</math> mEq/L (mmol/L) (ie, responders), change in serum sodium concentration from Day 2 (or 2a) at the end of Treatment Phase A to the end of Treatment Phase B for Early compared to Late Withdrawal groups.</li> </ul> <p><b>Key Secondary Efficacy Endpoint</b></p> <ul style="list-style-type: none"> <li>• For all subjects, the key secondary endpoint is the change in serum sodium concentration at the end of Day 2 (or 2a) in Treatment Phase A from baseline.</li> </ul> <p><b>Other Secondary Endpoints</b></p> <p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>• Percentage of subjects with overly rapid increase in serum sodium level [REDACTED]</li> </ul>

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	<p>post-last dose to 14 days post-randomization</p> <ul style="list-style-type: none"> <li>• Vital signs, blood pressure, clinical laboratory tests, and body weight</li> </ul> <p><u>Pharmacokinetic:</u></p> <ul style="list-style-type: none"> <li>• On Day 1, tolvaptan maximum (peak) plasma concentration (<math>C_{max}</math>), time to maximum (peak) plasma concentration (<math>t_{max}</math>), and area under the concentration-time curve from time zero to 24 hours (<math>AUC_{0-24h}</math>)</li> </ul> <p><u>Pharmacodynamic:</u></p> <ul style="list-style-type: none"> <li>• Fluid intake, urine output, and fluid balance (intake – output) every 6 hours on Days 1 and 2 (Phase A)</li> </ul> <p><b>Exploratory Endpoints:</b></p> <p><u>Efficacy:</u></p> <ul style="list-style-type: none"> <li>• In nonresponders continuing on tolvaptan therapy, change in trough serum sodium concentration on Day 6 compared to Day 4</li> </ul> <p><u>Safety:</u></p> <ul style="list-style-type: none"> <li>• Neurological examinations</li> </ul> <p><u>Pharmacodynamic:</u></p> <ul style="list-style-type: none"> <li>• In all subjects, 24-hour excretion of sodium, creatinine, and osmoles on Days 1 and 2</li> <li>• 24-hour sodium clearance</li> </ul>	<ul style="list-style-type: none"> <li>• Change in serum sodium level from 24 hours post-last dose to 7 days post-last dose</li> <li>• Percentage of subjects requiring rescue therapy (other than fluid restriction) during Treatment Phase A and Treatment Phase B</li> <li>• Percentage of subjects requiring fluid restriction during Treatment Phase A and Treatment Phase B</li> <li>• Vital signs, blood pressure, clinical laboratory tests, body weight, and neurological examinations</li> </ul> <p><u>Pharmacokinetic:</u></p> <ul style="list-style-type: none"> <li>• On Day 1 in Treatment Phase A, tolvaptan maximum (peak) plasma concentration (<math>C_{max}</math>), time to maximum (peak) plasma concentration (<math>t_{max}</math>), and area under the concentration-time curve from time zero to 24 hours (<math>AUC_{0-24h}</math>)</li> </ul> <p><u>Pharmacodynamic:</u></p> <ul style="list-style-type: none"> <li>• Fluid intake, urine output, and fluid balance (intake minus output) every 6 hours on Days 1 and 2 in Treatment Phase A</li> </ul> <p><b>Exploratory Endpoints</b></p> <ul style="list-style-type: none"> <li>• Efficacy will be assessed in nonresponders continuing on tolvaptan therapy by change from baseline in serum sodium concentration at the end of Treatment Phase B compared to the end of Treatment Phase A.</li> <li>• In all subjects, 24-hour excretion of sodium, creatinine, and osmolality on Days 1 and 2</li> <li>• 24-hour sodium clearance on Day 1</li> <li>• Neurocognition test battery</li> <li>• Quality of life (QoL) assessments</li> </ul>												
<b>List of Abbreviations and Definitions of Terms</b>		<table> <thead> <tr> <th data-bbox="967 1421 1127 1453"><u>Abbreviation</u></th> <th data-bbox="1127 1421 1318 1453"><u>Definition</u></th> </tr> </thead> <tbody> <tr> <td data-bbox="967 1453 1046 1484">BUN</td><td data-bbox="1046 1453 1405 1484">Blood urea nitrogen</td></tr> <tr> <td data-bbox="967 1484 1046 1516">FENa</td><td data-bbox="1046 1484 1405 1537">Fractional excretion of sodium</td></tr> <tr> <td data-bbox="967 1537 1046 1569">FE urate</td><td data-bbox="1046 1537 1405 1590">Fractional excretion of urate</td></tr> <tr> <td data-bbox="967 1590 997 1622">HF</td><td data-bbox="997 1590 1318 1622">Heart failure</td></tr> <tr> <td data-bbox="967 1622 1013 1653">SAP</td><td data-bbox="1013 1622 1405 1653">Statistical analysis plan</td></tr> </tbody> </table>	<u>Abbreviation</u>	<u>Definition</u>	BUN	Blood urea nitrogen	FENa	Fractional excretion of sodium	FE urate	Fractional excretion of urate	HF	Heart failure	SAP	Statistical analysis plan
<u>Abbreviation</u>	<u>Definition</u>													
BUN	Blood urea nitrogen													
FENa	Fractional excretion of sodium													
FE urate	Fractional excretion of urate													
HF	Heart failure													
SAP	Statistical analysis plan													
<b>1.2 Clinical Data</b>	Tolvaptan was approved in adults by the US FDA, in the European Union, and 9 other countries for the treatment of specific forms of hyponatremia, and by the Japanese Ministry of Health, Labour, and Welfare for volume overload in heart failure. Tolvaptan is currently being developed for the treatment of autosomal dominant polycystic	Tolvaptan is approved for (a) the treatment of specific forms of hyponatremia in adults by the European Medicines Agency (EMA), United States (US) Food and Drug Administration (FDA), and the regulatory authorities of 9 other countries, and (b) for volume overload in heart failure (HF) by the Japanese Ministry of Health, Labour, and												

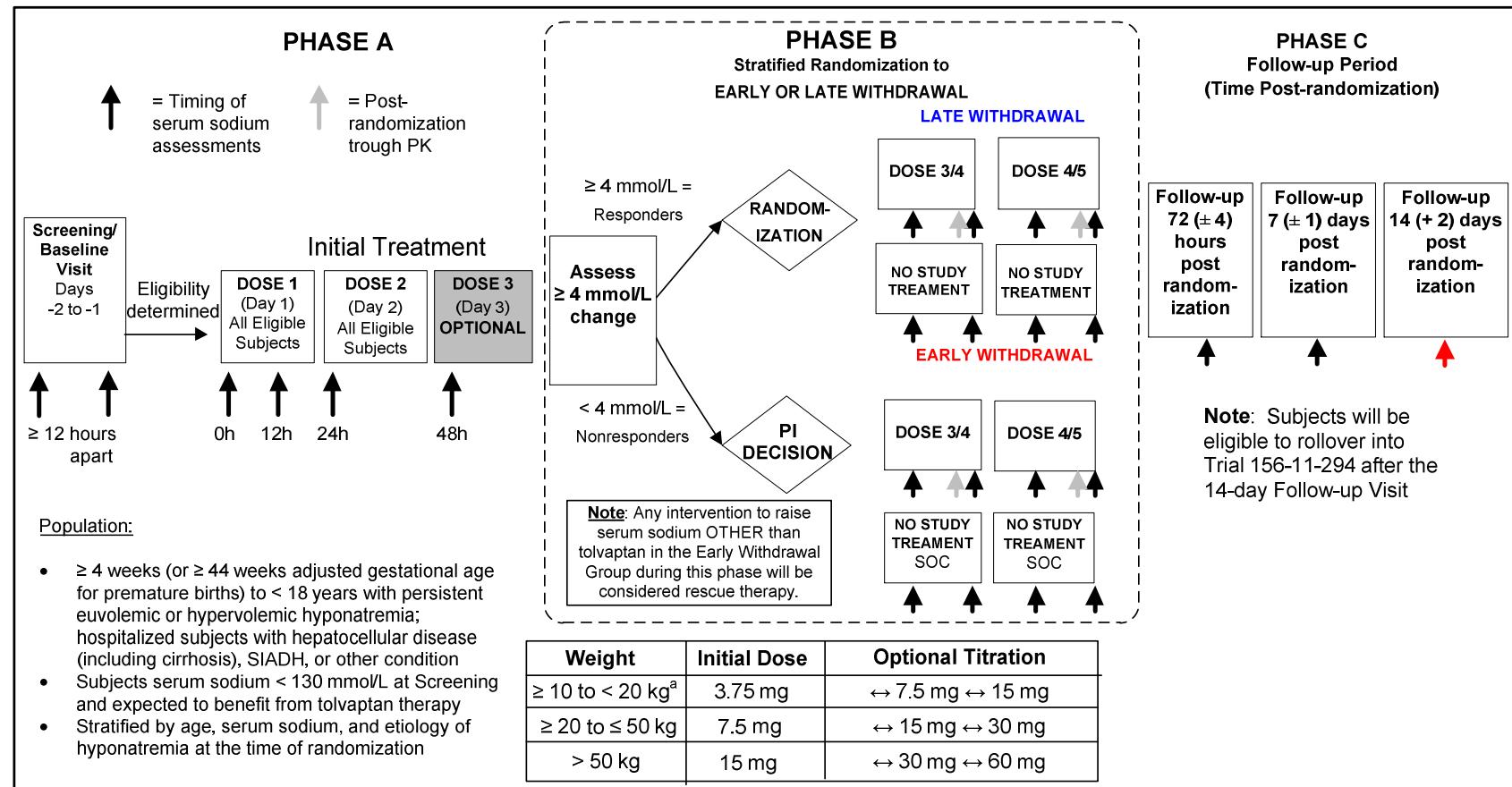
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	<p>kidney disease (ADPKD), and for the treatment of hepatic edema and carcinomatous edema. As of 31 Mar 2013, 83 trials have been completed, 2 trials were terminated due to slow enrollment, and 12 trials are ongoing.</p>	<p>Welfare. Tolvaptan is currently being investigated for the treatment of autosomal dominant polycystic kidney disease (ADPKD) and the treatment of hepatic edema and carcinomatous edema. As of 31 Mar 2013, 83 trials have been completed, 2 trials were terminated due to slow enrollment, and 12 trials were ongoing. More information is available in the IB.1</p>
<b>2.1 Trial Rationale</b>	<p>The purpose of this trial ... various etiologies. ... As the primary physiological effect of tolvaptan... The proposed population size of 100 subjects should provide 70 responders, ...</p>	<p>The purpose of this trial ... HF, hepatocellular disease (including cirrhosis), and SIADH/other. ... As the primary pharmacodynamic effect of tolvaptan... The proposed population size of 100 subjects is expected to yield 70 subjects who respond to tolvaptan (henceforth termed "responders"), ...</p>
<b>2.2.2 Secondary Objective</b>	<p>The secondary objective is to assess the PK of tolvaptan and the effect on fluid balance in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.</p>	<p>The key secondary objective is to assess the PK of tolvaptan and the effect on fluid balance in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.</p>
<b>3 Trial Design</b>	<p><b>3.1 Type/Design of Trial</b> See Figure 3.1-1 for a schematic of the trial design.  This will be an open-label, multicenter, multiple-dose, randomized withdrawal, parallel-group trial of tolvaptan in children and adolescent subjects hospitalized with euvolemic or hypervolemic hyponatremia. Pediatric and adolescent subjects who are diagnosed with euvolemic or hypervolemic hyponatremia (serum sodium &lt; 130 mmol/L) that persists despite initial standard background therapy (eg, including fluid restriction) are eligible to be screened for participation in this trial. Subjects who demonstrate prior resistance to vasopressin antagonist therapy will be excluded. All potential subjects must also be deemed by the investigator as likely to benefit from a therapy that raises serum sodium levels. Since hyponatremia in this patient population can often be transient and/or may be secondary to hypovolemic states, potential subjects will be screened for hyponatremic histories as well as clinically evaluated to rule out such cases. For the purpose of this protocol, persistent hyponatremia will be defined as serum sodium assessments &lt; 130 mmol/L documented as present for at least 48 hours.</p>	<p><b>3.1 Type of Trial</b> This is an open-label, multicenter, multiple-dose, randomized withdrawal, parallel-group trial of tolvaptan in children and adolescents hospitalized with chronic euvolemic or hypervolemic hyponatremia (serum sodium &lt; 130 mEq/L [mmol/L]) persisting despite initial standard therapy. A schematic of the trial design is provided in Figure 3.1-1.  This is the first clinical trial of tolvaptan in a pediatric population, and the majority of subjects may require only short-term treatment of hyponatremia, however some subjects may require prolonged treatment and additional follow-up information on their response to tolvaptan may be desired to better understand its long-term safety profile in this pediatric population. Hence, all subjects (responders and nonresponders) who complete this trial will be eligible for enrollment into an extension trial (156-11-294) to continue receiving tolvaptan, as clinically appropriate, until it is approved and available locally. If eligible, subjects could continue therapy with tolvaptan in that trial after completing the 14 (+2) day Follow-up Visit and completion of this trial. (The extension study will also provide long-term post-treatment safety follow-up information for a</p>

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	<p>Specifically, subjects must have at least 2 serum sodium assessments &lt; 130 mmol/L drawn at least 12 hours apart. These values can be documented using historical values previously obtained as per standard of care.</p> <p>A third (immediate [STAT]) serum sodium assessment &lt; 130 mmol/L, which will serve as the baseline value for efficacy endpoints, is to be obtained within 3 (<math>\pm</math> 1) hours of the first dose of trial medication.</p> <p>As stated above, all subjects will be evaluated to determine a minimal 48-hour history of hyponatremia to establish chronicity. However, it remains the responsibility of the investigator to determine the etiology of the hyponatremia and to assess the volume status for each subject using diagnostic tests (eg, fractional excretion of sodium [FeNa], fractional excretion of urine [Fe urine], urine osmolality, plasma osmolality) employed in the usual clinical course of care.</p> <p>Additionally, the following considerations should be noted per underlying etiology:</p> <ul style="list-style-type: none"> <li>Subjects diagnosed with hyponatremia secondary to SIADH will be evaluated specifically to ensure appropriate volume status. Hypovolemic states are not compatible with tolvaptan administration. Plasma and urine sodium, potassium, creatinine, and uric acid will be assessed in order to calculate and evaluate the FeNa and the Fe urine prior to dosing to ensure safety of tolvaptan administration.</li> <li>Subjects diagnosed with hyponatremia secondary to CHF are required to have a definitive diagnosis of CHF by a cardiologist and must have any diuretic regimen evaluated to ensure it is not contraindicated with tolvaptan administration.</li> <li>Subjects diagnosed with hyponatremia due to hepatocellular disease must have stable disease.</li> <li>All subjects must meet appropriate acute kidney injury (AKI) criteria per the exclusion criteria.</li> </ul> <p>The first dose of trial medication will be administered upon successful completion of</p>	<p>minimum of 6 months.)</p> <p>The trial will be conducted in two stages. The first stage will be conducted using the available tablet formulation of tolvaptan whereas the second stage will expand to the use of a suspension once that formulation becomes available.</p>

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	<p>all screening procedures.</p> <p>Subjects will undergo a treatment phase (2 to 5 days of tolvaptan) and a follow-up phase post-randomization of 14 days.</p> <p>Phase A (Treatment Phase): All subjects will initially receive tolvaptan once daily for the first 2 days. If a subject has not reached the desired sodium target improvement per the investigator's judgment (ie, the subject is a nonresponder) after Day 2 of tolvaptan administration (post 2 doses), a third day of treatment is permitted.</p> <p>At the end of Day 2 (optionally Day 3), subjects who are responders will be randomized to either the Early or Late Withdrawal group. <u>Responders</u> will be defined as those subjects who achieve an increase in serum sodium by <math>\geq 4</math> mmol/L. Randomized withdrawal assignment will be stratified by age [REDACTED]  [REDACTED] by serum sodium response [REDACTED]  [REDACTED], and by underlying etiology of hyponatremia. If the subject remains a nonresponder to tolvaptan at the end of Day 3, the investigator is permitted to continue tolvaptan for 2 additional days at the highest dose or to discontinue tolvaptan and treat the subject per the investigator's preferred standard of care.</p> <p>Phase B (Randomization Phase): Subjects who are randomized to the Late Withdrawal group and nonresponders continuing treatment after Day 3 will continue treatment with tolvaptan for 2 additional days. Subjects who are randomized to the Early Withdrawal group and nonresponders discontinuing treatment after Day 3 will discontinue tolvaptan treatment immediately after randomization.</p> <p>Nonresponders will be treated per the investigator's preferred standard of care during Days 3/4 and 4/5 (treatment day is dependent upon the number of doses that a subject receives during Phase A).</p> <p>Subjects who are randomized to the Early Withdrawal group will initially be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels. Those subjects whose serum sodium declines by <math>\geq 4</math> mmol/L or whose</p>	

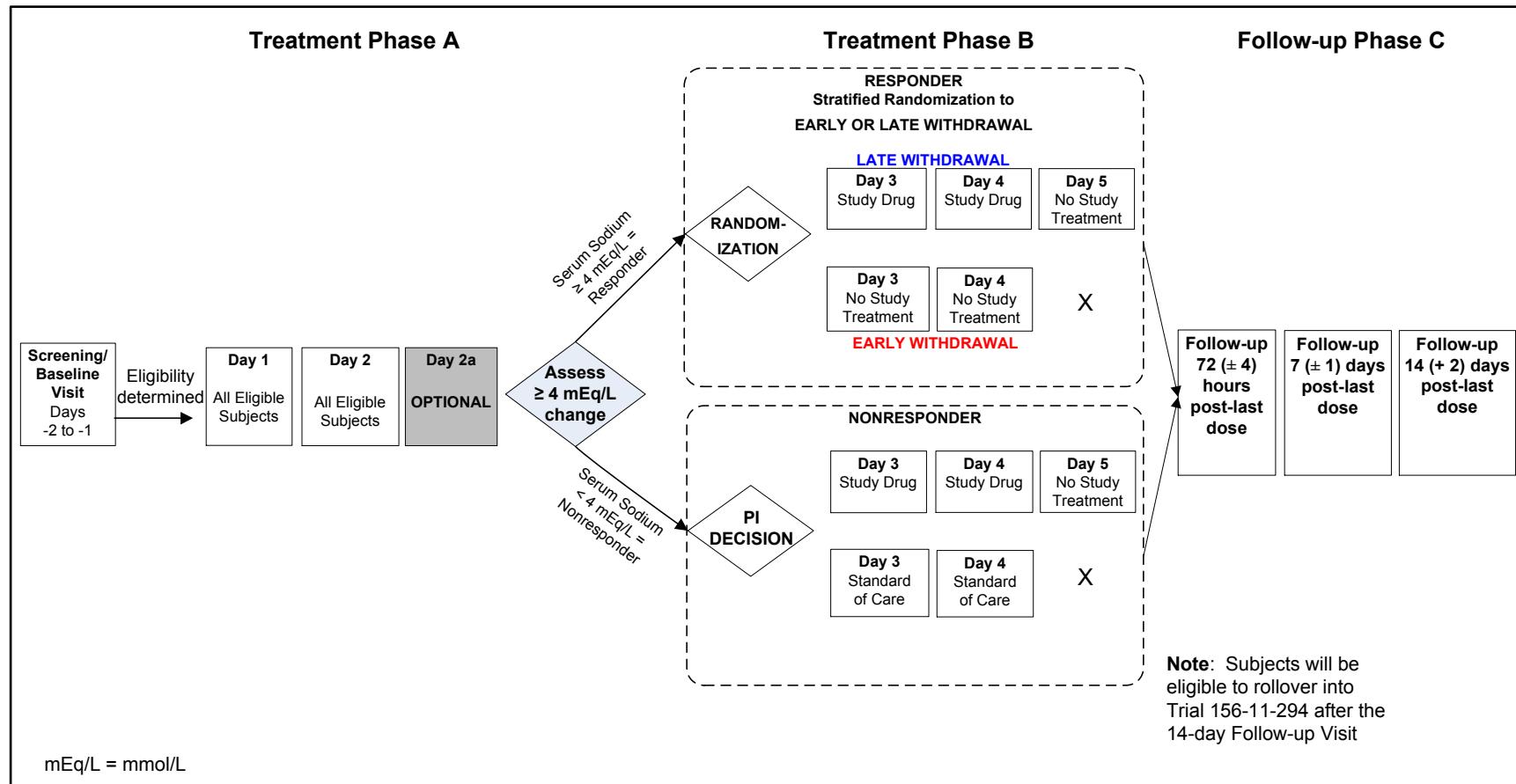
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	<p>overall clinical condition requires further treatment to increase serum sodium will be treated per the investigator's preferred standard of care. Any intervention intended to raise serum sodium during the first 48 hours of the Early Withdrawal phase (including fluid restriction) will be defined as rescue therapy; the subject will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.</p> <p>All subjects will have serum sodium measured at 12, 24, 36, and 48 (<math>\pm 4</math>) hours post-randomization. Serum sodium assessment time points for nonresponders will follow the same schedule, but the values will be reported separately from the primary efficacy analysis. For analysis purposes, these assessments for nonresponders will be referred to as "post-randomization."</p> <p>Phase C (Follow-up Phase): All subjects will be monitored and treated as clinically warranted per the investigator's preferred standard of care for up to 3 additional days after the last dose of tolvaptan (note: the Early Withdrawal group should be monitored for the first 48 hours post-last dose). All subjects will have an additional serum sodium measurement at 72 (<math>\pm 4</math>) hours post-randomization and 7 (<math>\pm 1</math>) days post-randomization. A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-randomization.</p> <p>Pharmacokinetic samples will be obtained on Day 1 (Phase A) and, for tolvaptan-treated subjects, at 24 and 48 hours post-randomization in Phase B. The PK profiles will be evaluated on an ongoing basis to determine the variability between subjects. Based on the findings, PK sampling will continue for as long as necessary to establish suitable estimates of clearance with a 90% confidence interval (CI) similar to that observed in the adult populations. Once these estimates are achieved, sampling will be discontinued in subsequent subjects in order to minimize blood draws in this population.</p>	

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	<p>Subjects will be required to be in the hospital during initiation or up-titration of the administration of tolvaptan. If a subject is in the withdrawal phase or is not expected to receive a higher dose of tolvaptan, continued administration can be done outside of the hospital setting. Follow-up for all subjects may occur in the hospital if the subject has not been discharged or the subject may return for outpatient visits if the subject has been discharged from the hospital.</p> <p>Subjects who do not improve on tolvaptan may receive rescue therapy per the investigator's judgment (see Section 3.2.2). These subjects will be withdrawn from trial treatment and will continue to Phase C to be followed as per protocol.</p> <p>While understanding that the majority of hyponatremia in this patient population may only require short-term treatment, it is recognized that some subjects may require prolonged treatment. Hence, all subjects (responders and nonresponders) who complete this trial may be eligible to be enrolled for an additional (planned) open-label use trial (156-11-294) to enable continued use of tolvaptan or to be clinically followed. If deemed eligible, these subjects could continue therapy with tolvaptan after the 14-day Follow-up Visit and completing this trial.</p>	

**Old Text:****3.1: Type of Trial****Figure 3.1-1 Trial Design Schematic**

**New Text:**

**Figure 3.1: Type of Trial**



**Figure 3.1-1 Trial Design Schematic**

Location:	Old Text:	New Text:
	<p>Subjects must be <math>\geq</math> 2 years of age and weigh <math>\geq</math> 10 kg until development of a liquid formulation is complete.</p> <p><b>3.2 Treatments</b></p> <p>Tolvaptan will be administered once daily orally, preferably in the morning hours, with a dose proportional amount of water. The acceptability and palatability of tolvaptan tablets will be recorded on the case report form (CRF). Doses of <math>\geq</math> 15 mg tolvaptan will be given with 240 mL of water...</p> <p>...Up-titration of tolvaptan doses can occur once daily and will be based on serum sodium levels at <math>&gt;</math> 20 hours following initiation of therapy and each subsequent dose; up-titration may not occur within 20 hours of the previous dose. A change in serum sodium <math>\leq</math> 4 mmol/L from baseline should warrant up-titration, which is limited to no more than twice the previous dose.</p> <ul style="list-style-type: none"> <li>• Subjects <math>&lt;</math> 2 years of age or weighing <math>&lt;</math> 10 kg are excluded until a liquid formulation is available. Tolvaptan metabolism is primarily mediated by CYP3A4 and intestinal and hepatic concentrations of this enzyme increase following birth. Developmental information from PK models of midazolam and cisapride, other CYP3A4 substrates, in neonates and infants will be used to provide dosing recommendations for the liquid formulation when available.</li> <li>• Subjects <math>\geq</math> 2 years of age and weighing <math>\geq</math> 10 to <math>&lt;</math> 20 kg will be given a 3.75 -mg tablet on Day 1 with possible up-titration to 7.5- and 15 -mg tablet doses.</li> <li>• Subjects weighing 20 to 50 kg, inclusive, will be given a 7.5 -mg tablet on Day 1 with possible up-titration to 15- and 30 -mg tablet doses.</li> <li>• Subjects weighing <math>&gt;</math> 50 kg will be given a 15 -mg tablet on Day 1 with possible up-titration to 30- and 60 -mg tablet doses.</li> </ul> <p>Subjects who cannot take an oral tablet are currently excluded due to their inability to safely swallow the spray-dried tablet. Subjects weighing <math>&lt;</math> 10 kg are also</p>	<p><b>3.1.1 Trial Phases</b></p> <p>Screening should be performed on Days -2 and -1 to confirm eligibility, followed by the 3 trial phases described in Section 3.7.1.</p> <p><b>3.1.1.1 Treatment Phase A</b></p> <p>All subjects will initially receive tolvaptan once daily on Days 1 and 2. If a subject's serum sodium level has not increased by at least 4 mEq/L (mmol/L) by Day 2, an additional day of treatment is required and is referred to as Day 2a. If subjects achieve an increase in serum sodium concentration of <math>\geq</math> 4 mEq/L (mmol/L) on Day 2 (or 2a) they will be defined as responders. If subjects do not achieve an increase in serum sodium concentration of <math>\geq</math> 4 mEq/L (mmol/L) on Day 2 (or 2a) they will be defined as nonresponders.</p> <p><b>3.1.1.2 Treatment Phase B</b></p> <p>On Day 3 responders will be randomized (Section 3.1.1.2.1) to either the Early Withdrawal group or the Late Withdrawal group. Nonresponders will not be randomized.</p> <p>For nonresponders from Treatment Phase A, the investigator will determine if the subject is to either:</p> <ul style="list-style-type: none"> <li>• Continue treatment with study drug or</li> <li>• Prescribe treatment per local standard of care for Days 3 and 4.</li> </ul> <p><b>3.1.1.2.1 Randomization</b></p> <p>Responders will be randomized to either:</p> <ul style="list-style-type: none"> <li>• Late Withdrawal group - subjects continue tolvaptan treatment on Days 3 and 4</li> <li>• Early Withdrawal group - subjects do not receive additional tolvaptan treatment on Days 3 and 4.</li> </ul> <p>Randomization will be stratified by age (&lt; [REDACTED]), serum sodium response [REDACTED], and underlying hyponatremia etiology [REDACTED].</p> <p>Subjects randomized to the Early Withdrawal group will be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels. Subjects whose serum sodium declines by <math>\geq</math> 4 mEq/L (mmol/L) or</p>

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	<p>excluded as that weight has not been studied in previous PK trials and, therefore, the dose of tolvaptan being delivered is not confirmed. To support the enrollment of these subjects, an age and weight appropriate suspension formulation is being developed. Once available, the protocol will be amended to include the formulation. Table 3.2-1 presents starting doses of tolvaptan (15, 7.5, or 3.75 mg) when adjusted for body weight.</p> <p>Consequently, the maximal starting dose for subjects weighing &gt; 50 kg is slightly less than 0.30 mg/kg; starting doses for subjects weighing 20 to 50 kg, inclusive, range from 0.38 to 0.15 mg/kg; starting doses for subjects weighing <math>\geq</math> 10 to &lt; 20 kg range from 0.375 mg/kg to slightly greater than 0.19 mg/kg. Therefore, the maximal starting doses planned for this pediatric trial are in the range previously used in adult hyponatremic subjects.</p> <p>For subjects weighing <math>\geq</math> 20 kg and taking moderate inhibitors of CYP3A4, a half dose will be used (3.75 or 7.5 mg, by weight).... The subjects will continue dosing according to a titration scheme (Section 3.2.1) targeting a final sodium concentration between 135 and 140 mmol/L. Titration guidelines are designed to ideally achieve a change in serum sodium concentration of at least 4 to 8 mmol/L/24 hours but not exceeding 12 mmol/L/24 hours.</p> <p>At the end of Day 2 (optionally Day 3 [Phase A]), subjects with a serum sodium increase of <math>\geq</math> 4 mmol/L will be randomized to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early Withdrawal). Early or Late Withdrawal assignment will be stratified by the ages of [REDACTED], serum sodium response [REDACTED], and underlying etiology of hyponatremia. Subjects with serum sodium response of &lt; 4 mmol/L may continue on tolvaptan therapy for 2 additional days at their highest dose or may be withdrawn from tolvaptan to be treated per the investigator's preferred standard of care.</p>	<p>whose overall clinical condition requires further treatment to raise serum sodium levels should be treated per local standard of care. Any intervention intended to raise serum sodium concentration during the first 48 hours of the Early Withdrawal phase (including fluid restriction) will be defined as rescue therapy. Subjects receiving rescue therapy will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.</p> <p><b>3.1.1.3 Follow-up Phase C</b> All subjects will have an additional serum sodium measurement at 72 (<math>\pm</math> 4) hours post-last dose and 7 (<math>\pm</math> 1) days post-last dose. A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-last dose.</p> <p><b>3.2.1 Tablet Formulation</b> Tolvaptan tablets will be administered orally once daily, preferably in the morning hours, with a dose proportional amount of water. Doses of <math>\geq</math> 15 mg tolvaptan will be given with 240 mL of water... The maximum starting doses, by weight, for subjects are shown in Table 2.1.1-1 and are within the range previously used in trials involving adult hyponatremic subjects. The palatability of tolvaptan tablets will be assessed.</p> <p><b>3.2.2 Suspension Formulation</b> Additional information on the proposed suspension formulation of tolvaptan (currently in development) will be added to the protocol in an amendment when available. Until that time, subjects &lt; 2 years of age or weighing &lt; 10 kg and those unable to swallow tablets, are excluded from the trial.</p> <p><b>3.2.3 Dosing Guidelines</b> ...Titration of tolvaptan doses can occur once daily and will be based on serum sodium levels assessed at &gt; 20 hours following initiation of therapy and each subsequent dose; titration may not occur within 20 hours of the previous dose. Up-titration is limited to no more than twice the previous dose.</p>

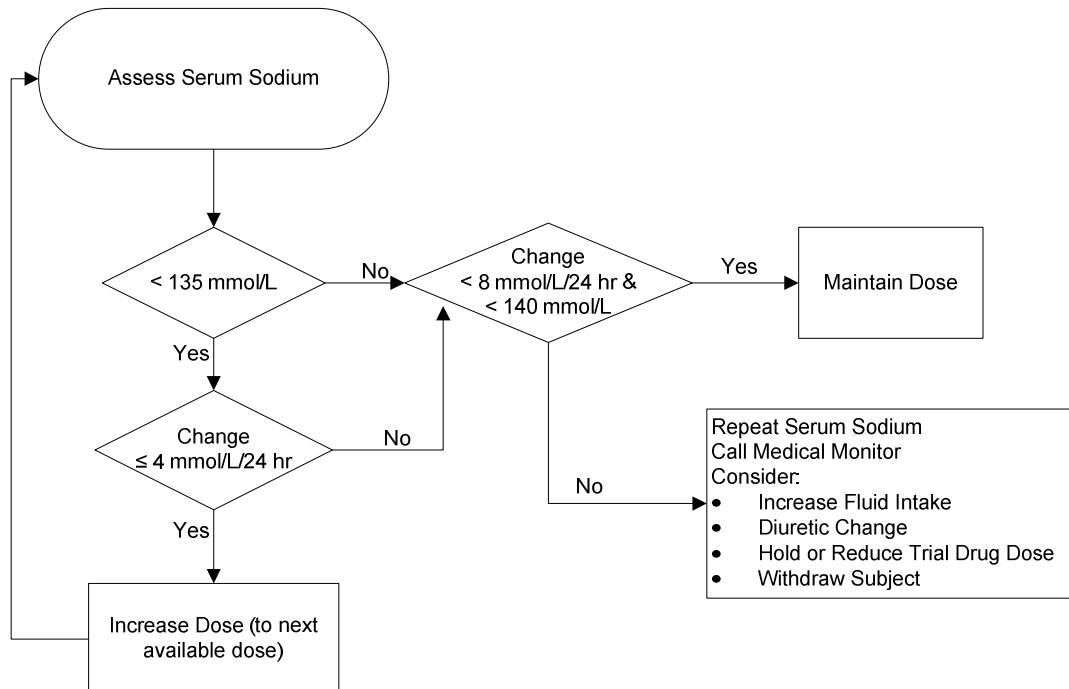
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	<p><b>3.2.1 Titration Guidelines</b></p> <p>The titration scheme is presented in Figure 3.2.1-1.</p> <ul style="list-style-type: none"> <li>• If serum sodium increases <math>&gt; 4</math> to <math>&lt; 8</math> mmol/L/24 hours, then the dose of tolvaptan should remain the same. If serum sodium increases <math>\geq 8</math> mmol/L/24 hours or reaches a concentration <math>\geq 140</math> mmol/L, then the dose of tolvaptan should be held and the medical monitor should be called. If serum sodium changes by <math>\leq 4</math> mmol/L/24 hours and the subject is still below the therapeutic target for serum sodium (135 mmol/L), then the tolvaptan dose may be titrated up to the next scheduled dose appropriate to the subject's body weight. If at any point serum sodium or symptoms worsen or fail to improve and definitive therapy (eg, isotonic or hypertonic saline) is required, the subject will be withdrawn from the trial to receive "rescue therapy." These subjects will be withdrawn from trial treatment and will continue to Phase C to be followed as per protocol. The medical monitor should be contacted at any point if questions arise regarding titration. The rationale for any up- or down-titration of tolvaptan must be documented. Any initiation or titration of tolvaptan must occur in a hospital setting.</li> <p><b>3.2.1.1 Rescue Therapy</b></p> <p>Subjects with worsening hyponatremia symptoms during the trial may receive rescue therapy. ....commercial vaptans, or any treatment intended to raise the level of serum sodium.</p> <p>Subjects who are randomized to the Early Withdrawal group will initially be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels. Those subjects whose serum sodium declines by <math>\geq 4</math> mmol/L or whose overall clinical condition requires further treatment to increase serum sodium will be treated per the investigator's preferred standard of care. Any intervention intended to raise serum sodium during the first 48 hours of the Early Withdrawal phase (including fluid</p> </ul>	<ul style="list-style-type: none"> <li>• Subjects <math>&lt; 2</math> years of age or weighing <math>&lt; 10</math> kg are excluded until an oral suspension formulation is available.</li> <li>• Subjects <math>\geq 2</math> years of age and weighing <math>\geq 10</math> to <math>&lt; 20</math> kg will receive a 3.75 mg tablet on Day 1 with possible up-titration to 7.5 mg and 15 mg tablet doses.</li> <li>• Subjects weighing 20 to 50 kg, inclusive, will receive a 7.5 mg tablet on Day 1 with possible up-titration to 15 mg and 30 mg tablet doses.</li> <li>• Subjects weighing <math>&gt; 50</math> kg will receive a 15 mg tablet on Day 1 with possible up-titration to 30 mg and 60 mg tablet doses.</li> </ul> <p>For subjects weighing <math>\geq 20</math> kg and taking moderate inhibitors of CYP3A4, one half of the standard dose will be used (3.75 or 7.5 mg, by weight)....</p> <p>Following their initial tolvaptan dose in the trial subjects will continue dosing according to the titration scheme (see Section 3.2.4), targeting a final serum sodium concentration between 135 and 140 mEq/L (mmol/L). Titration guidelines are designed to achieve a change in serum sodium concentration of at least 4 to 8 mEq/L (mmol/L)/24 hours but not exceeding [REDACTED].</p> <p><b>3.2.4 Titration Guidelines and Rescue Therapy</b></p> <p>Initiation and titration of tolvaptan must occur in a hospital setting. Up titration can only take place on Treatment Day 2 (or 2a). Down titration can occur at any point in the trial but should be discussed with the medical monitor. Titration (up or down) may not occur within 20 hours of the previous dose. Up-titration is limited to no more than twice the previous dose. The medical monitor should be contacted at any point if questions arise regarding titration or initiation of rescue therapy. The rationale for any up- or down-titration of tolvaptan must be documented. The evaluation of serum sodium levels, management of tolvaptan titration and rescue therapy is described in Figure 3.2.4-1.</p> <p><b>3.2.4.1 Titration</b></p> <p>Tolvaptan dose titration (after the initial</p>

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	<p>restriction) will be defined as rescue therapy. The subject will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.</p> <p>Subjects receiving rescue therapy will be considered treatment failures. A subject requiring rescue therapy at any time after enrollment will be discontinued from the trial treatment and will continue to Phase C to be followed as per protocol.</p>	<p>dose) should be based on changes in serum sodium levels as follows:</p> <ul style="list-style-type: none"> <li>• If the serum sodium level increases by <math>\leq</math> 4 mEq/L (mmol/L)/24 hours and the subject is still below the therapeutic target for serum sodium level (135 mEq/L [mmol/L]), then the tolvaptan dose may be titrated up to the next scheduled dose appropriate for the subject's body weight.</li> <li>• If the serum sodium level increases <math>&gt; 4</math> to <math>\leq 8</math> mEq/L (mmol/L)/24 hours in response to tolvaptan treatment and the serum sodium is <math>\leq 140</math> mEq/L (mmol/L), then the dose of tolvaptan should remain the same for the subsequent day.</li> <li>• If the serum sodium level increases <math>&gt; 8</math> mEq/L (mmol/L)/24 hours or reaches a concentration of <math>&gt; 140</math> mEq/L (mmol/L), then the next dose of tolvaptan should not be given and the medical monitor should be contacted to consider options (ie, down-titration, tolvaptan interruption, concomitant medication adjustment, fluid supplementation and/or withdrawal).</li> <li>• If serum sodium level increases by [REDACTED] period following dosing, or, at any time after dosing, the serum sodium level is 145 mEq/L (mmol/L), the next dose of tolvaptan should not be given and the medical monitor should be contacted immediately to consider options.</li> </ul> <p><b>3.2.4.2 Rescue Therapy</b>  Subjects with worsening hyponatremia symptoms or whose serum sodium level declines may receive rescue therapy. ....commercially available vaptans, or any treatment intended to raise the level of serum sodium at any time during the trial. If at any point during the trial serum sodium levels or hyponatremia symptoms worsen or fail to improve adequately and definitive therapy (eg, isotonic or hypertonic saline) is required, the subject will be withdrawn from trial treatment to receive rescue therapy. These subjects will continue to Follow-up Phase C for collection of safety information. Additional guidelines for rescue therapy concerning hyponatremia symptoms and</p>

Location:	Old Text:	New Text:
		<p>decreasing serum sodium level:</p> <ul style="list-style-type: none"> <li>• If a subject has worsening symptoms and/or has a serum sodium level at or below the baseline value, repeat serum sodium [STAT] to confirm level, and begin rescue therapy.</li> <li>• If a subject is asymptomatic and serum sodium has decreased by <math>\geq 4</math> mEq/L (mmol/L), but is still above the baseline value, consider need for rescue therapy.</li> <li>• If a subject is asymptomatic and serum sodium has decreased by <math>\leq 3</math> mEq/L (mmol/L), but is still above the baseline value, no action is required.</li> </ul> <p>Subjects who are randomized to the Early Withdrawal group will initially be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels. Those subjects whose serum sodium declines by <math>\geq 4</math> mEq/L (mmol/L) or whose overall clinical condition requires further treatment to increase serum sodium will be treated per standard of care. Any intervention intended to raise serum sodium level during the first 48 hours in the responder Early Withdrawal group (including fluid restriction) will be defined as rescue therapy. These subjects will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.</p> <p>Subjects randomized to the Late Withdrawal group who receive rescue therapy will be considered treatment failures. A subject requiring rescue therapy at any time after starting tolvaptan will be discontinued from trial treatment and will proceed to Follow-up Phase C.</p> <p><b>3.2.4.3 Fluid Restriction Considerations</b>  In subjects with chronic hyponatremia, fluid restriction coadministered with initiation of treatment with a vaptan has the potential to accentuate the rate of sodium correction and to cause overly rapid correction or over correction of hyponatremia. Therefore, during treatment, subjects must have access to water and maintain fluid intake levels per institutional guidelines. Fluid restriction at any time</p>

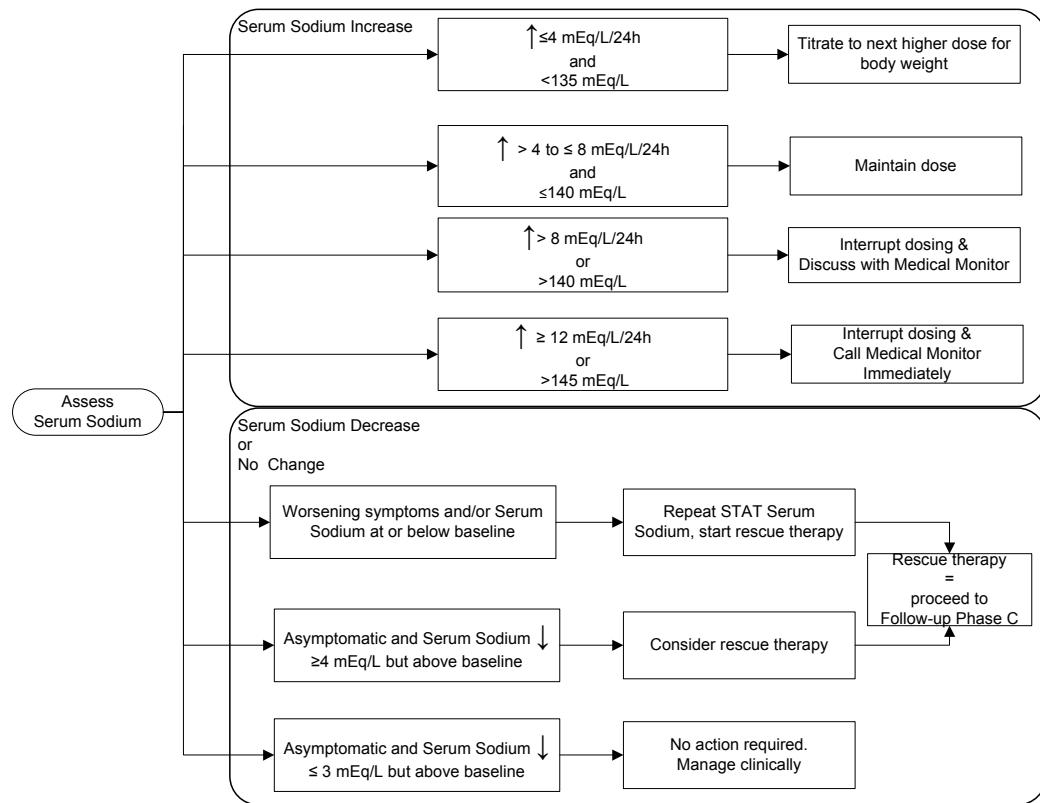
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		during the trial including during the first 48 hours after discontinuation of tolvaptan will be considered rescue therapy.

### Old Text: 3.7 Trial Procedures



**Figure 3.2.1-1 Titration Scheme**

### New Text: 3.7 Trial Procedures



**Figure 3.2.4-1 Titration and Rescue Therapy Scheme**

Location:	Old Text:	New Text:
3.3 Trial Population	<p>This trial will include up to 100 male and female subjects aged <math>\geq 4</math> weeks (or <math>\geq 44</math> weeks adjusted gestational age for premature births) to <math>&lt; 18</math> years, who have been diagnosed with euvolemic or hypervolemic hyponatremia (<math>&lt; 130</math> mmol/L) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). It is expected that 70 subjects will have a serum sodium increase of <math>\geq 4</math> mmol/L (ie, responders).</p>	<p>This trial will include up to 100 male and female subjects aged <math>\geq 4</math> weeks (or <math>\geq 44</math> weeks adjusted gestational age) to <math>&lt; 18</math> years who have been diagnosed with euvolemic or hypervolemic hyponatremia (<math>&lt; 130</math> mEq/L [mmol/L]) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). Age groups will be enrolled such that 50% of these subjects will be <math>&lt; 10</math> years old and at least 25% of subjects <math>&lt; 6</math> years old. Subjects who are defined as responders will be further stratified by the magnitude of serum sodium response to tolvaptan (<math>\leq 7</math> and <math>&gt; 7</math> mEq/L [mmol/L]), and underlying etiology of hyponatremia.</p> <p>Subjects with euvolemic or hypervolemic hyponatremia eligible to be screened for participation in this trial include, but are not limited to, those diagnosed and admitted to a hospital for treatment of HF, hepatocellular disease (including cirrhosis), or SIADH/other. ....</p>

Location:	Old Text:	New Text:
	<p>The trial will be conducted at up to 50 centers globally. Subjects with euvolemic or hypervolemic hyponatremia eligible to be screened for participation in this trial include, but are not limited to, those diagnosed and admitted to a hospital for treatment of heart failure, hepatocellular disease (including cirrhosis), or SIADH... Hospitalized hyponatremic encephalopathy is seen in association with SIADH or in the post-operative period. Hyponatremic encephalopathy is a medical emergency that requires immediate intervention; thus, subjects with known risk factors for developing hyponatremic encephalopathy will be excluded from this trial (ie, hypoxia, infection, brain injury, neurosurgery, seizure disorders, cerebritis, encephalopathy, central nervous system disorders such as cytotoxic and vasogenic cerebral edema, space-occupying brain lesion, or elevated AVP levels).<sup>22</sup></p> <p>Age groups will be stratified such that half (35) of these subjects will be age &lt; 10 years with at least 25% (17) of subjects &lt; 6 years old. Subjects who are defined as responders will be further stratified by the magnitude of serum sodium response to tolvaptan (<math>\leq 7</math> and <math>&gt; 7</math> mmol/L) and underlying etiology of hyponatremia. All subjects will be initially identified based on serum sodium concentrations that persist at levels</p>	<p>All potential subjects must have chronic (<math>\geq 48</math> hours) dilutional hyponatremia (euvolemic or hypervolemic) associated with HF, hepatocellular disease (including cirrhosis), or SIADH/other and be deemed by the investigator as likely to benefit from a therapy that raises serum sodium levels. The etiology of hyponatremia (presumed cause) must be documented and evaluated per Section 3.3.1. Those subjects who have acute or transient hyponatremia, have overt symptoms of hyponatremia requiring immediate intervention, or who are at increased risk for developing hyponatremic encephalopathy or osmotic demyelination are excluded from this trial.</p> <p>Since hyponatremia in this patient population can often be transient and/or may be secondary to hypovolemic states, potential subjects will be screened for hyponatremic histories as well as clinically evaluated to rule out such cases. For the purpose of this protocol, persistent hyponatremia will be defined as serum sodium level <math>&lt; 130</math> mEq/L (mmol/L) documented as present for at least 48 hours. Specifically, subjects must have at least 2 serum sodium assessments <math>&lt; 130</math> mEq/L (mmol/L) drawn at least 12 hours apart. These values can be documented using historical values previously obtained as per standard of care. A third (STAT) serum sodium assessment <math>&lt; 130</math> mEq/L (mmol/L), which will serve as the baseline value for efficacy endpoints, is to be obtained within 2-4 hours prior to the first dose of trial medication.</p> <p>If a subject's serum sodium level during the screening period is <math>\geq 130</math> mEq/L (mmol/L), the subject will be determined to be a screen failure. Subjects deemed screen failures may be rescreened, as appropriate. Subjects who receive a randomization number may not be rescreened regardless of whether they receive trial medication.....</p> <p>Hospitalized hyponatremic encephalopathy is seen in association with SIADH or in the immediate post-operative period. Hyponatremic encephalopathy is a medical emergency that requires immediate intervention; thus, subjects with known risk factors for developing hyponatremic encephalopathy will be excluded from this trial (ie, hypoxia, infection, brain injury, neurosurgery, active seizure disorders, cerebritis, encephalopathy, central nervous system disorders such as cytotoxic and vasogenic cerebral edema, space-occupying brain lesion, or elevated AVP levels).<sup>22</sup></p> <p><b>3.3.1.1 General Guidelines</b> Investigators should assess subjects' appropriateness to receive tolvaptan. Investigators should ultimately use their medical judgment to make the final determination. It remains the responsibility of the investigator to determine the etiology of hyponatremia and to assess the volume status for each subject using diagnostic tests (eg, fractional excretion of sodium [FENa], fractional excretion of urate [FE urate], urine osmolality, serum osmolality) employed in the usual clinical course of care.</p>

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	<p>&lt; 130 mmol/L despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). Upon determination of eligibility, each subject's serum sodium will be reassessed just before tolvaptan administration to confirm it remains persistent below this threshold prior to intended treatment initiation. If any result, during the Screening period is ≥ 130 mmol/L, the subject will be determined a screen failure. Subjects deemed screen failures may be rescreened, as appropriate. Subjects who receive a randomization number may not be rescreened regardless of whether they receive trial medication or complete the trial.</p> <p><b>3.3.1 Tolvaptan Administration by Hyponatremia Etiology</b>      Investigators should assess subjects' appropriateness to receive tolvaptan. Each investigator should ultimately use their medical judgment to make the final determination. The guidelines listed in Table 3.3.1-1 are to help guide the medical judgment of each investigator.</p> <p><b>Table 3.3.1-1 Screening Algorithms by Hyponatremia Etiology</b></p> <table border="1" data-bbox="404 1558 719 1902"> <thead> <tr> <th data-bbox="404 1558 502 1685">SIADH/ Other</th> <th data-bbox="502 1558 600 1685">CHF</th> <th data-bbox="600 1558 719 1685">Hepatocellular Disease</th> </tr> </thead> <tbody> <tr> <td data-bbox="404 1685 502 1902">Two serum sodium assessments of &lt; 130 mmol/L</td> <td data-bbox="502 1685 600 1902">Two serum sodium assessments of &lt; 130 mmol/L</td> <td data-bbox="600 1685 719 1902">Two serum sodium assessments of &lt; 130 mmol/L</td> </tr> </tbody> </table>	SIADH/ Other	CHF	Hepatocellular Disease	Two serum sodium assessments of < 130 mmol/L	Two serum sodium assessments of < 130 mmol/L	Two serum sodium assessments of < 130 mmol/L	<p><b>3.3.1.2 Specific Guidelines by Etiology</b></p> <ul style="list-style-type: none"> <li>Subjects diagnosed with hyponatremia secondary to SIADH will be evaluated specifically to ensure appropriate volume status. Hypovolemic states are not compatible with tolvaptan administration. Plasma and urine sodium, potassium, creatinine, and uric acid should be assessed in order to calculate and evaluate FENa and FE urate prior to dosing to ensure safety of tolvaptan administration.</li> <li>For hyponatremia due to hepatocellular disease (including cirrhosis), in addition to the above guidelines, the underlying etiology of hepatocellular disease must be documented.</li> <li>For hyponatremia due to HF:             <ol style="list-style-type: none"> <li>A definitive diagnosis of HF by a cardiologist must be documented.</li> <li>Loop diuretic use should be assessed and minimized where possible. Steady doses of diuretics are acceptable. Thiazide diuretics must be stopped before tolvaptan administration; the time that these medications must be stopped prior to the first tolvaptan dose depends on the half-life of the diuretic.</li> </ol> </li> </ul> <p>The medical monitor should be contacted if there are questions. The guidelines listed in Table 3.3.1-1 are to help guide the medical judgment of the investigator.</p> <p><b>Table 3.3.1-1 Screening Algorithms by Hyponatremia Etiology</b></p> <table border="1"> <thead> <tr> <th data-bbox="719 1115 817 1157">Etiology</th> <th data-bbox="817 1115 1439 1157">Instruction</th> </tr> </thead> <tbody> <tr> <td data-bbox="719 1157 817 1284">All etiologies</td> <td data-bbox="817 1157 1439 1284">Two documented serum sodium assessments of &lt; 130 mEq/L (mmol/L) at least 12 hours apart</td> </tr> <tr> <td data-bbox="719 1284 817 1410"></td> <td data-bbox="817 1284 1439 1410">One serum sodium assessment of &lt; 130 mEq/L (mmol/L) within 2-4 hours prior to tolvaptan administration</td> </tr> <tr> <td data-bbox="719 1410 817 1537"></td> <td data-bbox="817 1410 1439 1537">Screen subjects for AKI criteria per exclusion criteria</td> </tr> <tr> <td data-bbox="719 1537 817 1579"></td> <td data-bbox="817 1537 1439 1579">Collect labs<sup>a</sup></td> </tr> <tr> <td data-bbox="719 1579 817 1622"></td> <td data-bbox="817 1579 1439 1622">Calculate serum osmolality, FENa, and FE urate at pretreatment baseline only</td> </tr> <tr> <td data-bbox="719 1622 817 1769">HF</td> <td data-bbox="817 1622 1439 1769">Cardiologist documented diagnosis of HF</td> </tr> <tr> <td data-bbox="719 1769 817 1812"></td> <td data-bbox="817 1769 1439 1812">Discontinue or stabilize diuretic use prior to tolvaptan administration</td> </tr> <tr> <td data-bbox="719 1812 817 1902">Hepatocellular disease (including cirrhosis)</td> <td data-bbox="817 1812 1439 1902">The underlying etiology of hepatocellular disease must be documented</td> </tr> </tbody> </table>	Etiology	Instruction	All etiologies	Two documented serum sodium assessments of < 130 mEq/L (mmol/L) at least 12 hours apart		One serum sodium assessment of < 130 mEq/L (mmol/L) within 2-4 hours prior to tolvaptan administration		Screen subjects for AKI criteria per exclusion criteria		Collect labs <sup>a</sup>		Calculate serum osmolality, FENa, and FE urate at pretreatment baseline only	HF	Cardiologist documented diagnosis of HF		Discontinue or stabilize diuretic use prior to tolvaptan administration	Hepatocellular disease (including cirrhosis)	The underlying etiology of hepatocellular disease must be documented
SIADH/ Other	CHF	Hepatocellular Disease																								
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	at least 12 hours apart	at least 12 hours apart	at least 12 hours apart	<sup>a</sup> Refer to Table 3.7.4.2-1 for complete lists of laboratory assessments.
	One serum sodium assessment 3 ( $\pm$ 1) hours before tolvaptan administration of < 130 mmol/L	One serum sodium assessment 3 ( $\pm$ 1) hours before tolvaptan administration of < 130 mmol/L	One serum sodium assessment 3 ( $\pm$ 1) hours before tolvaptan administration of < 130 mmol/L	
	Screen subjects per AKI criteria per exclusion criteria	Screen subjects per AKI criteria per exclusion criteria	Screen subjects per AKI criteria per exclusion criteria	
	Collect labs a	Collect labs <sup>a</sup>	Collect labs <sup>a</sup>	
	Calculate plasma osmolality, FENa, and FE urate at pretreatment baseline only	Calculate plasma osmolality, FENa, and FE urate at pretreatment baseline only	Calculate plasma osmolality, FENa, and FE urate at pretreatment baseline only	
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	<table border="1" data-bbox="393 255 714 354"> <tr> <td></td> <td data-bbox="502 255 600 354">n adminis tration</td> <td></td> </tr> </table> <p data-bbox="393 354 714 508"><sup>a</sup>Refer to Table 3.7-1 and Table 3.7.4.2-1 for a complete list of laboratory assessments.</p> <p data-bbox="393 540 714 1733"><b>3.3.1.1 Hyponatremia due to Syndrome of Inappropriate Secretion of Antidiuretic Hormone</b> Evidence of low serum sodium should be demonstrated for at least 48 hours prior to scheduled tolvaptan administration. Two serum sodium assessments of &lt; 130 mmol/L should be collected at least 12 hours apart. One serum sodium assessment of &lt; 130 mmol/L should be collected 3 (<math>\pm</math> 1) hours before the initial tolvaptan administration. If any result, during the Screening period is <math>\geq</math> 130 mmol/L, the subject will be determined a screen failure. Subjects determined screen failures may be rescreened, as appropriate. Subjects who receive a randomization number may not be rescreened regardless of whether they receive trial medication or complete the trial. At Screening/Baseline, urine chemistry should be assessed and the plasma osmolality, FENa, and FE urate should be calculated for all subjects prior to the first dose of tolvaptan. Please see Table 3.7-1 for a full schedule of assessments and timing.</p> <p data-bbox="393 1765 714 1886">Subjects must be screened per the AKI criteria detailed in the exclusion criteria (Section 3.4.3).</p>		n adminis tration		
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	<ul style="list-style-type: none"> <li>• Hyponatremia due to Congestive Heart Failure</li> </ul> <p>Evidence of low serum sodium should be demonstrated for at least 48 hours prior to scheduled tolvaptan administration. Two serum sodium assessments of &lt; 130 mmol/L should be collected at least 12 hours apart. One serum sodium assessment of &lt; 130 mmol/L should be collected 3 (<math>\pm</math> 1) hours before the initial tolvaptan administration. If any result, during the Screening period is <math>\geq</math> 130 mmol/L, the subject will be determined a screen failure. Subjects determined screen failures may be rescreened, as appropriate. Subjects who receive a randomization number may not be rescreened regardless of whether they receive trial medication or complete the trial. At Screening/Baseline, urine chemistry should be assessed and the plasma osmolality, FENa, and FE urate should be calculated for all subjects prior to the first dose of tolvaptan. Please see Table 3.7-1 for a full schedule of assessments and timing.</p> <p>5) Loop diuretic use should be assessed and minimized where possible. Steady doses of diuretics are acceptable. Thiazide diuretics must be stopped before tolvaptan administration; the time that these medications must be stopped prior to the first tolvaptan dose depends on the half-life of the diuretic. The medical monitor should</p>	

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	<p>be contacted if there are questions.</p> <p>A definitive diagnosis of CHF by a cardiologist must be documented.</p> <p>Subjects must be screened per the AKI criteria detailed in the exclusion criteria (Section 3.4.3).</p> <p><b>3.3.1.2 Hyponatremia due to Hepatocellular Disease</b></p> <p>Evidence of low serum sodium should be demonstrated for at least 48 hours prior to scheduled tolvaptan administration.</p> <p>Two serum sodium assessments of &lt; 130 mmol/L should be collected at least 12 hours apart. One serum sodium assessment of &lt; 130 mmol/L should be collected 3 (<math>\pm</math> 1) hours before the initial tolvaptan administration. If any result, during the Screening period is <math>\geq</math> 130 mmol/L, the subject will be determined a screen failure. Subjects determined screen failures may be rescreened, as appropriate.</p> <p>Subjects who receive a randomization number may not be rescreened regardless of whether they receive trial medication or complete the trial. At Screening/Baseline, urine chemistry should be assessed and the plasma osmolality, FENa, and FE urate should be calculated for all subjects prior to the first dose of tolvaptan.</p> <p>Please see Table 3.7-1 for a full schedule of assessments and timing.</p> <p>Subjects must be screened per the AKI criteria detailed in the exclusion criteria (Section 3.4.3).</p> <p>The underlying etiology of hepatocellular disease must</p>	

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	be documented.	
<b>3.4 Eligibility Criteria</b>		Eligible subjects must satisfy all informed consent requirements, as well as meet all inclusion and exclusion criteria. Subjects who do not meet all of these requirements are to be defined as screen failures and may rescreen, if eligible, at a later date.
<b>3.4.2 Inclusion Criteria</b>	Eligible subjects must satisfy all informed consent requirements, as well as meet all inclusion criteria and none of the exclusion criteria. It is required to have documentation of chronic hyponatremia, defined by serum sodium < 130 mmol/L persisting for $\geq$ 48 hours duration and assessed at least 12 hours apart. Finally, there must be a final serum sodium assessed STAT prior to the initial dose of tolvaptan. This final serum sodium screening assessment must be verified to be < 130 mmol/L prior to the initial dose. Subjects who do not meet all of these requirements are to be defined as screen failures and may rescreen if eligible at a later date....	
<b>3.5 Outcome Variables</b>	<p><b>3.5.1 Primary Outcome Variables</b></p> <p><b>3.5.2 Efficacy Variables</b></p> <p>For subjects with serum sodium increases of <math>\geq</math> 4mmol/L (ie, responders), the primary endpoint is the change in serum sodium concentration from randomization (at the end of Day 2/3 [end of Phase A]) to the end of Day 4/5 (Phase B) for Early compared to Late Withdrawal groups.</p> <p><b>3.5.3 Secondary Outcome Variables</b></p> <p><b>3.5.4 Efficacy Variables</b></p> <p>For all subjects, the key secondary endpoint is the change in serum sodium concentration at the end of</p>	<p><b>3.5.1 Primary Efficacy Outcome Variable</b></p> <p>For subjects with serum sodium level increases of <math>\geq</math> 4 mEq/L (mmol/L) (ie, responders), change in serum sodium concentration from Day 2 (or 2a) at the end of Treatment Phase A to the end of Treatment Phase B for Early compared to Late Withdrawal groups.</p> <p><b>3.5.2 Key Secondary Efficacy Outcome Variable</b></p> <p>For all subjects, the key secondary endpoint is the change in serum sodium concentration at the end of Day 2 (or 2a) in Treatment Phase A from baseline.</p> <p><b>3.5.3.1 Safety Variables</b></p> <ul style="list-style-type: none"> <li>Percentage of subjects with overly rapid increase in serum sodium level (██████████)</li> <li>Change in serum sodium level from 24 hours post-last dose to 7 days post-last dose</li> <li>Percentage of subjects requiring rescue therapy (other than fluid restriction) during Treatment Phase A and Treatment Phase B</li> <li>Percentage of subjects requiring fluid restriction during</li> </ul>

Location:	Old Text:	New Text:
	<p>Day 2/3 from baseline in Phase A.</p> <p><b>3.5.4.1 Safety Variables</b></p> <ul style="list-style-type: none"> <li>Percentage of subjects with overly rapid increase in serum sodium (<math>\geq 12\text{mmol/L}</math>) in 24 hours after first dose).</li> <li>Percentage of subjects requiring rescue medication during Phase A and Phase B of the trial.</li> <li>Change in serum sodium from 24 hours post-last dose to 14 days post-randomization.</li> <li>Vital signs, blood pressure, clinical laboratory tests, and body weight.</li> </ul> <p><b>3.5.4.3 Pharmacodynamic Variables</b></p> <p>Pharmacodynamic endpoints are fluid intake, urine output, and fluid balance (intake – output) every 6 hours on Days 1 and 2 (Phase A).</p> <p><b>3.5.5 Exploratory Variables</b></p> <p><b>3.5.5.1 Efficacy Variables</b></p> <ul style="list-style-type: none"> <li>The other efficacy endpoint in nonresponders continuing on tolvaptan therapy is the change in trough serum sodium concentration on Day 6 compared to Day 4.</li> </ul> <p><b>3.5.5.2 Safety Variable</b></p> <p>The other safety variable is neurological examinations.</p> <p><b>3.5.5.3 Pharmacodynamic Variables</b></p> <p>The other PD endpoints include:</p>	<p>Treatment Phase A and Treatment Phase B</p> <ul style="list-style-type: none"> <li>Vital signs, blood pressure, clinical laboratory tests, body weight, and neurological examinations</li> </ul> <p><b>3.5.3.3 Pharmacodynamic Variables</b></p> <p>Pharmacodynamic endpoints are fluid intake, urine output, and fluid balance (intake minus output) every 6 hours on Days 1 and 2 in Treatment Phase A.</p> <p><b>3.5.4 Exploratory Variables</b></p> <ul style="list-style-type: none"> <li>Efficacy will be assessed in nonresponders continuing on tolvaptan therapy by change from baseline in serum sodium concentration at the end of Treatment Phase B compared to the end of Treatment Phase A</li> <li>In all subjects, 24-hour excretion of sodium, creatinine, and urine osmolality on Days 1 and 2</li> <li>24-hour sodium clearance on Day 1</li> <li>Neurocognition test battery</li> <li>QoL assessments</li> </ul>

Location:	Old Text:	New Text:
	<ul style="list-style-type: none"> <li>In all subjects, 24-hour excretion of sodium, creatinine, and osmoles on Days 1 and 2.</li> </ul>	
<b>3.6 Measures to Minimize/void Bias</b>	<p>This is an open-label trial. Subjects defined as responders (serum sodium increase of <math>\geq 4</math> mmol/L) will be randomized to either the Early Withdrawal group or the Late Withdrawal group. The assignments will be stratified by age (&lt; 10 and <math>\geq 10</math> to &lt; 18 years), magnitude of serum sodium response (<math>\leq 7</math> and <math>&gt; 7</math> mmol/L), and underlying etiology of hyponatremia. The dose of the investigational medicinal product (IMP) assigned to a subject is determined by the subject's age, weight, and the use of CYP3A4 inhibitors.</p>	<p>This is an open-label trial. Subjects defined as responders from Treatment Phase A will be randomized to either the Early Withdrawal group or the Late Withdrawal group in Treatment Phase B. Treatment assignments for Treatment Phase B will be based on a computer-generated randomization code provided by OPDC Biometrics Department.</p>
<b>3.7 Trial Procedures</b>	<p>Treatment in this trial will be up to 5 days. Any initiation or titration of tolvaptan must occur in a hospital setting. Parents or legal guardians will consent and subjects will assent (as appropriate) and be screened up to 24 hours prior to dosing. Subjects who meet the inclusion and exclusion criteria will be enrolled and will be administered a 3.75-, 7.5-, or 15-mg dose tablet based on age, weight, and the use of CYP3A4 inhibitors.</p> <p>At the end of Treatment Day 2 (optionally Day 3 [Phase A]), subjects who are responders will be randomized to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early Withdrawal). Subjects who</p>	<p>Treatment in this trial will last up to 5 days. Any initiation or titration of tolvaptan must occur in a hospital setting. Parents or legal guardians must provide informed consent and subjects must provide informed assent (as appropriate) and be screened up to 24 hours prior to dosing.</p> <p>In Treatment Phase A, subjects who meet the inclusion and exclusion criteria will be enrolled and will be administered a 3.75-, 7.5-, or 15-mg dose tablet based on age, weight, and the use of CYP3A4 inhibitors. At the end of Day 2 (or 2a) in Treatment Phase A, subjects who are responders will be randomized to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early Withdrawal).</p> <p>In Treatment Phase B, subjects who are nonresponders may continue on tolvaptan therapy for 2 additional days or may be withdrawn from tolvaptan to be treated per the investigator's preferred standard of care. During Treatment Phase B, subjects in the Late Withdrawal group and nonresponders continuing treatment will continue to receive tolvaptan for 2 additional days and all subjects will have serum sodium levels measured at 12 (<math>\pm 4</math>) hours post-dose and at trough each day. Subjects in the Early Withdrawal group should be monitored for the first 48 hours post-last dose.</p> <p>In Follow-up Phase C, all subjects will be monitored and will have an additional serum sodium measurement at 72 (<math>\pm 4</math>) hours</p>

Location:	Old Text:	New Text:
	<p>are nonresponders may continue on tolvaptan therapy for 2 additional days at their highest dose or may be withdrawn from tolvaptan to be treated per the investigator's preferred standard of care.</p> <p>During Phase B, subjects in the Late Withdrawal group and nonresponders continuing treatment will continue treatment with tolvaptan for 2 additional days and all subjects will have serum sodium measured every 12 (<math>\pm</math> 4) hours post-randomization.</p> <p>In Phase C, or Follow-up Phase, subjects will be monitored and treated as clinically warranted per the investigator's preferred standard of care for up to 3 additional days after the last dose of tolvaptan (note: the Early Withdrawal group should be monitored for the first 48 hours post-last dose) and will have an additional serum sodium concentration measurement at 72 (<math>\pm</math> 4) hours post-randomization and 7 (<math>\pm</math> 1) days post-randomization. A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-randomization.</p> <p>Trial assessment time points are summarized in Table 3.7-1.</p> <p>Pharmacokinetic samples will be obtained on Day 1 (Phase A) for all subjects and at 24 and 48 hours post-randomization for tolvaptan-treated subjects in Phase B, including subjects who are</p>	<p>post-last dose as well as at 7 (<math>\pm</math> 1) days post-last dose. A final safety follow-up telephone contact/visit will be performed 14 (+ 2) days post-last dose.</p> <p>Trial assessment time points are summarized in Table 3.7-1. Section 3.7.1 provides a flow overview that describes the sequence of assessments during a visit. Section 3.7.2 provides details around efficacy assessments, Section 3.7.3 provides details around pharmacokinetic/pharmacodynamic assessments and Section 3.7.4 provides details around safety assessments.</p> <p>Pharmacokinetic samples will be obtained for all subjects on Day 1 at 2 and 8 hours post-first dose and at trough on Days 2, 3, 4 and 5 for all subjects when dosed with tolvaptan on Days 1, 2, 3, and 4, respectively, regardless of responder status. Once adequate PK data are obtained, PK sampling will be discontinued for all subjects.</p> <p>Subjects will be required to be in a hospital setting during initiation or titration of tolvaptan. A subject is allowed to be discharged, if they:</p> <ol style="list-style-type: none"> <li>1) Continue to come to the clinic for daily study assessments and</li> <li>2) Are either: <ol style="list-style-type: none"> <li>a) A nonresponder on standard of care or</li> <li>b) On a stable dose of study drug, or</li> <li>c) In the early withdrawal group without study treatment.</li> </ol> </li> </ol> <p>Follow-up for all subjects may occur in the hospital if the subject has not been discharged or the subject may return for outpatient visits if the subject has been discharged from the hospital.</p>

Location:	Old Text:	New Text:
	deemed nonresponders and continue on tolvaptan. Once adequate PK data are obtained, PK sampling will be discontinued for all subjects.	

**Old Text:****3.7 Trial Procedures**

Procedures	Phase A		Phase B	Phase C		
	Screening/ Baseline Visit Days -2 to -1	Initial Treatment Phase Days 1 and 2/3	Randomization Phase Days 3/4 and 4/5	Follow-up Phase Day 5/6 or ET	Follow-up (7 [ $\pm$ 1] days post-random.)	Follow-up Phone Call/Visit (14 [ $\pm$ 2] days post-random.)
Informed consent and assent	X					
Review inclusion/exclusion criteria	X	Day 1: predose				
Demographic information	X					
Medical and hyponatremia history	X					
Alcohol and drug screen	X					
Pregnancy test (if applicable) <sup>a</sup>	X					
Serum chemistry	X			X		
Plasma osmolality, FeNa, and Fe urate	X					
TSH and cortisol <sup>b</sup>	X					
Hematology and coagulation	X			X		
Urinalysis	X			X		
Urine chemistry	X	Days 1 and 2 only: 6-hour intervals starting at Hour 0				
Serum sodium <sup>c</sup>	2 assessments at least 12 hours apart	Baseline (Hour 0; within 3 [ $\pm$ 1] hours of dosing), 12 hours post-first dose, and 24 ( $\pm$ 4) hours post-previous dose	12, 24, 36, and 48 ( $\pm$ 4) hours post-random.	72 ( $\pm$ 4) hours post-random.	X	
Vital signs <sup>d</sup>	X	2, 4, 8, and 24 hours post-first dose and on Day 3, if applicable	X	X	X	
Fluid intake and urine volume		Days 1 and 2 only: 6-hour				

**Table 3.7-1 Schedule of Assessments**

Procedures	Phase A		Phase B	Phase C		
	Screening/ Baseline Visit Days -2 to -1	Initial Treatment Phase Days 1 and 2/3	Randomization Phase Days 3/4 and 4/5	Follow-up Phase Day 5/6 or ET	Follow-up (7 [ $\pm$ 1] days post-random.)	Follow-up Phone Call/Visit (14 [ $\pm$ 2] days post-random.)
		intervals starting at Hour 0				
PK plasma samples <sup>e</sup>		1, 2, 4, 12, and 24 hours post-first dose	24 and 48 hours post-random.	ET only		
12-lead ECG	X					
Directed physical examination	X	Baseline (Hour 0), 8 hours post-first dose, and Day 2/3	Daily	X	X	
Neurological examination	X	Baseline (Hour 0), 8 hours post-first dose, and Day 2/3	Daily	X	X	
Body height and weight <sup>f</sup>	X	Daily (predose): weight only	Daily (predose): weight only	Weight only	Weight only	
Clinical assessment <sup>g</sup>	X	End of Day 2/3	Day 4/5	X	X	
Randomization		Responders: End of Day 2 (optionally Day 3)				
Tolvaptan dosing <sup>h</sup>		Once daily	Once daily <sup>i</sup>			
Follow-up phone call						X
Concomitant medications	<----->					
Adverse events	<----->					

ECG = electrocardiogram; ET = early termination; post-random. = post-randomization; TSH = thyroid-stimulating hormone.

Note: See Table 3.7.4.2-1 for further details regarding laboratory tests.

<sup>a</sup>Pregnancy tests will be performed on female subjects  $\geq$  12 years of age and all female subjects  $<$  12 years of age if menstruation has started.

<sup>b</sup>Results of these tests will further characterize hyponatremia etiology for the Hyponatremia History CRF and are not required to determine eligibility.

<sup>c</sup>Results of the serum sodium from the chemistry panel are sufficient for the protocol. It is not necessary to collect a separate serum sodium concentration.

<sup>d</sup>Vital signs to be assessed include supine blood pressure, heart rate, respiratory rate, and temperature. Vital signs should be assessed prior to any blood draws per protocol.

<sup>e</sup>An ET sample will be collected only if ET is before the last scheduled PK assessment. The PK samples in Phase B will be collected for all subjects who are on tolvaptan, including subjects who are deemed nonresponders and continue on tolvaptan. Pharmacokinetic blood samples should be taken within  $\pm$  5 minutes for each draw up to 2 hours postdose and  $\pm$  30 minutes for later time points.

<sup>f</sup>Weight will be taken predose as possible during administration of tolvaptan.

<sup>g</sup>Subject clinical status assessments will be performed per inpatient standard of care, ie, review patient chart entries (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate overall subject eligibility in terms of hyponatremia state.

<sup>h</sup>The dose will be titrated at a minimum of 24 ( $\pm$  4)-hour intervals from 3.75 to 7.5 to 15 mg for subjects  $\geq$  2 years of age and weighing  $\geq$  10 to  $<$  20 kg, from 7.5 to 15 to 30 mg for subjects weighing 20 to 50 kg, inclusive, or from 15 to 30 to 60 mg for subjects weighing  $>$  50 kg. Subjects starting at lower doses may be sequentially titrated to the maximal dose allowed for their weight group. Each upward titration may not exceed twice the previous dose.

- In Phase B, tolvaptan will only be administered to subjects randomized to the Late Withdrawal group and to nonresponders who are continuing on tolvaptan. Subjects randomized to the Late Withdrawal group will receive the same dose that they received on Day 2/3; nonresponders may continue on tolvaptan therapy for 2 additional days at their highest dose at the discretion of the investigator.

New Text:

## 3.7 Trial Procedures

Procedures	Screening	Treatment Phase A			Treatment Phase B			Follow-up Phase C			
	Day -2 and -1	Day 1	Day 2	Day 2a (optional)	Day 3	Day 4	Day 5	72 ( $\pm 4$ ) h post last dose	7 ( $\pm 1$ ) days post-last dose	14 (+2) days post-last dose	Early Termination (ET)
Informed Consent/Assent	X										
Inclusion/exclusion criteria <sup>a</sup>	X	X									
Demographic information	X										
Medical and hyponatremia history	X										
Vital signs <sup>b</sup>	X	X	X	X	X	X	X	X	X		X
12-lead ECG	X										
Height	X										
Body weight <sup>c</sup>	X	X	X	X	X	X	X	X	X		X
Directed physical examination	X	X	X	X	X	X		X	X		X
Tanner staging	X										
Neurological examination	X	X	X		X	X		X	X		X
Neurocognitive assessment <sup>d</sup>	X	X	X	X	X	X	X	X	X		X
Quality of life assessment	X					X			X		
Clinical status assessment <sup>e</sup>	X	X	X	X	X	X		X	X		X
Alcohol/drug screen	X										
Pregnancy test (if applicable) <sup>f</sup>	X										
Fluid intake <sup>g</sup>		X	X								
Urine volume <sup>g</sup>		X	X								
Urinalysis	X							X			X
Urine chemistry <sup>g,h</sup>	X	X	X								
Serum sodium <sup>i</sup>	X	X	X	X	X	X	X	X	X		X

**Table 3.7-1 Schedule of Assessments**

Procedures	Screening	Treatment Phase A			Treatment Phase B			Follow-up Phase C			
	Day -2 and -1	Day 1	Day 2	Day 2a (optional)	Day 3	Day 4	Day 5	72 (±4) h post last dose	7 (±1) days post-last dose	14 (+2) days post-last dose	Early Termination (ET)
Hematology, coagulation, and serum chemistry <sup>j</sup>	X							X			X
Serum osmolality, FENa, and FE urate	X										
TSH and cortisol <sup>k</sup>	X										
PK plasma samples <sup>l</sup>		X	X		X	X	X				X
Tolvaptan dosing <sup>m</sup>		X	X	X	X	X					
Assessment for response to tolvaptan			X	X							
Palatability assessment			X								
Randomization					X						
Follow-up phone call or visit										X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

ECG = electrocardiogram; TSH = thyroid-stimulating hormone.

<sup>a</sup>Inclusion/exclusion criteria will be checked at screening and predose on Day 1.

<sup>b</sup>Vital signs to be assessed include supine blood pressure, heart rate, respiratory rate, and temperature. Vital signs should be assessed prior to any blood draws.

<sup>c</sup>Weight will be taken predose as possible.

<sup>d</sup>Neurocognitive assessments are closely tied to serum sodium assessments and should be done within 1 hour of sodium blood draws.

<sup>e</sup>Clinical status assessments will be performed per inpatient standard of care, ie, review patient chart entries (including hyponatremia assessment notes and laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate overall subject eligibility in terms of hyponatremia state.

<sup>f</sup>Urine pregnancy tests will be performed on female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started.

<sup>g</sup>Intervals starting immediately after dosing at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).

<sup>h</sup>Samples within a collection interval are to be refrigerated and pooled. An aliquot for urine chemistry tests will be taken for each collection interval. Uric acid is to be measured at screening only.

<sup>i</sup>Serum sodium assessments are closely tied to neurocognitive assessments, dosing time points and PK blood draws.

- Screening: 2 assessments should be taken, at least 12 hours apart (may be part of medical history). 1 assessment can be combined with the serum chemistry panel.

- Treatment Phase A: Baseline [STAT] assessment will be at 2-4 hours prior to first dose. Post-first dose assessments: 8 and 24 (trough) hours. Then every 12 hours thereafter (alternating 12 hours post-dose and at trough)
- Treatment Phase B: Assessments to be taken every 12 hours (alternating 12 hours post-dose and at trough)
- Treatment Phase C: Assessments to be taken at 72 ( $\pm$  4) hours post-last dose (can be combined with the serum chemistry panel) and at the 7 day post-last dose visit.

<sup>j</sup>Serum chemistry panel includes serum sodium and assessments can be combined for visits where both assessments are indicated.

<sup>k</sup>Results of these tests will further characterize hyponatremia etiology for the Hyponatremia History CRF and are not required to determine eligibility.

Subjects who have clinically relevant TSH or cortisol levels may not respond properly to tolvaptan and will be withdrawn from the trial.

<sup>l</sup>PK samples are closely tied to dosing time points and serum sodium assessments. An ET sample will be collected only if ET is before the last scheduled PK assessment.

- In Treatment Phase A PK samples should be collected at 2 and 8 hours and at trough post-first dose.
- In Treatment Phase B PK will be assessed in subjects continuing treatment with tolvaptan (Late Withdrawal group and nonresponders continuing on tolvaptan) at trough on Days 3, 4 and 5.

<sup>m</sup>The tolvaptan dose will be titrated based on serum sodium levels as described in Section 3.2.4.

Location:	Old Text:	New Text:
<b>3.7.1 Schedule of Assessments</b>	<p><b>3.7.1.1 Phase A: Treatment Phase</b></p> <p><b>3.7.1.2 Screening/Baseline</b></p> <p>The following procedures will be performed during the Screening/Baseline Visit (Days -2 to -1 prior to dosing) to ensure the subject qualifies for the trial:</p> <ol style="list-style-type: none"> <li>1) Trial procedures and information regarding the nature of the trial will be reviewed and written informed consent/assent will be obtained prior to any trial-related procedures.             <ol style="list-style-type: none"> <li>a) Informed consent will be obtained from each subject's parent or legal guardian prior to any trial procedures being conducted.</li> <li>b) Each subject who is able will indicate willingness to participate in the trial by signing or marking an assent form (as applicable) supplied for this purpose.</li> </ol> </li> <li>2) Inclusion and exclusion criteria will be reviewed.</li> <li>3) Demographic information will be collected.             <ol style="list-style-type: none"> <li>a) Medical and hyponatremia history will be recorded separately. Medical history should include the subject's current list of medical problems that impacts the subject's current hospital stay.</li> <li>b) The hyponatremia medical history should include the etiology of subject's hyponatremia (including tests per protocol) and what treatment was administered before trial enrollment. A detailed history specific to etiology of hyponatremia will also be recorded.</li> <li>c) Any observable symptoms of hyponatremia will be assessed and recorded separately.</li> </ol> </li> <li>4) Alcohol and drug screens will be performed.</li> <li>5) A urine or serum pregnancy test will be performed on all female subjects <math>\geq</math> 12 years of age and all female subjects <math>&lt;</math> 12 years of age if menstruation has started.</li> <li>6) Two samples for serum sodium</li> </ol>	<p><b>3.7.1.1 Screening</b></p> <p>The procedures listed below will be performed during the Screening Visit (Days -2 to -1) to ensure that the subject qualifies for the trial.</p> <ol style="list-style-type: none"> <li>1) Trial procedures and information regarding the nature of the trial will be reviewed and written informed consent/assent will be obtained prior to any trial-related procedures.             <ol style="list-style-type: none"> <li>a) Informed consent will be obtained from each subject's parent or legal guardian prior to any trial procedures being conducted.</li> <li>b) Each subject who is able will indicate willingness to participate in the trial by signing or marking an assent form (as applicable) supplied for this purpose.</li> </ol> </li> <li>2) Inclusion and exclusion criteria will be reviewed.</li> <li>3) Demographic information will be collected.</li> <li>4) Medical and hyponatremia history will be recorded.             <ol style="list-style-type: none"> <li>a) Medical history should include the subject's current list of medical problems that impacts the subject's current hospital stay.</li> <li>b) The hyponatremia medical history should include the etiology of subject's hyponatremia (see Section 3.2.1) and what treatment was administered prior to trial enrollment. A detailed history specific to etiology of hyponatremia will also be recorded.</li> <li>c) Any observable symptoms of hyponatremia will be assessed and recorded.</li> </ol> </li> <li>5) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq</math> 3 minutes. Vital signs should be assessed prior to blood draws.</li> <li>6) A resting 12-lead electrocardiogram (ECG) will be performed after the subject has</li> </ol>

Location:	Old Text:	New Text:
	<p>testing will be collected at least 12 hours apart. (These blood draws can be combined with the serum chemistry panel as appropriate to minimize blood draws.)</p> <p>7) Urinalysis and urine chemistry laboratory samples will be collected.</p> <p>8) Plasma osmolality, FENa, and FE urate will be calculated.</p> <p>9) Thyroid-stimulating hormone (TSH) and cortisol blood samples will be collected to determine need for alternate mode of therapy.</p> <p>10) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq 3</math> minutes. Vital signs should be performed prior to the blood draws.</p> <p>11) A resting 12-lead electrocardiogram (ECG) will be performed after the subject has been supine and at rest <math>\geq 10</math> minutes.</p> <p>12) A directed physical examination will be performed.</p> <p>13) A neurological examination will be performed.</p> <p>14) Body height and weight will be measured and body mass index will be calculated.</p> <p>15) Clinical status assessments will be performed per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate overall subject eligibility in terms of hyponatremia state.</p> <p>16) Concomitant medications will be recorded.</p> <p>17) Adverse events will be assessed.</p> <p><b>3.7.1.2.1 Day 1</b> The following procedures will be performed on Day 1 for all subjects:</p> <p>1) Inclusion and exclusion criteria will be reviewed prior to dosing to confirm eligibility.</p>	<p>been supine and at rest <math>\geq 10</math> minutes.</p> <p>7) Body height and weight will be measured.</p> <p>8) A directed physical examination will be performed.</p> <p>9) Tanner staging will be performed.</p> <p>10) A neurological examination will be performed.</p> <p>11) A neurocognitive assessment will be performed, as appropriate by age and where available.</p> <p>12) Quality-of-life (QoL) assessment will be performed, as appropriate by age and where available.</p> <p>13) Clinical status assessments will be performed per inpatient standard of care.</p> <p>14) Alcohol and drug screens will be performed, as age appropriate.</p> <p>15) A urine pregnancy test will be performed on all female subjects <math>\geq 12</math> years of age and all female subjects <math>&lt; 12</math> years of age if menstruation has started.</p> <p>16) Urinalysis and urine chemistry laboratory samples will be collected for analysis.</p> <p>17) Two blood samples for serum sodium testing will be collected at least 12 hours apart and can be part of the recent medical history to document chronic hyponatremia. (One of these blood draws can be combined with the serum chemistry panel as appropriate to minimize blood draws.)</p> <p>18) Hematology, coagulation, and serum chemistry laboratory samples will be collected for analysis.</p> <p>19) Serum osmolality, FENa, and FE urate will be determined.</p> <p>20) Thyroid-stimulating hormone (TSH) and cortisol blood samples will be collected to determine possible need for alternate mode of therapy.</p> <p>21) Concomitant medications will be recorded.</p> <p>22) Adverse events will be recorded.</p> <p><b>3.7.1.2 Treatment Phase A</b> During Treatment Phase A every effort</p>

Location:	Old Text:	New Text:
	<p>2) Blood samples for STAT serum sodium testing will be collected at baseline (Hour 0; within 3 [<math>\pm</math> 1] hours prior to dosing) and 12 hours post-first dose per protocol, but can be assessed as often as desired per clinician preference.</p> <p>3) Vital signs will be assessed at 2, 4, and 8 hours post-first dose. Blood pressure, heart rate, respiratory rate, and temperature will be assessed after the subject has been supine for <math>\geq</math> 3 minutes. Vital signs should be performed prior to the blood draws at each nominal time point.</p> <p>4) Fluid intake and urine volume will be recorded at 6-hour intervals starting at Hour 0.</p> <p>5) Urine chemistry will be assessed using 6-hour collection intervals starting at Hour 0.</p> <p>6) Any observable symptoms of hyponatremia will be assessed at baseline (prior to dosing) to confirm eligibility.</p> <p>7) A directed physical examination will be performed at baseline (prior to dosing) and 8 hours post-first dose.</p> <p>8) A neurological examination will be performed at baseline (prior to dosing) and 8 hours post-first dose.</p> <p>9) Body weight will be measured predose as possible.</p> <p>10) Blood samples for PK analysis of tolvaptan will be collected at 1, 2, 4, and 12 hours post-first dose.</p> <p>11) Tolvaptan will be administered as a 3.75-, 7.5-, or 15-mg dose based on weight and the use of CYP3A4 inhibitors.</p> <p>12) Concomitant medications will be recorded.</p> <p>13) Adverse events will be assessed.</p>	<p>should be made to have accurate dosing time points and follow the sequence of assessments specified below as PK/PD assessments, serum sodium blood draws and neurocognitive assessments are closely tied to dosing time points.</p> <p><b>3.7.1.2.1 Day 1</b> The procedures listed below will be performed on Day 1 for all subjects.</p> <p><u>Predose</u></p> <ol style="list-style-type: none"> <li>1) Any observable symptoms of hyponatremia will be assessed within 2 hours prior to first dose to confirm eligibility as part of a clinical status assessment.</li> <li>2) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq</math> 3 minutes. Vital signs should be assessed prior to blood draws.</li> <li>3) A blood sample for STAT serum sodium testing will be collected within 2 to 4 hours prior to dosing.</li> <li>4) A neurocognitive assessment will be performed, as appropriate by age and where available.</li> <li>5) Body weight will be measured.</li> <li>6) A directed physical examination will be performed.</li> <li>7) A neurological examination will be performed.</li> <li>8) Inclusion and exclusion criteria will be reviewed and confirmed</li> </ol> <p><u>Dosing</u></p> <ol style="list-style-type: none"> <li>9) Tolvaptan will be administered.</li> </ol> <p><u>Postdose</u></p> <ol style="list-style-type: none"> <li>10) A blood sample will be collected at 2 hours post-first dose for PK analysis</li> <li>11) Vital signs will be assessed at 4 and 8 hours post-first dose. Blood pressure, heart rate, respiratory rate, and temperature will be assessed after the subject has been supine for <math>\geq</math> 3 minutes. Vital signs should be assessed prior to blood draws at 8 hours.</li> <li>12) Fluid intake will be recorded at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).</li> <li>13) Urine will be collected at 6-hour intervals starting at Hour 0 (0-6,</li> </ol>

Location:	Old Text:	New Text:
	<p>subsequent tolvaptan dosing.</p> <p>2) Vital signs will be assessed at 24 hours post-first dose and on Day 3, if applicable. Blood pressure, heart rate, respiratory rate, and temperature will be assessed after the subject has been supine for <math>\geq 3</math> minutes. Vital signs should be performed prior to the blood draws.</p> <p>3) Fluid intake and urine volume will be recorded at 6-hour intervals on Day 2.</p> <p>4) Urine chemistry will be assessed using 6-hour collection intervals on Day 2.</p> <p>5) A directed physical examination will be performed.</p> <p>6) A neurological examination will be performed.</p> <p>c) Body weight will be measured predose daily during administration of tolvaptan as possible.</p> <p>d) A blood sample for PK analysis of tolvaptan will be collected at 24 hours post-first dose.</p> <p>7) If the subject's serum sodium concentration is <math>&lt; 135</math> mmol/L and a <math>\leq 4</math>-mmol/L increase, tolvaptan should be titrated per the titration guidelines (Section 3.2.1) for the assigned weight group.</p> <p>8) Clinical status assessments will be performed at the end of Day 2/3 per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate overall subject eligibility in terms of hyponatremia state.</p> <p>2) Concomitant medications will be recorded.</p> <p>3) Adverse events will be assessed.</p> <p>a) At the end of Day 2 (optionally Day 3), subjects who are responders (serum sodium increase of <math>\geq 4</math></p>	<p>6-12, 12-18, and 18-24 hours). Subjects should be asked to void just prior to the end time of each collection interval, as possible.</p> <p>a) Urine volume will be determined from urine voids made during the 6-hour collection intervals which will be pooled prior to determination of final volume.</p> <p>b) A urine chemistry sample will be collected and assessed from each 6-hour volume interval starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).</p> <p>14) Blood samples will be collected concurrently at 8 hours post-first dose for:</p> <p>a) Serum sodium testing</p> <p>b) PK analysis</p> <p>15) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</p> <p>16) A neurological examination will be performed at 8 hours post-first dose.</p> <p><u>Throughout the visit</u></p> <p>17) Concomitant medications will be recorded.</p> <p>18) Adverse events will be assessed.</p> <p><b>3.7.1.2.2 Day 2</b></p> <p>The following procedures will be performed on Day 2 for all subjects.</p> <p><u>Through (24 hours post-first dose)</u></p> <p>At trough the following assessments will be performed:</p> <p>1) Vital signs will be assessed. Blood pressure, heart rate, respiratory rate, and temperature will be assessed after the subject has been supine for <math>\geq 3</math> minutes. Vital signs should be performed prior to blood draws.</p> <p>2) Blood samples will be collected concurrently at 24 (<math>\pm 4</math>) hours for:</p> <p>a) A blood sample for STAT serum sodium testing should be taken and the results known prior to subsequent tolvaptan dosing.</p> <p>b) A blood sample for PK analysis of tolvaptan (at a</p>

Location:	Old Text:	New Text:
	<p>mmol/L) will be randomized to the Early or Late Withdrawal group.</p> <p>11) Subjects who are nonresponders at the end of Day 3 may continue on tolvaptan therapy for 2 additional days at their highest dose or may be withdrawn from tolvaptan to be treated per the investigator's preferred standard of care.</p> <p><b>3.7.1.3 Phase B: Randomization Phase</b> The following procedures will be performed on Days 3/4 and 4/5 for all subjects:</p> <ol style="list-style-type: none"> <li>1) A blood sample for STAT serum sodium testing should be taken 12, 24, 36, and 48 (<math>\pm</math> 4) hours post-randomization and the results known prior to subsequent treatment.</li> <li>2) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed daily after the subject has been supine for <math>\geq</math> 3 minutes. Vital signs should be performed prior to the blood draws.</li> <li>3) A directed physical examination will be performed daily.</li> <li>4) A neurological examination will be performed daily.</li> <li>5) Body weight will be measured predose daily during administration of tolvaptan as possible.</li> <li>6) Blood samples for PK analysis of tolvaptan will be collected at 24 and 48 hours post-randomization for all subjects on tolvaptan, including subjects who are deemed nonresponders and continue on tolvaptan.</li> <li>7) Tolvaptan will be administered once daily to subjects randomized to the Late Withdrawal group and nonresponders continuing on tolvaptan.</li> <li>8) Subjects randomized to the Early Withdrawal group will be initially observed to determine whether additional intervention is required to maintain appropriate serum sodium levels. Nonresponders discontinuing tolvaptan will be</li> </ol>	<p>central lab) will be collected at 24 hours post-first dose.</p> <p>3) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</p> <p><u>Predose</u></p> <ol style="list-style-type: none"> <li>4) Complete fluid intake and urine volume collection for specified intervals prior to next dosing with tolvaptan.</li> <li>5) Fluid intake will be recorded at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).</li> <li>6) Urine will be collected at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours). Subjects should be asked to void just prior to the end time of each collection interval, as possible. <ul style="list-style-type: none"> <li>a) Urine volume will be determined from urine voids made during the 6-hour collection intervals which will be pooled prior to determination of final volume.</li> <li>b) A urine chemistry sample will be collected and assessed from each 6-hour volume interval starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).</li> </ul> </li> <li>7) A directed physical examination will be performed.</li> <li>8) Body weight will be measured.</li> <li>9) A neurological examination will be performed.</li> </ol> <p><u>Dosing</u></p> <ol style="list-style-type: none"> <li>10) Tolvaptan will be administered. If the subject's serum sodium concentration is <math>&lt;</math> 135 mEq/L (mmol/L) and a <math>\leq</math> 4 mEq/L (mmol/L) increase, tolvaptan dose should be adjusted per the titration guidelines (Section 3.2.4) for the assigned weight group.</li> </ol> <p><u>Postdose</u></p> <ol style="list-style-type: none"> <li>2) Assess palatability of tolvaptan tablets for subjects.</li> <li>3) Fluid intake will be recorded at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).</li> <li>4) Urine will be collected at 6-hour</li> </ol>

Location:	Old Text:	New Text:
	<p>treated per the investigator's preferred standard of care for 3 additional days after the last dose of tolvaptan.</p> <p>9) Clinical status assessments will be performed on Day 4/5 per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate overall subject eligibility in terms of hyponatremia state.</p> <p>10) Concomitant medications will be recorded.</p> <p>11) Adverse events will be assessed.</p> <p><b>3.7.1.4 Phase C: Follow-up Phase</b></p> <p><b>3.7.1.4.1 Follow-up (Day 5/6)/Early Termination</b></p> <p>The following procedures will be performed on Day 5/6 or at early termination (ET) for all subjects:</p> <p>1) Hematology, coagulation, and serum chemistry laboratory samples will be collected.</p> <p>2) A blood sample for serum sodium testing will be collected <u>at 72</u> (<math>\pm 4</math>) hours post-randomization. (This blood draw can be combined <u>with</u> the chemistry panel as appropriate to minimize blood draws.)</p> <p>3) A urinalysis laboratory sample will be collected.</p> <p>4) A blood sample for PK analysis of tolvaptan will be collected at ET only if ET occurs before the last scheduled PK assessment (ie, <u>48 hours post-randomization</u> for subjects continuing on tolvaptan).</p> <p>5) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq 3</math> minutes. Vital signs should be performed prior to the blood draws.</p> <p>6) A directed physical examination will be performed.</p> <p>7) A neurological examination will</p>	<p>intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours). Subjects should be asked to void just prior to the end time of each collection interval, as possible.</p> <p>a) Urine volume will be determined from urine voids made during the 6-hour collection intervals which will be pooled prior to determination of final volume.</p> <p>b) A urine chemistry sample will be collected and assessed from each 6-hour volume interval starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).</p> <p>5) Clinical status assessments will be performed per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.</p> <p>6) A blood sample will be collected for serum sodium testing at 12 hours post-dose.</p> <p>7) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</p> <p>8) At the end of the Day 2 visit subjects will be assessed for response to tolvaptan treatment. Subjects who are:</p> <p>a) Responders (serum sodium level increase of <math>\geq 4</math> mEq/L [mmol/L]) will proceed to Treatment Phase B (see Section 3.7.1.3) for randomization.</p> <p>b) Nonresponders (serum sodium level increase of <math>&lt; 4</math> mEq/L [mmol/L]) will proceed to Day 2a (see Section 3.7.1.2).</p> <p><u>Throughout the visit</u></p> <p>9) Concomitant medications will be recorded.</p> <p>10) Adverse events will be assessed.</p>

Location:	Old Text:	New Text:
	<p>be performed.</p> <p>8) Body weight will be measured as possible.</p> <p>9) Subjects will be monitored and treated as clinically warranted per the investigator's preferred standard of care for up to 3 additional days after the last dose of tolvaptan (note: the Early Withdrawal group should be monitored for the first 48 hours post-last dose).</p> <p>10) Concomitant medications will be recorded.</p> <p>11) Adverse events will be assessed.</p> <p><b>3.7.1.4.2 Follow-up</b></p> <p>1) Subjects will be assessed for maintenance of normal or target serum sodium concentration at 7 (<math>\pm 1</math>) days post-randomization. If the subject was discharged, he/she should return to the clinic for the serum sodium collection.</p> <p>2) A blood sample for serum sodium testing will be collected.</p> <p>3) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq 3</math> minutes. Vital signs should be performed prior to the blood draws.</p> <p>4) A directed physical examination will be performed.</p> <p>5) A neurological examination will be performed.</p> <p>6) Body weight will be measured.</p> <p>7) Concomitant medications will be recorded.</p> <p>8) Adverse events will be assessed.</p> <p><b>3.7.1.4.3 Follow-up Telephone Contact/Visit</b></p> <p>Subjects (or their parents or legal guardians) will be contacted via telephone or via a visit 14 (+ 2) days post-randomization to assess any new or ongoing AEs and to collect information on any medications administered since the last visit. Ongoing follow-up may be required after trial closure for health status before the analysis of all trial results is completed.</p>	<p><b>3.7.1.2.3 Day 2a (optional)</b></p> <p>The following procedures will be performed on Day 2a for all subjects who are not responsive to tolvaptan treatment at the end of Day 2.</p> <p><u>Predose</u></p> <p>1) Vital signs will be assessed at 24 hours post-previous dose. Blood pressure, heart rate, respiratory rate, and temperature will be assessed after the subject has been supine for <math>\geq 3</math> minutes. Vital signs should be performed prior to the blood draws.</p> <p>2) A blood sample for STAT serum sodium testing should be taken at 24 (<math>\pm 4</math>) hours post-previous dose and the results known prior to subsequent tolvaptan dosing.</p> <p>3) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</p> <p>4) A directed physical examination will be performed.</p> <p>5) Body weight will be measured.</p> <p><u>Dosing</u></p> <p>6) Tolvaptan will be administered. If the subject's serum sodium concentration is <math>&lt; 135</math> mEq/L (mmol/L) and a <math>\leq 4</math> mEq/L (mmol/L) increase, tolvaptan dose should be adjusted per the titration guidelines (Section 3.2.4) for the assigned weight group.</p> <p><u>Postdose</u></p> <p>7) Clinical status assessments will be performed per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.</p> <p>8) A blood sample will be collected for serum sodium testing at 12 hours post-dose.</p> <p>9) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</p> <p>10) At the end of the Day 2a visit subjects will be assessed for</p>

Location:	Old Text:	New Text:
		<p>response to tolvaptan treatment. Subjects who are:</p> <ul style="list-style-type: none"> <li>a) Responders (serum sodium level increase of <math>\geq 4</math> mEq/L [mmol/L]) will proceed to Treatment Phase B (see Section 3.7.1.3) for randomization.</li> <li>b) Nonresponders (serum sodium level increase of <math>&lt; 4</math> mEq/L [mmol/L]) will continue to Treatment Phase B where they either continue on tolvaptan therapy for 2 additional days or are withdrawn from tolvaptan to be treated per the investigator's preferred standard of care.</li> </ul> <p><u>Throughout the visit</u></p> <ul style="list-style-type: none"> <li>11) Concomitant medications will be recorded.</li> <li>12) Adverse events will be assessed.</li> </ul> <p><b>3.7.1.3.1 Day 3</b>  The following procedures will be performed on Day 3. Some assessments are required for all subjects while other assessments only apply to certain subsets of subjects as indicated.</p> <p><b>For all subjects (at trough)</b></p> <ul style="list-style-type: none"> <li>1) At trough (24 hours post-previous dose) the following assessments will be performed: <ul style="list-style-type: none"> <li>a) Vital signs will be assessed. Blood pressure, heart rate, respiratory rate, and temperature will be assessed after the subject has been supine for <math>\geq 3</math> minutes. Vital signs should be performed prior to blood draws.</li> </ul> </li> <li>2) Blood samples will be collected concurrently at 24 (<math>\pm 4</math>) hours for: <ul style="list-style-type: none"> <li>a) STAT serum sodium testing and the results known prior to subsequent tolvaptan dosing.</li> <li>b) PK analysis of tolvaptan</li> </ul> </li> <li>3) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</li> </ul> <p><b>For all subjects classified as Responders at the end of Treatment Phase A</b></p>

Location:	Old Text:	New Text:
		<p>4) Randomize the subject to the Early or Late Withdrawal group using the trial's interactive response system.</p> <p><b><u>For subjects receiving tolvaptan (Late Withdrawal group and non-responders with continuing treatment)</u></b></p> <p>5) Body weight will be measured.</p> <p>4) Tolvaptan will be administered.</p> <p><b><u>For subjects not receiving tolvaptan treatment (Early Withdrawal group and non-responders treated with standard of care)</u></b></p> <p>6) Early Withdrawal subjects will be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels.</p> <p>3) Nonresponders discontinuing tolvaptan will be treated per the investigator's preferred standard of care.</p> <p><b><u>For all subjects at later time points during the visit</u></b></p> <p>4) A directed physical examination will be performed.</p> <p>5) A neurological examination will be performed.</p> <p>6) A blood sample will be collected for serum sodium testing at 12 hours post the nominal dosing time (regardless of treatment).</p> <p>7) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</p> <p>8) Clinical status assessments will be performed per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.</p> <p><b><u>For all subjects throughout the visit</u></b></p> <p>9) Concomitant medications will be recorded.</p> <p>10) Adverse events will be assessed.</p>

Location:	Old Text:	New Text:
		<p><b>3.7.1.3.2 Day 4</b>  The following procedures will be performed on Day 4. Some assessments are required for all subjects while other assessments only apply to certain subsets of subjects as indicated.</p> <p><b><u>For subjects receiving tolvaptan (Late Withdrawal group and non-responders with continuing treatment)</u></b></p> <p><b><u>At trough</u></b></p> <ol style="list-style-type: none"> <li>1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq 3</math> minutes. Vital signs should be performed prior to blood draws.</li> <li>2) A blood sample for STAT serum sodium level testing should be taken and the results known prior to subsequent treatment.</li> <li>3) Blood samples for PK analysis of tolvaptan will be collected.</li> <li>4) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</li> </ol> <p><b><u>At later time points during the visit</u></b></p> <ol style="list-style-type: none"> <li>5) Body weight will be measured.</li> <li>6) Tolvaptan will be administered.</li> </ol> <p><b><u>For subjects not receiving tolvaptan treatment (Early Withdrawal group and nonresponders treated with standard of care)</u></b></p> <p><b><u>For all subjects at 48 hours post last dose</u></b></p> <ol style="list-style-type: none"> <li>1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq 3</math> minutes. Vital signs should be performed prior to blood draws.</li> <li>2) A blood sample for serum sodium level testing should be taken.</li> <li>3) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</li> </ol> <p><b><u>At later time points during the visit</u></b></p> <ol style="list-style-type: none"> <li>4) Early Withdrawal subjects will be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels.</li> <li>5) Nonresponders discontinuing tolvaptan will continue to be</li> </ol>

Location:	Old Text:	New Text:
		<p>treated per the investigator's preferred standard of care.</p> <p><b><u>For all subjects at later time points during the visit</u></b></p> <ul style="list-style-type: none"> <li>7) A directed physical examination will be performed.</li> <li>8) A neurological examination will be performed.</li> <li>9) A blood sample will be collected for serum sodium testing at 12 hours post the nominal dosing time (regardless of treatment).</li> <li>10) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</li> <li>11) A QoL assessment will be conducted.</li> <li>12) Clinical status assessments will be performed per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.</li> </ul> <p><b><u>For all subjects throughout the visit</u></b></p> <ul style="list-style-type: none"> <li>13) Concomitant medications will be recorded.</li> <li>14) Adverse events will be assessed.</li> </ul> <p><b>3.7.1.3.3 Day 5</b>  The following procedures will be performed on Day 5.</p> <p><b><u>For subjects receiving tolvaptan (Late Withdrawal group and non-responders with continuing tolvaptan treatment)</u></b></p> <p><u>At trough</u></p> <ul style="list-style-type: none"> <li>1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq 3</math> minutes. Vital signs should be performed prior to blood draws.</li> <li>2) A blood sample for STAT serum sodium level testing should be taken and the results known prior to subsequent treatment.</li> </ul>

Location:	Old Text:	New Text:
		<p>3) A blood sample for PK analysis of tolvaptan will be collected.</p> <p>4) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</p> <p>5) Body weight will be measured.</p> <p><u>Throughout the visit</u></p> <p>6) Concomitant medications will be recorded.</p> <p>7) Adverse events will be assessed.</p> <p><b><u>For subjects not receiving tolvaptan treatment (Early Withdrawal group and nonresponders treated with standard of care)</u></b></p> <p>13) Proceed to Follow-up Phase C as for these subjects the 72h post-last dose time point (Section 3.7.1.4.1) falls on the morning of Day 5.</p> <p><b>3.7.1.4 Follow-up Phase C</b></p> <p><b>3.7.1.4.1 72 Hours Post-last Dose or ET</b></p> <p>The following procedures will be performed for all subjects at 72 (<math>\pm</math> 4) hours post-last dose or at early termination (ET).</p> <ol style="list-style-type: none"> <li>1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq</math> 3 minutes. Vital signs should be performed prior to blood draws.</li> <li>2) Hematology, coagulation, and serum chemistry laboratory samples will be collected.</li> <li>3) For Early Termination only: Blood sample for PK analysis of tolvaptan will be collected at 24 hours post-last dose for all subjects on tolvaptan. The sample is to be taken concurrently with the serum sodium sample (part of the serum chemistry panel).</li> <li>4) A neurocognitive assessment will be performed within 1 hour of the serum chemistry sample.</li> <li>5) A directed physical examination will be performed.</li> <li>6) A neurological examination will be performed.</li> <li>7) Body weight will be measured.</li> <li>8) A urinalysis laboratory sample will be collected.</li> <li>9) For Early Termination: Subjects will be monitored and treated as</li> </ol>

Location:	Old Text:	New Text:
		<p>clinically warranted per the investigator's preferred standard of care for up to 3 additional days after the last dose of tolvaptan.</p> <p>10) Concomitant medications will be recorded.</p> <p>11) Adverse events will be assessed.</p> <p><b>3.7.1.4.2 7 Days Post-last Dose</b></p> <p>Subjects will be assessed for maintenance of normal or target serum sodium concentration at 7 (<math>\pm</math> 1) days post-last dose. All clinical labs will be performed locally. If the subject was discharged, he/she should return to the clinic for this visit.</p> <ol style="list-style-type: none"> <li>1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq</math> 3 minutes. Vital signs should be performed prior to blood draws.</li> <li>2) A blood sample for serum sodium testing will be collected.</li> <li>3) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</li> <li>4) A QoL assessment will be conducted.</li> <li>5) A directed physical examination will be performed.</li> <li>6) A neurological examination will be performed.</li> <li>7) Clinical status assessments will be performed per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.</li> <li>8) Body weight will be measured.</li> <li>9) Concomitant medications will be recorded.</li> <li>10) Adverse events will be assessed.</li> </ol> <p><b>3.7.1.4.3 14 Days Post-last Dose</b></p> <p>Subjects (or their parents or legal guardians) will be contacted via telephone or will be asked to come back to the clinic for a visit at 14 (+ 2) days post-last dose to assess any new or ongoing AEs and to collect information on any medications</p>

Location:	Old Text:	New Text:
<b>3.7.2.1 Serum Sodium Concentration</b>	<p>Monitoring frequency of serum sodium is at the discretion of the clinical investigator; however, the trial requires the minimum sample collection for all subjects noted in Section 3.7.1.</p> <p>Within 48 hours of initial tolvaptan administration, 2 blood samples will be collected at least 12 hours apart for assessment of baseline serum sodium to determine subject eligibility. A third (STAT) serum sodium sample should be drawn within 3 (<math>\pm</math> 1) hours prior to dosing; the results must be verified to be &lt; 130 mmol/L prior to the first dose. A STAT serum sodium sample should be drawn and recorded in the CRF at the time of every hyponatremia symptoms assessment (Section 3.7.1). During Phase A, serum sodium will be assessed at 12 hours post-first dose and 24 (<math>\pm</math> 4) hours post-previous dose. Serum sodium must also be assessed at 12, 24, 36, 48, and 72 (<math>\pm</math> 4) hours and 7 (<math>\pm</math> 1) days post-randomization.</p>	<p>administered since the last visit. Ongoing follow-up may be required after a subject's trial completion for health status before the analysis of all trial results is completed.</p> <p>Monitoring frequency of serum sodium is at the discretion of the clinical investigator; however, the minimum sample collection required for all subjects is described in Section 3.7.1.</p> <p>In order to qualify for this trial, subjects must have documentation of chronic dilutional hyponatremia (serum sodium &lt; 130 mEq/L [mmol/L]) that is present for <math>\geq</math> 48 hours. Specifically, each subject must have 2 blood samples collected at least 12 hours apart over a minimum of 48 hours for assessment of baseline serum sodium level to determine subject eligibility. These can be either part of the recent medical history concerning the current hospital stay or prospectively collected as part of this trial.</p> <p>On Day 1, a third (STAT) serum sodium sample should be drawn within 2-4 hours prior to dosing; the results must be verified to be &lt; 130 mmol/L prior to the first dose. Serum sodium assessments should be performed at 8 hours post-first dose and at trough 24 hours post-first dose (this assessment will fall on Day 2 predose). On Day 2 (or 2a), Day 3, and Day 4 (through the following morning on Day 5):</p> <ul style="list-style-type: none"> <li>• For all subjects receiving tolvaptan (Late Withdrawal and Nonresponders continuing on tolvaptan) serum sodium assessments will be performed at trough and 12 hours post-dose each day during Treatment Phase A and Treatment Phase B.</li> <li>• For all subjects not receiving tolvaptan (Early Withdrawal and Nonresponders on standard of care) serum sodium assessments will be performed every 12 hours throughout Treatment Phase A and Treatment Phase B.</li> </ul> <p>For all subjects final serum sodium assessments will be taken at 24 (<math>\pm</math> 4) and 72 (<math>\pm</math> 4) hours post-last dose as well as at 7 days post-last dose.</p>
		<b>3.7.2.3 Quality of Life Assessments</b> Two patient-reported outcomes instruments (acute versions with 7 day recall period)

Location:	Old Text:	New Text:
		<p>will be used to assess subject quality of life: PedsQL Generic Core Scale and PedsQL Multidimensional Fatigue Scale. Both instruments are appropriate for <math>\geq 2</math> years of age, however availability may be limited for certain ages and languages. The age groups covered by these assessments are Toddler (2–4 years), Young child (5–7 years), Child (8–12 years), and Adolescent (13–18 years). Depending on the subject's age, the questionnaire may be completed by either the subject or the parent/caregiver, as appropriate.</p> <p>The PedsQL Generic Core Scale consists of 23 items encompassing physical, emotional, social, and school domains. The PedsQL Multidimensional Fatigue Scale consists of 18 items in 3 subscales: general fatigue, sleep/rest fatigue, and cognitive fatigue. The instrument focuses on the domains of processing speed, attention/vigilance, visual and working memory.</p> <p>The assessment time points are at screening, Day 4 and 7 days post-last dose.</p> <p><b>3.7.2.4 Neurocognitive Assessments</b>  An age-appropriate (4–18 years of age) neurocognitive assessment will be performed using a computerized test battery provided by CogState Ltd. The instruments used for this assessment include 4 tests: the Detection Test, Identification Test, One Card Learning Test, One Back Test. The tests will focus on the domains of processing speed, attention/vigilance, visual memory and working memory.</p> <p>For subjects 6 to 18 years of age all tests will be administered. For subjects 4 to 5 years of age, the Detection Test and the Identification Test will be administered. Availability of the assessment may be limited for certain subject ages and languages.</p> <p>The assessment time points correlate with serum sodium assessments and should occur within an hour of serum sodium blood draws.</p>
<b>3.7.3.1.1 Blood Collection Times</b>	<ul style="list-style-type: none"> <li>Tolvaptan plasma concentrations will be measured. On Day 1, blood samples</li> </ul>	<p>Blood samples will be taken so that tolvaptan and metabolite concentrations can be determined. Samples will be taken</p>

Location:	Old Text:	New Text:
	<p>(1 mL) for tolvaptan concentrations will be taken at 1, 2, 4, 12, and 24 hours (<math>\pm</math> 5 minutes for each draw up to 2 hours postdose and <math>\pm</math> 30 minutes for later time points) post-first dose, at 24 and 48 hours post-randomization (for subjects on tolvaptan in Phase B, including subjects who are deemed nonresponders and continue on tolvaptan), or at ET, if ET is before the last scheduled PK assessment. Each subject contributing samples to the PK analysis will be required to submit a total 5 mL of blood in 24 hours and 2 additional samples after randomization. All samples will be collected from each subject according to local guidelines and best practices for pediatric care.</p>	<p>on Day 1 at 2 hours (<math>\pm</math> 5 minutes) and 8 hours (concurrent with 8 h serum sodium sample) post-first dose. On Days 2, 3, 4 and 5 samples will be taken at trough (24 hours post previous dose but prior to the subsequent dose), concurrent with serum sodium samples, for subjects dosed with tolvaptan on Days 1, 2, 3, and/or 4, respectively, regardless of status as responder/non-responder. An early termination (ET) sample will be taken if ET occurs prior to the last planned PK sample. No ET sample is required if ET occurs at the same visit where a PK sample has already been obtained.</p> <p>For each PK blood sample collected volumes are not expected to exceed 1.2 mL. Total volume per sample may be lower depending on finalization of blood collection supplies.</p> <p>Serum sodium assessments and other clinically necessary blood samples take priority, therefore, due to restrictions in allowable total daily blood volumes based on local guidelines and subject age, it may not be possible to take more than one PK sample per day. If so, the PK sampling should be changed to:</p> <ul style="list-style-type: none"> <li>• Day 1: 2 hours post dose (<math>\pm</math> 5 minutes)</li> <li>• Day 2: 8 (<math>\pm</math> 2) hours post dose (may be concurrent with serum sodium or other blood sampling)</li> <li>• Day 3 at trough, ie, pre-dose/24 hours post prior dose (concurrent with serum sodium sample)</li> </ul> <p>For each subject all samples will be collected according to local guidelines and best practices for pediatric care. If a sample is missing due to limitations in allowable blood volumes based on local regulations or local practice this will not count as a protocol deviation.</p>
3.7.3.3	<p><b>3.7.3.3.1 Fluid Balance (Intake/Output)</b>            Fluid intake (both oral and IV) and urine volume will be measured at the times presented in the schedule of assessments (Section 3.7.1). The fluid content of foods with significant water content (eg, soup) should be added to the total fluid intake. Fluid balance will be monitored per institutional guidelines.</p> <p><b>3.7.3.3.2 Laboratory Tests</b></p>	<p><b>3.7.3.2.1 Fluid Intake</b>            Fluid intake (both oral and IV) will be measured at the times presented in the schedule of assessments (Section 3.7.1). The fluid content of foods with significant water content (eg, soup) should be added to the total fluid intake. Fluid intake will be monitored per institutional guidelines.</p> <p><b>3.7.3.2.2 Urine Volume</b></p>

Location:	Old Text:	New Text:
	<p>Urine chemistry will be determined in urine samples that will be collected at the intervals presented in the schedule of assessments, Section 3.7.1. The list of urine chemistry tests to be collected is presented in Table 3.7.4.2-1. All urine voids within a collection interval will be kept refrigerated and at the end of the collection interval, the samples pooled together, the urine volume determined, and an aliquot taken according to instructions from the clinical chemistry laboratory.</p>	<p>Urine volume will be determined in urine samples that will be collected at the intervals presented in the schedule of assessments, Section 3.7.1. All urine voids within a collection interval should be kept refrigerated and pooled according to the size of available collection containers. At the end of the collection interval all samples should be pooled and the urine volume determined.</p> <p><b>3.7.3.2.3 Urine Chemistry</b> Urine chemistry will be determined from pooled urine samples collected for the intervals presented in the schedule of assessments, Section 3.7.1. An aliquot will be taken for each collection interval according to the procedures of the local clinical chemistry laboratory. The list of urine chemistry tests to be conducted is presented in Table 3.7.4.2-1.</p>
<p><b>3.7.4 Safety Assessments</b></p> <p><b>3.7.4.1 Adverse Events</b></p>	<ul style="list-style-type: none"> <li>In particular, the following AEs must be actively monitored: absolute serum sodium level <math>\geq 145</math> mmol/L, overly rapid rise in serum sodium defined as an increase in serum sodium of <math>&gt; 8</math> mmol/L over a 10-hour period, <math>\geq 12</math> mmol/L over a 24-hour period, or a rate of increase in serum sodium that the investigator deems too rapid, neurological symptoms, or other signs or symptoms suggestive of osmotic demyelination (see Section 5.3.1 for more detail).</li> </ul>	<p>In addition, active monitoring is required for:</p> <ul style="list-style-type: none"> <li>Absolute serum sodium level <math>\geq 145</math> mEq/L (mmol/L) or an overly rapid rise in serum sodium level (an increase in serum sodium of <math>&gt; 8</math> mEq/L [mmol/L] over a 10-hour period, <math>\geq 12</math> mEq/L [mmol/L] over a 24-hour period, or a rate of increase in serum sodium concentration that the investigator deems too rapid), neurological symptoms, or other signs or symptoms suggestive of osmotic demyelination (see Section 5.3.1 for more details).</li> <li>Elevations in AST or ALT that are <math>\geq 2 \times</math> ULN or levels that increase <math>\geq 2</math> times their previously observed level. If this occurs, a total bilirubin level should also be evaluated. See Section 3.7.4 for more information and Section 5.4.1 for detailed instructions on how this type of event should be captured.</li> <li>Worsening symptoms of hyponatremia</li> <li>Hypovolemia or hypotension requiring intervention</li> </ul>

Location:	Old Text:	New Text:
		<p><b>3.7.4.2.1 Serum Osmolality</b>            Serum osmolality will be calculated to help guide dosing. Local site personnel will determine serum osmolality using one of the following equations:</p> <ul style="list-style-type: none"> <li>a) Where Na, glucose, and BUN are measured in mg/dL:  <math display="block">\text{Serum Osmolality (mOsm/kg)} = 2 \text{ Na} + \text{BUN} / 2.8 + (\text{glucose} / 18)</math></li> <li>b) Where Na, glucose, and urea are measured in mmol/L:  <math display="block">\text{Serum Osmolality (mOsm/kg)} = 2 \text{ Na} + \text{glucose} + \text{urea}</math></li> </ul>
<b>3.7.4.1.1 Clinical Laboratory Tests</b>	<p>Table 3.7.4.2-1 presents the protocol-required clinical laboratory results (serum chemistry, hematology, coagulation, urinalysis, and urine chemistry) that will be reported as part of the trial results. Serum cortisol and TSH will be measured at the Screening/Baseline Visit using the remaining blood sample obtained for serum chemistry....assessments (Table 3.7-1).</p>	<p>Table 3.7.4.2-1 presents required clinical laboratory assessments (serum chemistry, hematology, coagulation, urinalysis, and urine chemistry). All clinical laboratory tests will be performed by local laboratories. Serum cortisol and TSH will be measured during screening using the remaining blood sample obtained for serum chemistry....assessments (Section 3.7.1). Uric acid will be measured during screening for calculation of FENa and FE urate.</p> <p>WBC = white blood cell; RBC = red blood cell.</p> <p>In case of limited blood or urine volume availability the bolded assessments take priority. Serum Sodium and liver function tests are essential to the conduct of the trial.</p>
<b>3.7.4.2.3 Monitoring of Liver Transaminases</b>	<p>...Based on previous research in the adult polycystic kidney disease population, the expected onset of the elevation is between 3 and 14 months of chronic treatment with tolvaptan.</p> <p>For a subject that experiences an elevation in AST or ALT that is <math>\geq 3 \times \text{ULN}</math> or whose levels increase <math>\geq 3</math> times their previous observed value, a total bilirubin level should also be evaluated. If the total bilirubin is <math>\geq 2 \times \text{ULN}</math> or <math>\geq 2</math> times their previous observed value, an immediately reportable event (IRE) form with all values listed should be completed and also reported as an AE on the CRFs. See Section 5.4.1 for detailed instructions on how this type of event should be captured.</p>	<p>...Based on previous research in the adult polycystic kidney disease population, the expected onset of the elevation, if it occurs, is between 3 and 14 months of chronic treatment with tolvaptan.</p> <p>For a subject who experiences an elevation in AST or ALT that is <math>\geq 2 \times \text{ULN}</math> or whose levels increase <math>\geq 2</math> times their previous observed value, a total bilirubin level should also be evaluated. These elevated values should be confirmed by retesting. If total bilirubin is <math>\geq 2 \times \text{ULN}</math> or <math>\geq 2</math> times their previous observed value, an immediately reportable event (IRE) form with all values listed should be completed and also reported as an AE on the CRFs. See Section 5.4.1 for detailed instructions on how this type of event should be captured.</p>
<b>3.7.4.3 Physical Examination</b>	<p>All physical examination assessments should include assessments of all major</p>	<p>All physical examination assessments should include assessments of all major</p>

Location:	Old Text:	New Text:
	<p>body systems, including but not limited to, ears, nose, and throat, the thorax area, abdomen, urogenital, extremities, and skin and mucosae. Neurological examinations will be performed in an age-appropriate manner per Section 3.7.4.4.</p> <p>Body weight will be measured predose each day,...</p>	<p>body systems, including but not limited to, ears, nose, and throat, the thorax area, abdomen, urogenital, extremities, and skin and mucosae. Neurological examinations will be performed in an age-appropriate manner per Section 3.7.4.3.1. ...</p> <p>Body weight will be measured predose each day throughout Treatment Phase A, Treatment Phase B and at each clinic visit in Follow-up Phase C...</p>
<b>3.7.4.4 Tanner Staging</b>		<p>Tanner Staging will be completed together with the physical examination by the same trial affiliated clinician in the most inconspicuous manner for the subject as possible. Tanner Staging assessment consists of 2 domains (pubic hair and breast development) for girls and 3 domains (pubic hair, penis development, and testes development) for boys. The investigator will arrive at a single score summarizing the domains (not individual domain scores) when evaluating the subject.</p>
<b>3.7.4.5 Vital Sign Assessments</b>	<p>Vital sign data (including supine blood pressure, heart rate, respiratory rate, and temperature) will be performed and documented according to Section 3.7.1 of this protocol. Supine vital signs will be taken when the subject has been lying down (bed positioned &lt; 45 degree angle) for at least 3 minutes. All post-baseline assessments for vital signs should be performed around the time of the formal hyponatremia assessment during tolvaptan dosing and anytime during the Follow-up Visits consistent with the timing of other trial assessments. All vital sign assessments should be performed prior to the blood draw at the nominal time point.</p>	<p>Vital signs (including supine blood pressure, heart rate, respiratory rate, and temperature) will be assessed at time points according to Section 3.7.1 of this protocol. Supine vital signs will be taken when the subject has been lying down (bed positioned &lt; 45 degree angle) for at least 3 minutes. All assessments for vital signs should be performed around the time of the formal hyponatremia assessment (sodium blood draw) during Screening, Treatment Phase A and Treatment Phase B and anytime during the Follow-up Period consistent with the timing of other trial assessments. All vital sign assessments should be performed prior to the blood draw at the nominal time point.</p>
<b>3.7.4.6 Fluid Restriction</b>	<p>In subjects with chronic hyponatremia, fluid restriction coadministered with initiation of treatment with a vaptan has the potential to accentuate the rate of sodium correction and to cause overly rapid correction or over correction of hyponatremia. Therefore, during treatment, subjects must have access to water and maintain fluid intake levels per institutional guidelines. Fluid restriction during the first 48 hours after discontinuation of tolvaptan will be considered rescue therapy.</p>	
<b>3.9 Screen</b>	A screen failure subject is one from whom	A screen failure subject is one from whom

Location:	Old Text:	New Text:
<b>Failures</b>	informed consent/assent (if applicable) is obtained and is documented in writing (ie, the subject's parent or legal guardian signs an ICF), but who is not enrolled into the trial....	informed consent/assent (if applicable) has been obtained and is documented in writing (ie, the subject's parent or legal guardian signs an ICF), but who is not enrolled into the trial. If a subject's serum sodium level during the Screening period is $\geq 130$ mEq/L [mmol/L], that subject will be determined a screen failure....
<b>3.10 Definition of Completed Subjects</b>	<p>The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete the final Follow-up Visit at 14 days post-randomization will be defined as trial completers.</p>	<p>The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the tolvaptan.</p> <p>For purposes of this trial, subjects who are randomized responders and who complete required trial assessments (including their assigned trial treatment) through the end of the trial will be defined as responder trial completers.</p> <p>For purposes of this trial, subjects who are nonresponders (not randomized) but who complete required trial assessments through the end of the trial will be defined as nonresponder trial completers.</p> <p>Subjects who discontinue tolvaptan prior to the end of Treatment Phase B, but who continue in the trial and complete some or all of their required assessments to the end of the trial, will be considered "early" end of treatment (EEOT) completers.</p>
<b>4.2 Other Restrictions</b>	<p>...The use of saline in this population should be closely monitored. The use of hypertonic saline (3%) within 8 hours of the initial screening laboratory collection is prohibited.</p> <p>Please see Section 3.4.3 for the list of prohibited medications. The use of normal saline (0.9%) is allowed during the Screening Period until the beginning of Phase A; normal saline use can resume in Phase C. Subjects should no longer be on maintenance fluids containing normal saline during treatment with tolvaptan.</p>	<p>...Other treatment for the purpose of increasing serum sodium, eg with urea, lithium, demeclocycline, conivaptan or tolvaptan, concurrent with dosing of trial medication or within 4 days of qualifying serum sodium assessments at screening is prohibited.</p> <p>The use of saline in this population should be closely monitored. The use of hypertonic saline (3%), including normal saline challenge) within 8 hours of the qualifying screening serum sodium laboratory assessment is prohibited.</p> <p>The use of normal saline (0.9%) is allowed during screening until the beginning of Treatment Phase A; normal saline use can resume in Phase C. Subjects should no longer be on maintenance fluids containing normal saline during treatment with</p>

Location:	Old Text:	New Text:
<b>5.1 Definitions</b>	<p><b>IMP Causality:</b> Assessment of causal relationship of an AE to the use of the IMP: <b>Related:</b> There is a reasonable possibility of a causal relationship.</p> <p><b>Possibly related:</b> There is a reasonable causal relationship between the IMP and the AE. Dechallenge is lacking or unclear.</p> <p><b>Unlikely related:</b> There is a temporal relationship to IMP administration but there is not a reasonable causal relationship between the IMP and the AE.</p> <p><b>Not Related:</b> There is no temporal or reasonable relationship to the IMP administration.</p>	<p><b>IMP Causality:</b> Assessment of causal relationship of an AE to the use of the IMP: <b>Related:</b> There is a reasonable probability or possibility of a temporal and causal relationship between the study drug and the AE.</p> <p><b>Not Related:</b> There is no temporal or causal relationship to the study drug administration.</p>
<b>5.4 Potential Hy's Law Cases</b>	<p>For a subject who experiences an elevation in AST or ALT that is <math>\geq 3 \times</math> ULN or whose levels increase <math>\geq 3</math> times their initial baseline value, a total bilirubin level should also be evaluated. If the total bilirubin is <math>\geq 2 \times</math> ULN or <math>\geq 2</math> times their baseline value, an IRE form should be completed with all values listed and also should be reported as an AE on the CRFs.</p>	<p>The definition of Hy's Law criteria is provided in Section 5.1. To err on the side of caution Otsuka decided to set a lower threshold for identification of potential Hy's Law cases. For a subject who experiences an elevation in AST or ALT that is <math>\geq 2 \times</math> ULN or whose levels increase <math>\geq 2</math> times their initial baseline value, a total bilirubin level should also be evaluated. Elevated values should be confirmed via retest. If the total bilirubin is <math>\geq 2 \times</math> ULN or <math>\geq 2</math> times their baseline value, an IRE form should be completed with all values listed and also should be reported as an AE on the CRFs.</p>
<b>5.4.1 Liver Transaminase Elevations</b>	<p>Management of abnormal liver function test results should be based on the investigator's clinical judgment. A liver function test result that is <math>3 \times</math> ULN is generally accepted as a medically significant occurrence across various medical cultures.</p> <p>For a subject that experiences an elevation in AST or ALT that is <math>\geq 3 \times</math> ULN or whose levels increase <math>\geq 3</math> times their initial baseline value in subjects with an elevated baseline value, a total bilirubin level should also be evaluated....</p> <p>The following guideline for repeat testing may be used by investigators as a reference for any subject with an ALT or AST <math>\geq 3 \times</math> ULN:</p> <p>2)Inquiries should be made about symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and/or rash).</p>	<p>Management of abnormal liver function test results should be based on the investigator's clinical judgment. A liver function test result that is <math>2 \times</math> ULN is generally accepted as a medically significant occurrence across various medical disciplines.</p> <p>For a subject that experiences an elevation in AST or ALT that is <math>\geq 2 \times</math> ULN or whose levels increase <math>\geq 2</math> times their initial baseline value in subjects with an elevated baseline value, a total bilirubin level should also be evaluated....</p> <p>The following guideline for repeat testing may be used by investigators as a reference for any subject with an ALT or AST <math>\geq 2 \times</math> ULN:</p> <p>2) Inquiries should be made about symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and/or rash) and signs like jaundice,</p>

Location:	Old Text:	New Text:
<b>5.4.1.1 Criteria for Discontinuation Due to Liver Transaminase Elevations</b>	A subject must be discontinued from the trial on confirmation of any of the following criteria:	yellowish discoloration of sclera, etc
	1) ALT or AST $\geq 3 \times$ ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $> 5\%$ )	A subject must be discontinued from the trial on confirmation of any of the following criteria: 1) ALT or AST $\geq 3 \times$ ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $> 5\%$ ) and signs of jaundice
<b>5.7 Follow-up of Adverse Events</b>	For this trial, information on AEs will be followed for up to 14 days post-randomization.	For this trial, information on AEs will be followed for up to 14 days post-last dose for all subjects or until resolution, whichever is longer.
<b>5.7.2 Follow-up of Post Trial Serious Adverse Events</b>	This trial requires that subjects be actively monitored for SAEs up to 14 days post-randomization.	This trial requires that subjects be actively monitored for SAEs up to 14 days post-last dose or until resolution of the SAE, whichever is longer.
<b>6.1 Pharmacokinetic Analysis</b>	Tolvaptan plasma concentrations will be summarized using descriptive statistics (n, median, mean, standard deviation [SD], percent coefficient of variation [CV], minimum, and maximum) by dose group and time point.	Tolvaptan and metabolite plasma concentrations will be summarized using descriptive statistics (n, median, mean, standard deviation [SD], percent coefficient of variation [CV], minimum, and maximum) by dose group and time point.
<b>6.2 Pharmacodynamic Analysis</b>	<p>... Fluid intake and the calculated value of fluid balance will be summarized for each 6-hour period on Days 1 and 2 (Phase A) using descriptive statistics....</p> <p>Urine osmolality and urine creatinine, potassium, uric acid, and sodium concentrations will be summarized by collection interval and for zero to 24 hours on Days 1 and 2 (Phase A) using descriptive statistics....</p>	<p>... Fluid intake and the calculated value of fluid balance will be summarized for each 6-hour period and for the 24-hour daily interval on Days 1 and 2 in Treatment Phase A using descriptive statistics...</p> <p>Urine osmolality and urine creatinine, potassium, and sodium concentrations will be summarized by collection interval and for zero to 24 hours on Days 1 and 2 in Treatment Phase A using descriptive statistics...</p> <p>Correlations between tolvaptan AUC values and urine output on Day 1 may be explored graphically</p>
<b>7.1.1 Sample Size for Efficacy</b>	A total of 70 randomized subjects will provide 90% power to detect a treatment difference of 4 mmol/L in change in serum sodium from randomization (at the end of Day 2/3 [Phase A]) to the end of Day 4/5 (2 days after randomization [Phase B]) using a 2-sided alpha of 0.05. An SD of 5 in change of serum sodium was used for the sample size calculation. After the end of treatment at Day 2/3, subjects will be randomized at a ratio of 1:1 to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early	A total of 70 randomized subjects will provide 90% power to detect a treatment difference of 4 mEq/L (mmol/L) in change in serum sodium from Day 2 (or 2a) at the end of Treatment Phase A to the end of Treatment Phase B using a 2-sided alpha of 0.05. An SD of 5 in change of serum sodium was used for the sample size calculation. After the end of Treatment Phase A at Day 2 (or 2a), subjects will be randomized at a ratio of 1:1 to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early

<b>Location:</b>	<b>Old Text:</b>	<b>New Text:</b>
	Withdrawal). Sample size re-estimation will be conducted when 90% of the subjects finish (complete or discontinue) the trial.	Withdrawal). Sample size re-estimation will be conducted when 90% of the subjects finish (complete or discontinue) the trial.
<b>7.4.2.2 Safety</b>	<p>Other secondary endpoints include:</p> <ul style="list-style-type: none"> <li>Percentage of subjects with overly rapid increase in serum sodium (<math>\geq</math> 12mmol/L in 24 hours after the first dose).</li> <li>Percentage of subjects requiring rescue medication during Phase A and Phase B of the trial.</li> <li>Change in serum sodium from 24 hours post-last dose to 14 days post-randomization.</li> <li>Vital signs, blood pressure, clinical laboratory tests, and body weight.</li> </ul>	<p>Other secondary endpoints include:</p> <ul style="list-style-type: none"> <li>Percentage of subjects with overly rapid increase in serum sodium level ( [REDACTED] ).</li> <li>Change in serum sodium level from 24 hours post-last dose to 7 days post-last dose.</li> <li>Percentage of subjects requiring rescue therapy (other than fluid restriction) during Treatment Phase A and Treatment Phase B.</li> <li>Percentage of subjects requiring fluid restriction during Treatment Phase A and Treatment Phase B.</li> <li>Other secondary safety outcomes to be assessed are presented in Section 3.5.3.1 (Vital signs, blood pressure, clinical laboratory tests, body weight, and neurological examinations)</li> </ul>
<b>7.4.3 Exploratory Outcome Analysis</b>	Neurological examination data will be presented in the data listings.	<p>The change in serum sodium concentration in nonresponders continuing on tolvaptan therapy by change from baseline at the end of Treatment Phase B compared to the end of Treatment Phase A will be analyzed using a paired Student's t-test.</p> <p>The procedure for the analysis of data for the neurocognitive and QoL assessments will be provided in the SAP.</p> <p>The analysis for the following exploratory PD endpoints is described in Section 6.2:</p> <ul style="list-style-type: none"> <li>In all subjects, 24-hour excretion of sodium, creatinine, and osmolality on Days 1 and 2</li> <li>24-hour sodium clearance on Day 1</li> </ul>
<b>14 References</b>		<p>26 U.S. Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation [report on the internet]. 2009 Jul [cited 15 Feb 2014]; Available from: <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf</a>.</p> <p>27 U.S. Food and Drug Administration. [available on the internet, last updated 22Jan2014; cited 14Feb2014]. Available from: <a href="http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm0">http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm0</a></p>

Location:	Old Text:		New Text:	
			71471.htm	
<b>Appendix 1: Names of Sponsor Personnel: IRE</b>	<b>Country</b>	<b>Safety Fax Numbers</b>	<b>Country</b>	<b>Safety Fax Numbers</b>
United States		(primary) or (alternative)	Australia	
Argentina			Belgium	
Australia			Canada	(primary) or (alternative)
Belgium			Czech Republic	
Canada		(primary) or (alternative)	Germany	
Colombia			Italy	
Czech Republic			Netherlands	
Finland			Peru	
France			Poland	
Georgia	No toll free number available; please dial [REDACTED] (primary) or (alternative)		Romania	
Germany			Spain	
Hong Kong			Turkey	No toll free number available; please dial [REDACTED] (primary) or (alternative)
Israel			United Kingdom	
Italy			United States	(primary) or (alternative)
Korea				
Latvia				
Malaysia				
Mexico				
Netherlands				
Philippines				
Peru				
Poland				
Romania				
Russia				
Serbia				
Singapore				
South Africa				
Spain				
Taiwan				
Thailand				
Turkey	No toll free number available; please dial [REDACTED] (primary) or (alternative)			

Location:	Old Text:	New Text:
	Ukraine United Kingdom	
Medical Monitor:		3201 Beechleaf Court, Suite 600 Raleigh, North Carolina 27604 USA Phone [REDACTED] Mobile [REDACTED] E-Mail [REDACTED]
	Back-up:	
	Phone [REDACTED]; Mobile [REDACTED] E-Mail [REDACTED]	
	Europe/Rest of World:	
	Phone [REDACTED] E-Mail [REDACTED]	
Institutions Concerned With the Trial:	<u>Study Communications &amp; Patient/Site Support</u> BBK Worldwide 117 Kendrick Street, Suite 600 Needham, Massachusetts 02494, US Phone: [REDACTED]	<u>Study Communications &amp; Patient/Site Support</u> Mathews Media Group 700 King Farm Boulevard, Suite 500 Rockville, MD 20850, USA Phone: [REDACTED]
	<u>Central Laboratory (non-PK)</u> Covance Central Laboratory Services 8211 SciCor Drive Indianapolis, Indiana 46214, US Phone: [REDACTED]	<u>Clinical Laboratory Supplies</u> Covance Central Laboratory Services 8211 SciCor Drive Indianapolis, Indiana 46214, USA Phone: [REDACTED]
		<u>Neurocognitive Battery</u> Cogstate, Ltd. 195 Church Street 8th Floor New Haven, CT 06510 USA

Location:	Old Text:	New Text:
		Phone: [REDACTED]

**ADDITIONAL RISK TO THE SUBJECT:** There is no additional risk to the subjects.

**Amendment Number:** 3

**Issue Date:** 26 Feb 2015

**PURPOSE:**

- Implementation of additional serum sodium testing during drug titration to align with the current EU label (SmPC) for the adult indication of hyponatremia. We are adding safety testing for serum sodium at interim time points during titration with the option of using a point of care device to minimize impact on total blood volume required for the trial.
- Clarification of the “baseline” assessment for trial qualification.
- Additional background data from non-clinical juvenile toxicity studies.
- Updates to clarify the titration and rescue therapy schematic.
- Clarify roll-over into extension study 156-11-294.
- Implementation of a suspension formulation for short-term use in hospitalized subjects.
- Implementation of an optional swallow test for the tablet formulation.

**BACKGROUND:**

This protocol serves as the single trial for the Pediatric Written Request with the FDA and the Pediatric Research Equity Act (PREA) requirement for the US. The FDA has agreed to the current version of the protocol and updates have been made to address further comments from the FDA, the Medicines and Healthcare Products Regulatory (MHRA), and other regulatory agencies.

**MODIFICATIONS TO PROTOCOL:**

**Sectional Revisions:** changes made to specific sections of the protocol are listed in the table below.

Location	Old Text	Updated Text
<b>Title Page:</b>	<p>Issue Date: 03 Jul 2013</p> <p>Date of Amendment 1: 04 Nov 2013</p> <p>Date of Amendment 2: 19 May 2014</p>	<p>Issue Date: 03 Jul 2013</p> <p>Date of Amendment 1: 04 Nov 201</p> <p>Date of Amendment 2: 19 May 2014</p> <p>Date of Amendment 3: 26 February 2015</p>
<b>Protocol Synopsis</b> <b>Trial Design:</b>	<p>This is an open-label, multicenter, multiple-dose, randomized withdrawal, parallel-group trial of tolvaptan in children and adolescent subjects hospitalized with euvolemic or hypervolemic hyponatremia.</p> <p>The trial will be conducted in two stages. The first stage will be conducted using the available tablet formulation of tolvaptan whereas the second stage will expand to include the use of a suspension once that formulation becomes available.</p> <p>...Since hyponatremia in this patient population can often be transient and/or may be secondary to hypovolemic states, potential subjects will be screened for hyponatremic histories as well as clinically evaluated to rule out such cases. For the purpose of this protocol, persistent hyponatremia will be defined as serum sodium assessments &lt; 130 mEq/L (mmol/L) documented as present for at least 48 hours. Specifically, subjects must have at least 2 documented serum sodium assessments &lt; 130 mEq/L (mmol/L) drawn at least 12 hours apart. These values can be documented using historical values previously obtained as per standard of care. A third (immediate [STAT]) serum sodium assessment &lt; 130 mEq/L (mmol/L), which will serve as the baseline value for final trial qualification and clinical management strategy, is to be obtained within 2-4 hours prior to the first dose of tolvaptan. Additional qualification assessments will be performed as per etiology of hyponatremia. The first dose of tolvaptan will be administered upon successful completion of all screening procedures.</p>	<p>This is an open-label, multicenter, multiple-dose, randomized withdrawal, parallel-group trial of tolvaptan in children and adolescent subjects hospitalized with euvolemic or hypervolemic hyponatremia.</p> <p>...Since hyponatremia in this patient population can often be transient and/or may be secondary to hypovolemic states, potential subjects will be screened for hyponatremic histories as well as clinically evaluated to rule out such cases. For the purpose of this protocol, persistent hyponatremia will be defined as serum sodium assessments &lt; 130 mEq/L (mmol/L) documented as present for at least 48 hours. Specifically, subjects must have at least 2 documented serum sodium assessments &lt; 130 mEq/L (mmol/L) drawn at least 12 hours apart. These values can be documented using historical values previously obtained as per standard of care. A third (immediate [STAT]) serum sodium assessment &lt; 130 mEq/L (mmol/L), which will serve as the baseline value for final trial qualification and clinical management strategy, is to be obtained within 2-4 hours prior to the first dose of tolvaptan. Additional qualification assessments will be performed as per etiology of hyponatremia. The first dose of tolvaptan will be administered upon successful completion of all screening procedures.</p>

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	<p>endpoints, is to be obtained within 2-4 hours prior to the first dose of tolvaptan. Additional qualification assessments will be performed as per etiology of hyponatremia. The first dose of tolvaptan will be administered upon successful completion of all screening procedures.</p> <p>...All Subjects</p> <p>All subjects will have serum sodium levels measured at 8, 12, and 24 hours post-first dose and thereafter every 12 hours through completion of Treatment Phase B.</p>	<p>...All Subjects</p> <p>All subjects will have serum sodium levels measured at 8, 12, and 24 hours post-first dose and thereafter every 12 hours through completion of Treatment Phase B. In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment will be obtained on Day 1 at 4 to 6 hours postdose and at 18 hours postdose. This sodium safety assessment will be repeated at 6 and 18 hours postdose each day for the remainder of titration.</p>
<b>Protocol Synopsis Subject Population:</b>	<p>This trial will include up to 100 male and female subjects aged <math>\geq</math> 4 weeks (or <math>\geq</math> 44 weeks adjusted gestational age) to <math>&lt;</math> 18 years who have been diagnosed with euvolemic or hypervolemic hyponatremia (<math>&lt;</math> 130 mEq/L [mmol/L]) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). Age groups will be enrolled such that 50% of these subjects will be <math>&lt;</math> 10 years old and at least 25% of subjects <math>&lt;</math> 6 years old.</p>	<p>This trial will enroll approximately 100 male and female subjects to get approximately 70 randomized subjects aged <math>\geq</math> 4 weeks (or <math>\geq</math> 44 weeks adjusted gestational age) to <math>&lt;</math> 18 years who have been diagnosed with euvolemic or hypervolemic hyponatremia (<math>&lt;</math> 130 mEq/L [mmol/L]) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). Age groups will be enrolled such that at least 50% of these subjects will be <math>&lt;</math> 10 years old and at least 25% of subjects <math>&lt;</math> 6 years old.</p>
<b>Protocol Synopsis Inclusion/Exclusion Criteria:</b>	<p>Key inclusion criteria:</p> <p>Persistent euvolemic or hypervolemic hyponatremia defined as being documented as present for at least 48 hours,</p>	<p>Key inclusion criteria:</p> <p>Persistent euvolemic or hypervolemic hyponatremia defined as being documented as present for at least 48 hours, evidenced by at</p>

Location	Old Text	Updated Text
	<p>evidenced by at least 2 serum sodium assessments &lt; 130 mEq/L (mmol/L) drawn at least 12 hours apart (these values can be documented using historical values previously obtained per standard of care); a third (STAT) serum sodium assessment &lt; 130 mEq/L (mmol/L), which will serve as the baseline value for efficacy endpoints, is to be obtained 2-4 hours prior to the first dose of tolvaptan</p> <p>Key exclusion criteria:</p> <p>Use of potent cytochrome P450 (CYP) 3A4 inhibitors in subjects ≤ 50 kg or moderate CYP3A4 inhibitors in subjects &lt; 20 kg</p>	<p>least 2 serum sodium assessments &lt; 130 mEq/L (mmol/L) drawn at least 12 hours apart (these values can be documented using historical values previously obtained per standard of care); a third (STAT) serum sodium assessment &lt; 130 mEq/L (mmol/L), which will serve as the baseline value for final trial qualification and clinical management strategy, is to be obtained 2-4 hours prior to the first dose of tolvaptan</p> <p>Key exclusion criteria:</p> <p>Use of potent cytochrome P450 (CYP) 3A4 inhibitors in subjects &lt; 10 kg or moderate CYP3A4 inhibitors in subjects &lt; 6 kg</p>
<b>Protocol Synopsis Trial Sites:</b>	The trial will be conducted at up to 50 centers globally.	The trial will be conducted at approximately 60 centers globally.
<b>Protocol Synopsis Investigational Medicinal Product, Dose, Formulation, Mode of Administration:</b>	<p>Tolvaptan will initially be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets. Upon the availability of an oral suspension formulation, the protocol will be amended to reflect additional dosing options.</p> <p>Tolvaptan will be administered once daily orally with a dose proportional amount of water. Doses of ≥ 15 mg tolvaptan will be given with 240 mL of water, 7.5 mg tolvaptan will be given with 120 mL of water, and 3.75 mg of tolvaptan will be given with 60 mL of water. The treatment duration will be up to 5 days. Any initiation or titration of tolvaptan must occur in a hospital setting.</p>	<p>Tolvaptan will be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets and, where approved, as a 1 mg/mL (0.1% w/v) suspension.</p> <p>Tolvaptan tablets will be administered once daily, orally with a dose proportional amount of water. Doses of ≥ 15 mg tolvaptan will be given with 240 mL of water, 7.5 mg tolvaptan will be given with 120 mL of water, and 3.75 mg of tolvaptan will be given with 60 mL of water. The treatment duration will be up to 5 days. Any initiation or titration of tolvaptan must occur in a hospital setting.</p>

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	<p>...</p> <p>Subjects &lt; 2 years of age, weighing &lt; 10 kg, or who cannot safely swallow the tablet will be excluded until the availability of a suspension formulation.</p> <p>Subjects <math>\geq</math> 2 years of age and weighing <math>\geq</math> 10 to &lt; 20 kg will be given a 3.75-mg tablet on Day 1 with possible up-titration to 7.5- and 15-mg doses.</p> <p>Subjects weighing 20 to 50 kg, inclusive, will be given a 7.5-mg tablet on Day 1 with possible up-titration to 15- and 30-mg doses.</p> <p>Subjects weighing &gt; 50 kg will be given a 15-mg tablet on Day 1 with possible up-titration to 30- and 60-mg doses.</p>	<p>Tolvaptan suspension will be administered once daily, orally using the provided, appropriately-sized syringe (3 mL or 10mL) to measure the volume. The lowest volume that can be administered is 0.3 mL (0.3 mg).</p> <p>The investigator has the option of performing a swallow test and providing coaching on swallowing techniques using placebo tablets if it is known or suspected that the subject is unable to swallow tablets. Placebo tablets will be provided for use in performing this test at screening.</p> <p>...</p> <p>Subjects &lt; 2 years of age, weighing &lt; 10 kg will be given a 0.1 mg/kg dose of the suspension on Day 1 with possible up-titration to 0.2 mg/kg and 0.4 mg/kg doses.</p> <p>Subjects <math>\geq</math> 2 years of age, weighing <math>\geq</math> 10 to &lt; 20 kg and who can safely swallow a tablet will be given a 3.75-mg tablet on Day 1 with possible up-titration to 7.5- and 15-mg doses.</p> <p>Subjects weighing 20 to 50 kg, inclusive, and who can safely swallow a tablet, will be given a 7.5-mg tablet on Day 1 with possible up-titration to 15- and 30-mg doses.</p> <p>Subjects <math>\geq</math> 2 years of age, weighing <math>\leq</math> 30 kg and who cannot safely swallow a tablet, can be given a 0.15 mg/kg dose of the suspension on Day 1 with possible up-titration to 0.3 mg/kg and 0.6 mg/kg doses.</p> <p>Subjects weighing &gt; 50 kg will be given a 15-mg tablet on Day 1</p>

Location	Old Text	Updated Text
		with possible up-titration to 30- and 60-mg doses.
<b>Protocol Synopsis</b> <b>Trial Duration:</b>	<p>Overall trial duration of enrollment is expected to be 36 months with an enrollment rate of 33 subjects per year. Nominal trial duration for each subject is up to 21 days. Treatment duration is up to 5 days with ongoing monitoring of serum sodium levels. A serum sodium assessment and AE follow-up visit will be performed 7 (<math>\pm</math> 1) days post-last dose. A final safety follow-up telephone contact or visit will be performed 14 (+ 2) days post-last dose.</p>	<p>Overall trial duration of enrollment is expected to be approximately 3 years with an enrollment rate of approximately 33 subjects per year. Nominal trial duration for each subject is up to 21 days. Treatment duration is up to 5 days with ongoing monitoring of serum sodium levels. A serum sodium assessment and AE follow-up visit will be performed 7 (<math>\pm</math> 1) days post-last dose. A final safety follow-up telephone contact or visit will be performed 14 (+ 2) days post-last dose.</p>
<b>List of Abbreviations and Definitions of Terms:</b>	Added 5 terms: EMA, MHRA, PDCO, PREA, and WOCBP	<p>EMA European Medicines Agency  MHRA Medicines and Healthcare Products Regulatory  PDCO Paediatric Committee  PREA Pediatric Research Equity Act  WOCBP Women of child-bearing potential</p>
<b>1.1.1 Juvenile Animal Toxicity Data:</b>	<p>A 1-week dose range-finding study was conducted in rat pups at 4 or 7 days of age and results showed tolvaptan to be lethal at 1000 mg/kg/day and tolerable at 100 mg/kg/day and lower.</p>	<p>A 1-week dose range-finding study was conducted in rat pups at 4 or 7 days of age and results showed tolvaptan to be lethal at 1000 mg/kg/day and tolerable at 100 mg/kg/day and lower.</p> <p>In another study, male and female rat pups at 4 days of age were orally administered tolvaptan for 9 weeks at doses of 10, 30, and 100 mg/kg/day. Similar to the above study, pharmacologically mediated changes were noted in urine volume, water consumption, and urine electrolytes at all doses. Dilated renal pelvis considered to be attributable to increased urine volume during very early infancy was noted in males at 30 mg/kg/day and higher and females at 100 mg/kg/day. Toxicities were noted at 100 mg/kg/day, including death in one male, suppressed body weight gain and food consumption in males and females, and delayed</p>

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		balanopreputial separation and prolonged prothrombin time in males. Except for prolonged prothrombin time, all changes noted during the administration period showed reversibility after a 4-week recovery period. The no observed adverse effect level in both males and females was judged to be 30 mg/kg/day. <sup>16</sup>
<b>1.2.1 Pharmacokinetics:</b>	<p>Since inception of the program, a total of 45 phase 1 trials have been completed with tolvaptan (as of 31 Mar 2013) in healthy subjects or special populations in Argentina, China, Japan, Republic of Korea, the United Kingdom (UK), and the US.<sup>16</sup></p> <p>Following IV dosing, the terminal-phase elimination half-life (<math>t_{1/2,z}</math>) of tolvaptan is about 3 hours. Following single oral tablet doses, the <math>t_{1/2,z}</math> of tolvaptan increases with increasing dose with mean values around 3 hours for a 15-mg dose and 12 hours for 120- to 480-mg doses. Tolvaptan is very insoluble, with solubility being 0.00005 w/v% at 25°C and is pH independent. At lower doses, tolvaptan is mostly absorbed from the upper GI tract so the decline of the terminal portion of the concentration curve reflects elimination process only. With increasing dose, there is continued absorption of tolvaptan from the GI tract such that the rate of decline of the terminal portion of the concentration curve is reflective of both absorption and elimination processes.<sup>16</sup></p> <p>The limited early absorption of tolvaptan is exemplified by the fact that the maximum (peak) plasma concentration (<math>C_{max}</math>) values show less than dose proportional increases from 30 to 240 mg and then a plateau at doses from 240 to 480 mg.</p>	<p>Since inception of the program, a total of 53 clinical pharmacology trials have been completed with tolvaptan (as of 11 Jul 2013) in healthy subjects or special populations in Argentina, China, Japan, Republic of Korea, the United Kingdom (UK), and the US.<sup>16</sup></p> <p>In healthy subjects, following IV dosing, the terminal-phase elimination half-life (<math>t_{1/2,z}</math>) of tolvaptan is about 3 hours. Following single oral tablet doses, the <math>t_{1/2,z}</math> of tolvaptan increases with increasing dose with mean values around 3 hours for a 15-mg dose and 12 hours for 120- to 480-mg doses. Tolvaptan is very insoluble, with solubility being 0.00005 w/v% at 25°C and is pH independent. At lower doses, tolvaptan is mostly absorbed from the upper GI tract so the decline of the terminal portion of the concentration curve reflects elimination process only. With increasing dose, there is continued absorption of tolvaptan from the GI tract such that the rate of decline of the terminal portion of the concentration curve is reflective of both absorption and elimination processes.<sup>16</sup></p> <p>The limited early absorption of tolvaptan is exemplified by the fact that the maximum (peak) plasma concentration (<math>C_{max}</math>) values show less than dose proportional increases from 30 to 240 mg and then a plateau at doses from 240 to 480 mg. Despite the changes</p>

Location	Old Text	Updated Text
	<p>Despite the changes in tolvaptan absorption, tolvaptan AUC values increase proportionally with increasing dose and apparent clearance of drug from plasma after extravascular administration (CL/F) values are unchanged for single doses of 30 to 480 mg.<sup>16</sup></p> <p>Tolvaptan concentrations do not accumulate following once daily dosing. Following 300-mg doses, <math>C_{max}</math> and AUC during the dosing interval at steady state (<math>AUC_t</math>) were only 4.2- and 6.4-fold higher, respectively, when compared with the 30-mg dose. This indicates bioavailability decreases with increasing dose. Mean (range) absolute bioavailability of tolvaptan when administered as a 30-mg tablet was 56% (42% to 80%).</p> <p>Trials in subjects with hyponatremia secondary to liver disease showed that following a single oral dose, tolvaptan concentrations increase dose proportionally from 5 to 60 mg. The clearance following single oral doses of tolvaptan was independent of the dose and similar to clearance in healthy subjects. Following multiple oral doses, tolvaptan concentrations accumulated 2-fold and clearance was decreased about 50%.<sup>16</sup></p> <p>Once a day dosage regimen trials in CHF subjects with extracellular volume expansion showed that tolvaptan concentrations increased less than proportionally with dose upon multiple dosing regimens (10, 15, 30, 60, 90, and 120 mg once daily for 13 days) in this subject population. The <math>t_{1/2,z}</math> and CL/F were unchanged across dose groups. Compared to healthy subjects, the disposition of tolvaptan is</p>	<p>in tolvaptan absorption, tolvaptan AUC values increase proportionally with increasing dose and apparent clearance of drug from plasma after extravascular administration (CL/F) values are unchanged for single doses of 30 to 480 mg.<sup>16</sup></p> <p>Tolvaptan concentrations do not accumulate following once daily dosing. Following 300-mg doses, <math>C_{max}</math> and AUC during the dosing interval at steady state (<math>AUC_t</math>) were only 4.2- and 6.4-fold higher, respectively, when compared with the 30-mg dose. This indicates bioavailability decreases with increasing dose. Mean (range) absolute bioavailability of tolvaptan when administered as a 30-mg tablet was 56% (42% to 80%).</p> <p>In healthy subjects, tolvaptan pharmacokinetics following a 15 mg dose as a 1mg/mL suspension shows a more rapid absorption (the median <math>t_{max}</math> is shorter, 1.00 versus 2.00 hours respectively), when compared to a 15 mg tablet. The geometric mean ratio (90% CI), for suspension over the tablet, for <math>C_{max}</math> is 1.614 (1.484 to 1.754) but AUC is unchanged.</p> <p>Trials in subjects with hyponatremia secondary to liver disease showed that following a single oral dose, tolvaptan concentrations increase dose proportionally from 5 to 60 mg. The clearance following single oral doses of tolvaptan was independent of the dose and similar to clearance in healthy subjects. Following multiple oral doses, tolvaptan concentrations accumulated 2-fold and clearance was decreased about 50%.<sup>16</sup></p> <p>Once a day dosage regimen trials in CHF subjects with extracellular volume expansion showed that tolvaptan concentrations increased less than proportionally with dose upon</p>

Location	Old Text	Updated Text
	<p>slower with longer <math>t_{1/2,z}</math> (7.8 to 11.1 hours) and smaller CL/F (0.9 to 3.3 mL/min/kg). The <math>C_{max}</math> was 2- to 2.5-fold greater than that of healthy subjects (at 60- and 90-mg doses). The median volume of distribution following extravascular administration of tolvaptan ranged from 1 to 2.5 L/kg and was not different from healthy subjects.<sup>16</sup></p> <p>Tolvaptan is a weak substrate for cytochrome P450 (CYP) 3A4 and has no inhibitory activity at CYP3A4. Tolvaptan administration does not produce clinically significant changes in amiodarone, warfarin (or its 7-hydroxy and 10-hydroxy metabolites), lovastatin, furosemide, or hydrochlorothiazide plasma concentrations. Steady state digoxin concentrations were increased approximately 20% (as determined by <math>AUC_{\tau}</math>).<sup>16</sup></p> <p>When administered with the potent CYP3A4 inhibitor ketoconazole, the ketoconazole + tolvaptan/tolvaptan alone ratio for tolvaptan mean <math>C_{max}</math> and AUC from time zero to infinity values were 3.48 and 5.40, respectively. Therefore, a 4-fold reduction in tolvaptan dose is recommended when initiating tolvaptan therapy in subjects using potent CYP3A4 inhibitors and a 2-fold reduction in tolvaptan dose is recommended for subjects using moderate CYP3A4 inhibitors. Lovastatin increases tolvaptan <math>C_{max}</math> by approximately 20% but CL/F is unchanged. Tolvaptan <math>C_{max}</math> and AUC calculated to the last observable concentration at time <math>t</math> (<math>AUC_t</math>) are increased 1.9- and 1.6-fold, respectively, when tolvaptan is coadministered with grapefruit juice. Following coadministration with 600 mg once daily rifampin</p>	<p>multiple dosing regimens (10, 15, 30, 60, 90, and 120 mg once daily for 13 days) in this subject population. The <math>t_{1/2,z}</math> and CL/F were unchanged across dose groups. Compared to healthy subjects, the disposition of tolvaptan is slower with longer <math>t_{1/2,z}</math> (7.8 to 11.1 hours) and smaller CL/F (0.9 to 3.3 mL/min/kg). The <math>C_{max}</math> was 2- to 2.5-fold greater than that of healthy subjects (at 60- and 90-mg doses). The median volume of distribution following extravascular administration of tolvaptan ranged from 1 to 2.5 L/kg and was not different from healthy subjects.<sup>16</sup></p> <p>Tolvaptan is a sensitive substrate for cytochrome P450 (CYP) 3A4 and has no inhibitory activity at CYP3A4. Tolvaptan administration does not produce clinically significant changes in amiodarone, warfarin (or its 7-hydroxy and 10-hydroxy metabolites), lovastatin, furosemide, or hydrochlorothiazide plasma concentrations. Steady state digoxin concentrations were increased approximately 20% (as determined by <math>AUC_{\tau}</math>).<sup>16</sup></p> <p>When administered with the potent CYP3A4 inhibitor ketoconazole, the ketoconazole + tolvaptan/tolvaptan alone ratio for tolvaptan mean <math>C_{max}</math> and AUC from time zero to infinity values were 3.48 and 5.40, respectively. Therefore, a 4-fold reduction in tolvaptan dose is recommended when initiating tolvaptan therapy in subjects using potent CYP3A4 inhibitors and a 2-fold reduction in tolvaptan dose is recommended for subjects using moderate CYP3A4 inhibitors. Lovastatin increases tolvaptan <math>C_{max}</math> by approximately 20% but CL/F is unchanged. Tolvaptan <math>C_{max}</math> and AUC calculated to the last observable concentration at time <math>t</math> (<math>AUC_t</math>) are increased 1.9- and 1.6-fold, respectively, when tolvaptan is coadministered with grapefruit</p>

Location	Old Text	Updated Text
	<p>at steady state, tolvaptan <math>C_{max}</math> and <math>AUC_t</math> are decreased 83% and 87%, respectively.<sup>16</sup></p> <p>When 30- or 60-mg doses were given following a standard high-fat, high-calorie meal, no clinically significant differences in urine output were observed.<sup>32,33</sup></p>	<p>juice. Following coadministration with 600 mg once daily rifampin at steady state, tolvaptan <math>C_{max}</math> and <math>AUC_t</math> are decreased 83% and 87%, respectively.<sup>16</sup></p> <p>When 30- or 60-mg tablet doses were given following a standard high-fat, high-calorie meal, no clinically significant differences in urine output were observed.<sup>32,33</sup></p> <p>Following multiple oral doses, the tolvaptan metabolite DM-4103 was found to accumulate. This metabolite has no pharmacological activity and has shown an acceptable toxicity profile. The metabolite has not been shown to accumulate in nonclinical toxicokinetic studies; however, in a 26-week study in rats, DM-4103 plasma concentrations greater than those expected at the dose used in this trial revealed no evidence of time-dependent toxicological effects.<sup>13</sup></p>
<p><b>1.2.2</b></p> <p><b>Pharmacodynamics:</b></p>	<p>Tolvaptan increases urine excretion rate at concentrations around 20 ng/mL and maximal urine excretion rates are reached between 100 and 150 ng/mL. A single oral dose trial in healthy subjects using doses from 60 to 240 mg showed that there were 1) no further increases in urine excretion rate with doses beyond 180 mg; 2) no further increases in zero to 24 hour urine excretion with doses beyond 180 mg; and 3) as dose was increased, increases in urine excretion were sustained over time. Tolvaptan elevated electrolyte-free water clearance to a positive value, increased serum sodium and serum osmolality, and increased plasma AVP concentrations and renin activity, but no dose-related increases were</p>	<p><b>1.2.2 Pharmacodynamics</b></p> <p>Tolvaptan increases urine excretion rate at concentrations around 20 ng/mL and maximal urine excretion rates are reached between 100 and 150 ng/mL. A single oral dose trial in healthy subjects using doses from 60 to 240 mg showed that there were 1) no further increases in urine excretion rate with doses beyond 180 mg; 2) no further increases in zero to 24 hour urine excretion with doses beyond 180 mg; and 3) as dose was increased, increases in urine excretion were sustained over time. Tolvaptan elevated electrolyte-free water clearance to a positive value, increased</p>

Location	Old Text	Updated Text
	<p>observed for any other parameter.<sup>16</sup></p> <p>Following multiple oral doses, the tolvaptan metabolite DM-4103 was found to accumulate. This metabolite has no pharmacological activity and has shown an acceptable toxicity profile. The metabolite has not been shown to accumulate in nonclinical toxicokinetic studies; however, in a 26-week study in rats, DM-4103 plasma concentrations greater than those expected at the dose used in this trial revealed no evidence of time-dependent toxicological effects.<sup>16</sup></p> <p>Details of the currently available PK/PD data for the compound are available in the investigator's brochure (IB).<sup>16</sup></p>	<p>serum sodium and serum osmolality, and increased plasma AVP concentrations and renin activity, but no dose-related increases were observed for any other parameter.<sup>16</sup></p> <p>When compared to a 15-mg spray-dried tablet, the pharmacodynamic profiles of urine excretion rate, cumulative urine volume, free water clearance, urine osmolality, and serum sodium were not different for 15-mg of the suspension.<sup>16</sup></p> <p>Details of the currently available PK/PD data for the compound are available in the investigator's brochure (IB).<sup>16</sup></p>
<b>1.3 Known and Potential Risks and Benefits:</b>	<p>As of 31 Mar 2013, 6,794 adult subjects have been exposed to oral doses of tolvaptan in 82 completed or terminated tolvaptan trials in the US, Europe, South America, and Asia: 1,047 healthy subjects, 37 subjects with renal impairment (phase 1 trial), 3,115 subjects in trials for CHF, 425 subjects in trials for hyponatremia, 961 subjects in the pivotal long-term ADPKD trial, 137 subjects in short-term trials for ADPKD or renal impairment, 217 subjects with cardiac edema, and 855 subjects with hepatic edema. Additionally, 14 healthy adult subjects were exposed to a single 1-mg IV dose of tolvaptan in a phase 1 bioavailability trial (Trial 156-05-254) in the US.<sup>16</sup></p> <p>The most commonly reported treatment-emergent adverse events (TEAEs; &gt; 10% and greater than placebo) in healthy</p>	<p>As of 31 Mar 2013, 6,794 adult subjects have been exposed to oral doses of tolvaptan spray-dried tablets in 82 completed or terminated tolvaptan trials in the US, Europe, South America, and Asia: 1,047 healthy subjects, 37 subjects with renal impairment (phase 1 trial), 3,115 subjects in trials for CHF, 425 subjects in trials for hyponatremia, 961 subjects in the pivotal long-term ADPKD trial, 137 subjects in short-term trials for ADPKD or renal impairment, 217 subjects with cardiac edema, and 855 subjects with hepatic edema. Fourteen healthy adult subjects were exposed to a single 1-mg IV dose of tolvaptan in a phase 1 bioavailability trial (Trial 156-05-254) in the US.<sup>16</sup> As of 31 Mar 2014, additionally, 14 healthy adult subjects were also exposed to the tolvaptan suspension formulation.</p> <p>The most commonly reported treatment-emergent adverse events</p>

Location	Old Text	Updated Text
	<p>subjects treated with tolvaptan were thirst, pollakiuria, and headache. The most commonly reported TEAEs (&gt; 5% incidence) in hyponatremia trials for subjects treated with tolvaptan were thirst, dry mouth, peripheral edema, nausea, fatigue, dizziness, pollakiuria, diarrhea, headache, constipation, and pyrexia. The most commonly reported TEAE (by &gt; 5% incidence) in hyponatremia trials for subjects treated with placebo were peripheral edema, diarrhea, dyspnea, vomiting, fatigue, headache, and nausea. The IB provides a thorough review of the adverse events (AEs) experienced with this compound during clinical trials.<sup>16</sup></p> <p>Analyses of the completed 3-year pivotal Trial 156-04-251 (double-blind, placebo-controlled trial to determine long-term safety and efficacy of oral tolvaptan in adult subjects with ADPKD) have revealed new and important safety information. In this trial, a new signal for imbalanced elevations of liver transaminases in ADPKD subjects receiving tolvaptan compared with placebo was detected and formally adjudicated by an expert panel blinded to treatment.</p>	<p>(TEAEs; &gt; 10% and greater than placebo) in healthy subjects treated with tolvaptan were thirst, pollakiuria, and headache. The most commonly reported TEAEs (&gt; 5% incidence) in hyponatremia trials for subjects treated with tolvaptan were thirst, dry mouth, peripheral edema, nausea, fatigue, dizziness, pollakiuria, diarrhea, headache, constipation, and pyrexia. The most commonly reported TEAE (by &gt; 5% incidence) in hyponatremia trials for subjects treated with placebo were peripheral edema, diarrhea, dyspnea, vomiting, fatigue, headache, and nausea. The IB provides a review of the adverse events (AEs) experienced with the spray-dried tablet and suspension formulation of tolvaptan during clinical trials.<sup>16</sup></p> <p>There is the potential for osmotic diarrhea due to the sorbitol content in the suspension. D-Sorbitol is a hexahydric sugar alcohol that naturally occurs in fruits and animal tissue. The daily per capita consumption of sorbitol as a food ingredient is approximately 200mg. The compound is about 35-60% as sweet as sugar, and has been the impetus as a substitute for sugar to reduce caloric intake and prophylactic measures against the formation of dental caries. Absorption of sorbitol by humans is limited by its rate of diffusion from the gastrointestinal tract and by laxation that may occur after ingestion of high doses. Typically, 25-50 g in adults may cause osmotic diarrhea. The corresponding dose in children is thought to be 10 g and higher, but is dependent on body weight and types of foods ingested. Similar findings are also observed with other sugar alcohols, eg, xylitol.<sup>17</sup></p> <p>Following a single 15 mg tolvaptan dose of the suspension,</p>

Location	Old Text	Updated Text
		<p>containing 8 g of sorbitol, in healthy adults, no diarrhea was reported.<sup>34</sup></p> <p>Therefore, in this trial, suspension dosing is limited to subjects who weigh <math>\leq</math>30 kg; the maximum dose of sorbitol is expected to be approximately 9.6 grams in a 0.6 mg/kg dose for a subject who weighs 30 kg. Subjects will be started on the lowest dose for their weight and titrated to higher doses as appropriate for their clinical condition. Subjects will be in a hospital setting during titration and will be closely monitored for rate of sodium correction and signs of dehydration including diarrhea.</p> <p>Analyses of the completed 3-year pivotal Trial 156-04-251 (double-blind, placebo-controlled trial to determine long-term safety and efficacy of oral tolvaptan in adult subjects with ADPKD) have revealed new and important safety information. In this trial, a new signal for imbalanced elevations of liver transaminases in ADPKD subjects receiving tolvaptan compared with placebo was detected and formally adjudicated by an expert panel blinded to treatment.</p>
<b>2.1 Trial Rationale:</b>	<p>The proposed population size of 100 subjects is expected to yield 70 subjects who respond to tolvaptan (henceforth termed “responders”), which has adequate power (<math>&gt; 90\%</math>) to test for statistical significance in the primary endpoint. Enrollment is expected to take 3 years using up to 50 sites globally. Additional blood sampling will be included across populations to provide PK information.</p>	<p>The proposed population size of 100 subjects is expected to yield 70 subjects who respond to tolvaptan (henceforth termed “responders”), which has adequate power (<math>&gt; 90\%</math>) to test for statistical significance in the primary endpoint. Enrollment is expected to take approximately 3 years using approximately 60 sites globally. Additional blood sampling will be included across populations to provide PK information.</p>

Location	Old Text	Updated Text
	<p>Even with a limited size, recruitment for such a trial is expected to be challenging due to the low frequency of AVP-mediated hyponatremia in children. Therefore, the trial will be organized at major pediatric referral centers to access the largest patient population.</p>	<p>Even with a limited size, recruitment for such a trial is expected to be challenging due to the low frequency of AVP-mediated hyponatremia in children. Therefore, the trial will be organized at major pediatric referral centers to access the largest patient population.</p> <p>It is recognized that the pediatric population is a vulnerable subgroup and there are risks in conducting a clinical trial in the pediatric population. However, given the possible serious and life-threatening consequences of untreated hyponatremia, it is necessary to study hyponatremia treatment in children. Children have different physiology and metabolisms from adults and, therefore, it is not sufficient to study hyponatremia treatment in the adult population to determine the proper course of treatment for hyponatremia in the pediatric population. A clear understanding of exposure-response in adults that can be applied to pediatrics (or from one pediatric group to another) has not yet been established, furthering the need for this trial.<sup>19</sup></p> <p>Every effort will be made to anticipate and reduce known risks. This trial was designed to minimize the number of participants and the number of procedures, consistent with good study design.<sup>20</sup> Children will be continuously monitored for signs of distress during this trial. The risk threshold for subjects will be constantly monitored by the investigator. A detailed list and description of the safety monitoring to be conducted during this trial can be found in Section 3.7.4.</p>
<b>2.1.1 Dosing Rationale:</b>	<p>Enrolled subjects will be dosed based on age, weight, and the use of CYP3A4 inhibitors. Subjects &lt; 2 years of age or &lt; 10</p>	<p>Enrolled subjects will be dosed based on formulation type, age, weight, and the use of CYP3A4 inhibitors.</p>

Location	Old Text	Updated Text
	<p>kg will be excluded until the availability of an oral suspension formulation. Subjects <math>\geq</math> 2 years of age and weighing <math>\geq</math> 10 to &lt; 20 kg will receive an oral once daily dose of tolvaptan starting as a 3.75-mg spray-dried tablet. Subjects weighing 20 to 50 kg, inclusive, will receive an oral once daily dose of tolvaptan starting as a 7.5-mg spray-dried tablet. Subjects weighing &gt; 50 kg will receive an oral once daily dose of tolvaptan starting as a 15-mg spray-dried tablet. For subjects weighing <math>\geq</math> 20 kg and taking moderate inhibitors of CYP3A4, a half dose will be used (3.75 or 7.5 mg, by weight). For subjects weighing &gt; 50 kg and taking potent inhibitors of CYP3A4, a one-quarter dose will be used (3.75 mg). Subjects weighing &lt; 20 kg and who are taking any CYP3A4 inhibitors will be excluded from the trial until such time that an alternate dosing formulation is available.</p> <p>In the pivotal hyponatremia trials<sup>16,21,22</sup> the starting 15-mg dose was administered to adult subjects weighing 34.0 to 164.7 kg; in terms of mg/kg, the starting dose of tolvaptan ranged from 0.09 to 0.44 mg/kg. The weight cutoffs for this trial were selected to produce mg/kg doses of tolvaptan within the range observed for the adult trials. Table 2.1.1-1 outlines the mg/kg dose ranges for tolvaptan tablet doses and body weights of 10, 20, 50, 70 (standard adult man), and 100 kg.</p> <p>...Tolvaptan is a sensitive CYP3A4 substrate; plasma concentrations increased approximately 4-fold when tolvaptan was administered with the potent CYP3A4 inhibitor ketoconazole.<sup>16,24</sup> Where appropriate dose reductions are possible, tolvaptan doses may be coadministered with potent</p>	<p>In the pivotal hyponatremia trials,<sup>13,18,19</sup> the starting 15-mg dose was administered to adult subjects weighing 34.0 to 164.7 kg; in terms of mg/kg, the starting dose of tolvaptan ranged from 0.09 to 0.44 mg/kg. The weight cutoffs for use of tolvaptan tablets in this trial were selected to produce mg/kg doses of tolvaptan within the range observed for the adult trials. <a href="#">Table 2.1.1-1</a> outlines the mg/kg dose ranges for tolvaptan tablet doses and body weights of 10, 20, 50, 70 (standard adult man), and 100 kg.</p> <p>...Tolvaptan is metabolized by the CYP3A isozyme. At birth, the amount per gram liver of CYP3A is less than in an adult but adult levels of CYP3A are reached by 2 years of age. A physiologically-based pharmacokinetic model of adult tolvaptan concentrations was modified to estimate tolvaptan concentrations in subjects 44 weeks of gestational age to &lt; 2 years of age and then <math>\geq</math> 2 to &lt; 4 years of age. It was estimated that doses of 0.1 mg/kg and 0.15 mg/kg, respectively, would produce peak tolvaptan concentrations similar to those produced by a 15 mg tablet in an adult subject. However, overall exposure as determined by AUC would be 33% and 13% lower, respectively, for &lt; 2 years of age and <math>\geq</math> 2 to &lt; 4 years of age when compared to a 15 mg tablet in an adult. It is expected that a 0.15 mg/kg starting dose of tolvaptan suspension would also be suitable for children &gt; 4 years of age, as CYP3A expression would be the same as for children <math>\geq</math> 2 to 4 years of age. Suspension will only be dosed in children who weigh 30 kg or less to limit the amount of sorbitol administered; a 30 kg child titrated to a 0.6 mg/kg dose of tolvaptan as the suspension would receive approximately 9.6 g of sorbitol.</p>

Location	Old Text	Updated Text
	or moderate CYP3A4 inhibitors.	<p>Therefore, subjects &lt; 2 years of age or &lt; 10 kg will be administered tolvaptan as the suspension formulation with doses starting at 0.1 mg/kg. Subjects ≥ 2 years of age, weighing ≥ 10 to &lt; 20 kg and who can swallow a tablet will be administered an oral tablet once daily starting at a dose of 3.75-mg. Subjects weighing 20 to 50 kg, inclusive, and who can safely swallow a tablet, will receive an oral once daily dose of tolvaptan starting as a 7.5-mg spray-dried tablet. Subjects ≥ 2 years of age, weighing ≤ 30 kg and who cannot safely swallow a tablet, will receive an oral, once daily dose of tolvaptan suspension starting at 0.15 mg/kg. Subjects weighing &gt; 50 kg will receive an oral once daily dose of tolvaptan starting as a 15-mg spray-dried tablet.</p> <p>Tolvaptan is a sensitive CYP3A4 substrate; plasma concentrations increased approximately 4-fold when tolvaptan was administered with the potent CYP3A4 inhibitor ketoconazole.<sup>16,24</sup> Where appropriate dose reductions are possible, tolvaptan doses may be coadministered with potent or moderate CYP3A4 inhibitors. Table 2.1.1-2 outlines starting dose adjustments when tolvaptan is administered concurrently with potent or moderate CYP3A4 inhibitors. Tolvaptan doses will be reduced 75% and 50% if a potent or moderate inhibitor, respectively, is being concurrently administered. As the smallest volume of suspension that can be administered is 0.3 mL (0.3kg), subjects weighing &lt; 3 kg, &lt; 6 kg and taking a moderate CYP3A4 inhibitor or weighing &lt; 10kg and taking a potent CYP3A4 inhibitor may not be enrolled.</p>

**New Text: Table 2.1.1-2 Starting Tolvaptan Tablet Doses as mg/kg of Body Weight**

<b>Table 2.1.1-2 Starting Tolvaptan Tablet Doses in the Presence of Potent or Moderate CYP3A Inhibitors</b>			
<b>Tolvaptan Dose</b>	<b>Age/Body Weight (as applicable)</b>	<b>Potent Inhibitor</b>	<b>Moderate Inhibitor</b>
0.1 mg/kg suspension <sup>a</sup>	44 wk to < 2 y or < 10 kg	-	0.05 mg/kg suspension
0.15 mg/kg suspension	≥ 2 y, ≤ 30 kg	0.04 mg/kg suspension	0.8 mg/kg suspension
3.75 mg tablet	≥ 10 kg to < 20 kg	0.94 mL suspension	0.19 mL suspension
7.5 mg tablet	20 kg to 50 kg	1.90 mL suspension	3.75 mg tablet
15 mg tablet	≥ 50 kg	3.75 mg tablet	7.5 mg tablet

<sup>a</sup>The smallest volume of suspension that may be administered is 0.3 mL (0.3 mg), therefore dose reductions for potent inhibitors cannot be accommodated and for moderate inhibitors children weighing < 6 kg cannot be accommodated.

Location	Old Text	Updated Text
<b>3.1 Type of Trial:</b>	<p>This is the first clinical trial of tolvaptan in a pediatric population, and the majority of subjects may require only short-term treatment of hyponatremia, however some subjects may require prolonged treatment and additional follow-up information on their response to tolvaptan may be desired to better understand its long-term safety profile in this pediatric population. Hence, all subjects (responders and nonresponders) who complete this trial will be eligible for enrollment into an extension trial (156-11-294) to continue receiving tolvaptan, as clinically appropriate, until it is approved and available locally. If eligible, subjects could continue therapy with tolvaptan in that trial after completing the 14 (+2) day Follow-up Visit and completion of this trial. (The extension study will also provide long-term post-treatment safety follow-up information for a minimum of 6 months.)</p> <p>The trial will be conducted in two stages. The first stage will be conducted using the available tablet formulation of tolvaptan whereas the second stage will expand to the use of a suspension once that formulation becomes available.</p>	<p>This is the first clinical trial of tolvaptan in a pediatric population, and the majority of subjects may require only short-term treatment of hyponatremia, however some subjects may require prolonged treatment and additional follow-up information on their response to tolvaptan may be desired to better understand its long-term safety profile in this pediatric population. Hence, all subjects (responders and nonresponders) who participate in this trial will be eligible for enrollment into an extension trial (156-11-294) for a 6-month safety follow-up, regardless of treatment, and the option to continue receiving treatment with tolvaptan for hyponatremia based on clinical need.</p>
<b>Figure 3.1-1 Trial Design Schematic:</b>		Schematic revised to reflect updated text in this section.
<b>3.2.1 Tablet Formulation:</b>	<p>The maximum starting doses, by weight, for subjects are shown in <a href="#">Table 2.1.1-1</a> and are within the range previously used in trials involving adult hyponatremic subjects.</p> <p>The palatability of tolvaptan tablets will be assessed.</p>	<p>The maximum starting doses, by weight and age, for subjects are shown in <a href="#">Table 2.1.1-1</a> and are within the range previously used in trials involving adult hyponatremic subjects.</p> <p>The palatability and acceptability of tolvaptan tablets will be</p>

Location	Old Text	Updated Text
		<p>assessed.</p> <p>The investigator has the option of performing a swallow test and providing coaching on swallowing techniques using placebo tablets if it is known or suspected that the subject is unable to swallow tablets. Placebo tablets will be provided for use in performing this test at screening.</p>
<b>3.2.2 Suspension Formulation:</b>	<p>Additional information on the proposed suspension formulation of tolvaptan (currently in development) will be added to the protocol in an amendment when available. Until that time, subjects &lt; 2 years of age or weighing &lt; 10 kg and those unable to swallow tablets, are excluded from the trial.</p>	<p>Tolvaptan suspension, 1 mg/mL (0.1% w/v) will be administered orally once daily, preferably in the morning hours. The treatment duration will be up to 5 days. Any initiation or titration of tolvaptan must occur in a hospital setting.</p> <p>Subjects &lt; 2 years of age or &lt; 10 kg will be administered tolvaptan as the suspension formulation with doses starting at 0.1 mg/kg.</p> <p>Subjects ≥ 2 to &lt; 4 years of age, weighing ≥ 10 to &lt; 20 kg and who cannot swallow a tablet, can receive tolvaptan as the suspension formulation starting at 0.15 mg/kg.</p> <p>The palatability and acceptability of tolvaptan suspension will be assessed.</p>
<b>3.2.3 Dosing Guidelines:</b>	<p>Subjects will be administered tolvaptan on an age- and weight-based scale. Titration of tolvaptan doses can occur once daily and will be based on serum sodium levels assessed at &gt; 20 hours following initiation of therapy and each subsequent dose; titration may not occur within 20 hours of the previous dose. Up-titration is limited to no more than twice the previous dose.</p>	<p>Subjects will be administered tolvaptan on a formulation, age- and weight-based scale. Titration of tolvaptan doses can occur once daily and will be based on serum sodium levels assessed at &gt; 20 hours following initiation of therapy and each subsequent dose; titration may not occur within 20 hours of the previous dose. Up-titration is limited to no more than twice the previous dose.</p>

Location	Old Text	Updated Text
	<p>Subjects &lt; 2 years of age or weighing &lt; 10 kg are excluded until an oral suspension formulation is available.</p> <p>Subjects <math>\geq</math> 2 years of age and weighing <math>\geq</math> 10 to &lt; 20 kg will receive a 3.75 mg tablet on Day 1 with possible up-titration to 7.5 mg and 15 mg tablet doses.</p> <p>Subjects weighing 20 to 50 kg, inclusive, will receive a 7.5 mg tablet on Day 1 with possible up-titration to 15 mg and 30 mg tablet doses.</p> <p>Subjects weighing &gt; 50 kg will receive a 15 mg tablet on Day 1 with possible up-titration to 30 mg and 60 mg tablet doses.</p> <p>...For subjects weighing <math>\geq</math> 20 kg and taking moderate inhibitors of CYP3A4, one half of the standard dose will be used (3.75 or 7.5 mg, by weight). For subjects weighing &gt; 50 kg and taking potent inhibitors of CYP3A4, a one-quarter dose will be used (3.75 mg). Subjects weighing &lt; 20 kg and who are taking any CYP3A4 inhibitors will be excluded until such time that an alternate dosing formulation is available.</p> <p>Following their initial tolvaptan dose in the trial subjects will continue dosing according to the titration scheme (see <a href="#">Section 3.2.4</a>), targeting a final serum sodium concentration between 135 and 140 mEq/L (mmol/L). Titration guidelines are designed to achieve a change in serum sodium concentration of at least 4 to 8 mEq/L (mmol/L)/24 hours but not exceeding [REDACTED].</p>	<p>Subjects &lt; 2 years of age, weighing &lt; 10 kg will receive 0.1 mg/kg of the suspension on Day 1 with possible up-titration to 0.2 mg/kg and 0.4 mg/kg doses.</p> <p>Subjects <math>\geq</math> 2 years of age, weighing <math>\geq</math> 10 to &lt; 20 kg and who can safely swallow a tablet will receive a 3.75 mg tablet on Day 1 with possible up-titration to 7.5 mg and 15 mg tablet doses.</p> <p>Subjects weighing 20 to 50 kg, inclusive, and who can safely swallow a tablet, will receive a 7.5 mg tablet on Day 1 with possible up-titration to 15 mg and 30 mg doses.</p> <p>Subjects <math>\geq</math> 2 years of age, weighing <math>\leq</math> 30 kg and who cannot safely swallow a tablet, can be given a 0.15 mg/kg dose of the suspension on Day 1 with possible up-titration to 0.3 mg/kg and 0.6 mg/kg doses.</p> <p>Subjects weighing &gt; 50 kg will be given a 15 mg tablet on Day 1 with possible up-titration to 30 mg and 60 mg doses.</p> <p>...For subjects taking moderate inhibitors of CYP3A4, one half of the standard dose will be used. For subjects taking potent inhibitors of CYP3A4, a one-quarter dose will be used. The suspension formulation may be used in dose reductions for the tablet, see Table 2.1.1-2.</p> <p>Following their initial tolvaptan dose in the trial subjects will continue dosing according to the titration scheme (see <a href="#">Section 3.2.4</a>), targeting a final serum sodium concentration between 135 and 140 mEq/L (mmol/L). Titration guidelines are designed to achieve a change in serum sodium concentration of at</p>

Location	Old Text	Updated Text
		least 4 to 8 mEq/L (mmol/L)/24 hours but not exceeding [REDACTED] [REDACTED].

**Old Text: Table 3.2.3-1 Dosing Schedule**

<b>Table 3.2.3-1 Dosing Schedule</b>			
<b>Trial Day</b>	<b>Group</b>	<b>Time</b>	<b>Dose</b>
Day 1	All subjects	Hour 0	3.75, 7.5, or 15 mg (as applicable)
Day 2	All subjects	24 ( $\pm$ 4) h post first dose	3.75, 7.5, 15, or 30 mg (as applicable)
Day 2a	(optional)	24 ( $\pm$ 4) h post previous dose	3.75, 7.5, 15, 30 or 60 mg (as applicable)
Day 3	Late Withdrawal and Nonresponders continuing on tolvaptan	24 ( $\pm$ 4) h post previous dose	3.75, 7.5, 15, 30, or 60 mg (as applicable)
Day 4	Late Withdrawal and Nonresponders continuing on tolvaptan	24 ( $\pm$ 4) h post previous dose	3.75, 7.5, 15, 30, or 60 mg (as applicable)

**New Text: Table 3.2.3-1 Dosing Schedule**

<b>Table 3.2.3-1 Dosing Schedule</b>			
<b>Trial Day</b>	<b>Group</b>	<b>Time</b>	<b>Dose</b>
Day 1	All subjects	Hour 0	0.1 or 0.15 mg/kg suspension 3.75, 7.5, or 15 mg tablets (as applicable)
Day 2	All subjects	24 ( $\pm$ 4) h post first dose	0.1, 0.15, 0.2, or 0.3 mg/kg suspension 3.75, 7.5, 15, or 30 mg (as applicable)
Day 2a	(optional)	24 ( $\pm$ 4) h post previous dose	0.1, 0.15, 0.2, 0.3, 0.4, or 0.6 mg/kg suspension 3.75, 7.5, 15, 30 or 60 mg (as applicable)
Day 3	Late Withdrawal and Nonresponders continuing on tolvaptan	24 ( $\pm$ 4) h post previous dose	0.1, 0.15, 0.2, 0.3, 0.4, or 0.6 mg/kg suspension 3.75, 7.5, 15, 30, or 60 mg (as applicable)
Day 4	Late Withdrawal and Nonresponders continuing on tolvaptan	24 ( $\pm$ 4) h post previous dose	0.1, 0.15, 0.2, 0.3, 0.4, or 0.6 mg/kg suspension 3.75, 7.5, 15, 30, or 60 mg (as applicable)

Location	Old Text	New Text
<b>Figure 3.2.4-1 Titration and Rescue Therapy Scheme:</b>		Schematic revised to reflect updated text in this section.
<b>3.2.4.2 Rescue Therapy:</b>	<p>...If at any point during the trial serum sodium levels or hyponatremia symptoms worsen or fail to improve adequately and definitive therapy (eg, isotonic or hypertonic saline) is required, the subject will be withdrawn from trial treatment to receive rescue therapy.</p> <p>Additional guidelines for rescue therapy concerning hyponatremia symptoms and decreasing serum sodium level:</p> <ul style="list-style-type: none"> <li>• If a subject has worsening symptoms and/or has a serum sodium level at or below the baseline value, repeat serum sodium [STAT] to confirm level, and begin rescue therapy.</li> <li>• If a subject is asymptomatic and serum sodium has decreased by <math>\geq 4</math> mEq/L (mmol/L), but is still above the baseline value, consider need for rescue therapy.</li> <li>• If a subject is asymptomatic and serum sodium has decreased by <math>\leq 3</math> mEq/L (mmol/L), but is still above the baseline value, no action is required.</li> </ul> <p>Subjects who are randomized to the Early Withdrawal group will initially be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels. Those subjects whose serum sodium declines by <math>\geq 4</math> mEq/L (mmol/L) or whose overall clinical condition requires further treatment to increase serum sodium will be treated per standard of care. Any</p>	<p>...If at any point during the trial serum sodium levels or hyponatremia symptoms worsen or fail to improve adequately and definitive therapy (eg, isotonic or hypertonic saline) is required, the subject will be withdrawn from trial treatment to receive rescue therapy. Please see Section 4.2 for further details.</p> <p>Additional guidelines for rescue therapy concerning hyponatremia symptoms and decreasing serum sodium level:</p> <ul style="list-style-type: none"> <li>• If a subject has worsening symptoms and/or has a serum sodium level at or below the baseline value, repeat serum sodium [STAT] to confirm level, and begin rescue therapy.</li> <li>• If a subject is asymptomatic and serum sodium has decreased by <math>\geq 4</math> mEq/L (mmol/L), but is still above the baseline value, consider need for rescue therapy according to local standard of care.</li> <li>• If a subject is asymptomatic and serum sodium has decreased by <math>\leq 3</math> mEq/L (mmol/L), but is still above the baseline value, no action is required.</li> </ul> <p>Subjects who are randomized to the Early Withdrawal group will initially be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels. For those subjects whose serum sodium declines by <math>\geq 4</math> mEq/L (mmol/L) or whose overall clinical condition requires further treatment to</p>

Location	Old Text	New Text
	<p>intervention intended to raise serum sodium level during the first 48 hours in the responder Early Withdrawal group (including fluid restriction) will be defined as rescue therapy. These subjects will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.</p>	<p>increase serum sodium, the investigator may consider rescue therapy per local standard of care. Any intervention intended to raise serum sodium level during the first 48 hours in the responder Early Withdrawal group (including fluid restriction) will be defined as rescue therapy. These subjects will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.</p>
<b>3.3 Trial Population:</b>	<p>This trial will include up to 100 male and female subjects aged <math>\geq 4</math> weeks (or <math>\geq 44</math> weeks adjusted gestational age) to <math>&lt; 18</math> years who have been diagnosed with euvolemic or hypervolemic hyponatremia (<math>&lt; 130</math> mEq/L [mmol/L]) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). Age groups will be enrolled such that 50% of these subjects will be <math>&lt; 10</math> years old and at least 25% of subjects <math>&lt; 6</math> years old. Subjects who are defined as responders will be further stratified by the magnitude of serum sodium response to tolvaptan (<math>\leq 7</math> and <math>&gt; 7</math> mEq/L [mmol/L]), and underlying etiology of hyponatremia.</p> <p>Subjects with euvolemic or hypervolemic hyponatremia eligible to be screened for participation in this trial include, but are not limited to, those diagnosed and admitted to a hospital for treatment of HF, hepatocellular disease (including cirrhosis), or SIADH/other. Subjects with acute hyponatremia or hyponatremia expected to resolve spontaneously will be excluded from the trial. Children with an impaired ability to sense or communicate their thirst will either be required per protocol to undergo closer in-hospital observation, laboratory and urine</p>	<p>This trial will include approximately 100 male and female subjects aged <math>\geq 4</math> weeks (or <math>\geq 44</math> weeks adjusted gestational age) to <math>&lt; 18</math> years who have been diagnosed with euvolemic or hypervolemic hyponatremia (<math>&lt; 130</math> mEq/L [mmol/L]) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist). Age groups will be enrolled such that at least 50% of these subjects will be <math>&lt; 10</math> years old and at least 25% of subjects <math>&lt; 6</math> years old. Subjects who are defined as responders will be further stratified by the magnitude of serum sodium response to tolvaptan (<math>\leq 7</math> and <math>&gt; 7</math> mEq/L [mmol/L]), age, and underlying etiology of hyponatremia.</p> <p>Subjects with euvolemic or hypervolemic hyponatremia eligible to be screened for participation in this trial include, but are not limited to, those diagnosed and admitted to a hospital for treatment of HF, hepatocellular disease (including cirrhosis), or SIADH/other. Subjects with acute hyponatremia or hyponatremia expected to resolve spontaneously will be excluded from the trial. Children with an impaired ability to sense or communicate their thirst will either be required to undergo closer in-hospital observation, laboratory and urine output monitoring, or will be excluded from</p>

Location	Old Text	New Text
	<p>output monitoring, or will be excluded from the trial if this is not possible. Children with hypovolemic hyponatremia or those who are at risk of such, secondary to any underlying conditions that cause volume depletion, are excluded from this trial.</p> <p>All potential subjects must have chronic (<math>\geq 48</math> hours) dilutional hyponatremia (euvolemic or hypervolemic) associated with HF, hepatocellular disease (including cirrhosis), or SIADH/other and be deemed by the investigator as likely to benefit from a therapy that raises serum sodium levels. The etiology of hyponatremia (presumed cause) must be documented and evaluated per <a href="#">Section 3.3.1</a>. Those subjects who have acute or transient hyponatremia, have overt symptoms of hyponatremia requiring immediate intervention, or who are at increased risk for developing hyponatremic encephalopathy or osmotic demyelination are excluded from this trial.</p> <p>Since hyponatremia in this patient population can often be transient and/or may be secondary to hypovolemic states, potential subjects will be screened for hyponatremic histories as well as clinically evaluated to rule out such cases. For the purpose of this protocol, persistent hyponatremia will be defined as serum sodium level <math>&lt; 130</math> mEq/L (mmol/L) documented as present for at least 48 hours. Specifically, subjects must have at least 2 serum sodium assessments <math>&lt; 130</math> mEq/L (mmol/L) drawn at least 12 hours apart. These values can be documented using historical values previously obtained as per standard of care. A third (STAT) serum sodium assessment <math>&lt; 130</math> mEq/L (mmol/L), which will serve as the baseline value for efficacy endpoints, is to</p>	<p>the trial if this is not possible. Children with hypovolemic hyponatremia or those who are at risk of such, secondary to any underlying conditions that cause volume depletion, are excluded from this trial.</p> <p>All potential subjects must have chronic (<math>\geq 48</math> hours) dilutional hyponatremia (euvolemic or hypervolemic) associated with HF, hepatocellular disease (including cirrhosis), or SIADH/other and be deemed by the investigator as likely to benefit from a therapy that raises serum sodium levels. The etiology of hyponatremia (presumed cause) must be documented and evaluated per <a href="#">Section 3.3.1</a>. Those subjects who have acute or transient hyponatremia, have overt symptoms of hyponatremia requiring immediate intervention, or who are at increased risk for developing hyponatremic encephalopathy or osmotic demyelination are excluded from this trial.</p> <p>Since hyponatremia in this patient population can often be transient and/or may be secondary to hypovolemic states, potential subjects will be screened for hyponatremic histories as well as clinically evaluated to rule out such cases. For the purpose of this protocol, persistent hyponatremia will be defined as serum sodium level <math>&lt; 130</math> mEq/L (mmol/L) documented as present for at least 48 hours. Specifically, subjects must have at least 2 serum sodium assessments <math>&lt; 130</math> mEq/L (mmol/L) drawn at least 12 hours apart. These values can be documented using historical values previously obtained as per standard of care. A third (STAT) serum sodium assessment <math>&lt; 130</math> mEq/L (mmol/L), which will serve as the baseline value for final trial qualification and clinical management</p>

Location	Old Text	New Text
	be obtained within 2-4 hours prior to the first dose of trial medication.	strategy, is to be obtained within 2-4 hours prior to the first dose of trial medication. This assessment will also serve as the baseline value for secondary and exploratory endpoints.
<b>3.4 Eligibility Criteria:</b>	Eligible subjects must satisfy all informed consent requirements, as well as meet all inclusion and exclusion criteria. Subjects who do not meet all of these requirements are to be defined as screen failures and may rescreen, if eligible, at a later date.	Eligible subjects must satisfy all informed consent and assent requirements, as well as meet all inclusion and exclusion criteria. Subjects who do not meet all of these requirements are to be defined as screen failures and may rescreen, if eligible, at a later date.
<b>3.4.1 Informed Consent/Assent:</b>	<p><b>3.4.1 Informed Consent</b></p> <p>Written informed consent and assent as appropriate will be obtained from the subject's parent or legal guardian, in accordance with requirements of the trial center's institutional review board/independent ethics committee (IRB/IEC). The subject, as required by the trial center's IRB/IEC, must provide informed assent at Screening and as such must be able to understand that he or she can withdraw from the trial at any time.</p>	<p><b>3.4.1 Informed Consent/Assent</b></p> <p>Written informed consent and assent as appropriate will be freely obtained from the subject's parent or legal guardian, as applicable for local laws, in accordance with requirements of the trial center's institutional review board/independent ethics committee (IRB/IEC). The subject, as required by the trial center's IRB/IEC, must provide informed assent at Screening and as such must be able to understand that he or she can withdraw from the trial at any time.</p> <p>...Subjects' parents or legal guardian(s) may be asked to sign additional ICFs if the protocol is amended to significantly add or change procedures. Subjects who are able may be asked to re-assent as appropriate if the protocol is amended to significantly add or change procedures.</p>

**Old Text: Table 3.4.2-1 Inclusion Criteria**

Subjects are required to meet the following inclusion criteria:

<b>Table 3.4.2-1 Inclusion Criteria</b>	
1.	Male and female subjects $\geq$ 4 weeks (or $\geq$ 44 weeks adjusted gestational age for premature births) to $<$ 18 years old
2.	Subjects hospitalized with euvolemic or hypervolemic hyponatremia resistant to initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist) and who are deemed by the investigator as likely to benefit from a therapy that raises serum sodium levels
3.	Persistent euvolemic or hypervolemic hyponatremia defined as being documented as present for at least 48 hours, evidenced by at least 2 serum sodium assessments $<$ 130 mEq/L (mmol/L) drawn at least 12 hours apart (these values can be documented using historical values previously obtained per standard of care); a third (STAT) serum sodium assessment $<$ 130 mEq/L (mmol/L), which will serve as the baseline value for efficacy endpoints, is to be obtained within 2-4 hours prior to the first dose of tolvaptan
4.	Ability to take oral medication
5.	Ability to maintain adequate fluid intake whether orally or via IV support with adequate monitoring
6.	Ability to comply with all requirements of the trial
7.	Trial-specific written informed consent/assent obtained from a parent/guardian or legally acceptable representative, as applicable per age of subject or local laws, prior to the initiation of any protocol-required procedures. In addition, the subject as required by local laws must provide informed assent at Screening and must be able to understand that he or she can withdraw from the trial at any time. All informed consent/assent procedures must be in accordance with the trial center's IRB/IEC and local regulatory requirements
8.	Ability to commit to remain abstinent or practice double-barrier birth control during the trial and for 14 days following the last dose of IMP for sexually active females of childbearing potential

IMP = investigational medicinal product.

**New Text: Table 3.4.2-1 Inclusion Criteria**

Subjects are required to meet the following inclusion criteria:

<b>Table 3.4.2-1 Inclusion Criteria</b>	
1.	Male and female subjects $\geq$ 4 weeks (or $\geq$ 44 weeks adjusted gestational age for premature births) to $<$ 18 years old
2.	Subjects hospitalized with euvolemic or hypervolemic hyponatremia resistant to initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist) and who are deemed by the investigator as likely to benefit from a therapy that raises serum sodium levels
3.	Persistent euvolemic or hypervolemic hyponatremia defined as being documented as present for at least 48 hours, evidenced by at least 2 serum sodium assessments $<$ 130 mEq/L (mmol/L) drawn at least 12 hours apart (these values can be documented using historical values previously obtained per standard of care); a third (STAT) serum sodium assessment $<$ 130 mEq/L (mmol/L), which will serve as the baseline value for final trial qualification and clinical management strategy, is to be obtained within 2-4 hours prior to the first dose of tolvaptan
4.	Ability to take oral medication
5.	Ability to maintain adequate fluid intake whether orally or via IV support with adequate monitoring
6.	Ability to comply with all requirements of the trial
7.	Trial-specific written informed consent/assent obtained from a parent/guardian or legally acceptable representative, as applicable per age of subject or local laws, prior to the initiation of any protocol-required procedures. In addition, the subject as required by local laws must provide informed assent at Screening and must be able to understand that he or she can withdraw from the trial at any time. All informed consent/assent procedures must be in accordance with the trial center's IRB/IEC and local regulatory requirements
8.	Ability to commit to remain fully abstinent (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] or withdrawal are not acceptable methods of contraception) or practice double-barrier birth control during the trial and for 30 days following the last dose of IMP for sexually active females of childbearing potential

IMP = investigational medicinal product.

**Old Text: Table 3.4.3-1 Exclusion Criteria**

Subjects will be excluded if they meet any of the following exclusion criteria prior to trial entry.

**Table 3.4.3-1 Exclusion Criteria**

3.	Use of potent CYP3A4 inhibitors in subjects $\leq$ 50 kg or moderate CYP3A4 inhibitors in subjects $<$ 20 kg
25.	Subjects $<$ 2 years of age, weight $<$ 10 kg, or who cannot swallow an oral tablet are excluded until an oral suspension formulation becomes available

**New Text: Table 3.4.3-1 Exclusion Criteria**

Subjects will be excluded if they meet any of the following exclusion criteria prior to trial entry.

**Table 3.4.3-1 Exclusion Criteria**

3.	Current use or expected use during the trial of a potent CYP3A4 inhibitor in subjects weighing $<$ 10 kg or a moderate CYP3A4 inhibitor in subjects weighing $<$ 6 kg
25.	Subjects who weigh $<$ 3 kg
26.	Unable to swallow tablets if the suspension formulation is unavailable

Use of the suspension formulation is at the discretion of the local regulatory authorities and IRB/IECs. In such cases, subjects who require use of suspension for either standard dosing or adjusted dosing (eg, concomitant use of CYP3A4 inhibitors) cannot be enrolled.

Location	Old Text	Updated Text
<b>3.7 Trial Procedures:</b>	<p>In Treatment Phase A, subjects who meet the inclusion and exclusion criteria will be enrolled and will be administered a 3.75-, 7.5-, or 15-mg dose tablet based on age, weight, and the use of CYP3A4 inhibitors. At the end of Day 2 (or 2a) in Treatment Phase A, subjects who are responders will be randomized to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early Withdrawal).</p> <p>In Treatment Phase B, subjects who are nonresponders may continue on tolvaptan therapy for 2 additional days or may be withdrawn from tolvaptan to be treated per the investigator's preferred standard of care. During Treatment Phase B, subjects in the Late Withdrawal group and nonresponders continuing treatment will continue to receive tolvaptan for 2 additional days and all subjects will have serum sodium levels measured at 12 (<math>\pm</math> 4) hours post-dose and at trough each day. Subjects in the Early Withdrawal group should be monitored for the first 48 hours post-last dose.</p>	<p>In Treatment Phase A, subjects who meet the inclusion and exclusion criteria will be enrolled and will be administered tolvaptan doses based on age, weight, ability to swallow a tablet, and the use of CYP3A4 inhibitors. At the end of Day 2 (or 2a) in Treatment Phase A, subjects who are responders will be randomized to either continue treatment with tolvaptan for 2 additional days (Late Withdrawal) or to discontinue tolvaptan treatment (Early Withdrawal).</p> <p>In Treatment Phase B, subjects who are nonresponders may continue on tolvaptan therapy for 2 additional days or may be withdrawn from tolvaptan to be treated per the investigator's preferred standard of care. During Treatment Phase B, subjects in the Late Withdrawal group and nonresponders continuing treatment will continue to receive tolvaptan for 2 additional days and all subjects will have serum sodium levels measured at 12 (<math>\pm</math> 4) hours postdose and at trough each day. Subjects in the Early Withdrawal group should be monitored for the first 48 hours post-last dose.</p>

**Old Text: Table 3.7-1 Schedule of Assessments**

Procedures	Screening	Treatment Phase A			Treatment Phase B			Follow-up Phase C			
	Day -2 and -1	Day 1	Day 2	Day 2a (optional)	Day 3	Day 4	Day 5	72 ( $\pm 4$ ) h post last dose	7 ( $\pm 1$ ) days post-last dose	14 (+2) days post-last dose	Early Termination (ET)
Informed Consent/Assent	X										
Inclusion/exclusion criteria <sup>a</sup>	X	X									
Demographic information	X										
Medical and hyponatremia history	X										
Vital signs <sup>b</sup>	X	X	X	X	X	X	X	X	X		X
12-lead ECG	X										
Height	X										
Body weight <sup>c</sup>	X	X	X	X	X	X	X	X	X		X
Directed physical examination	X	X	X	X	X	X		X	X		X
Tanner staging	X										
Neurological examination	X	X	X		X	X		X	X		X
Neurocognitive assessment <sup>d</sup>	X	X	X	X	X	X	X	X	X		X
Quality of life assessment	X					X			X		
Clinical status assessment <sup>e</sup>	X	X	X	X	X	X		X	X		X
Alcohol/drug screen	X										
Pregnancy test (if applicable) <sup>f</sup>	X										
Fluid intake <sup>g</sup>		X	X								
Urine volume <sup>g</sup>		X	X								

**Table 3.7-1 Schedule of Assessments**

Procedures	Screening	Treatment Phase A			Treatment Phase B			Follow-up Phase C			
	Day -2 and -1	Day 1	Day 2	Day 2a (optional)	Day 3	Day 4	Day 5	72 (±4) h post last dose	7 (±1) days post-last dose	14 (+2) days post-last dose	Early Termination (ET)
Urinalysis	X							X			X
Urine chemistry <sup>g,h</sup>	X	X	X								
Serum sodium <sup>i</sup>	X	X	X	X	X	X	X	X			X
Hematology, coagulation, and serum chemistry <sup>j</sup>	X							X			X
Serum osmolality, FENa, and FE urate	X										
TSH and cortisol <sup>k</sup>	X										
PK plasma samples <sup>l</sup>		X	X		X	X	X				X
Tolvaptan dosing <sup>m</sup>		X	X	X	X	X					
Assessment for response to tolvaptan			X	X							
Palatability assessment			X								
Randomization					X						
Follow-up phone call or visit										X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

ECG = electrocardiogram; TSH = thyroid-stimulating hormone.

<sup>a</sup>Inclusion/exclusion criteria will be checked at screening and predose on Day 1.

<sup>b</sup>Vital signs to be assessed include supine blood pressure, heart rate, respiratory rate, and temperature. Vital signs should be assessed prior to any blood draws.

<sup>c</sup>Weight will be taken predose as possible.

<sup>d</sup>Neurocognitive assessments are closely tied to serum sodium assessments and should be done within 1 hour of sodium blood draws.

<sup>e</sup>Clinical status assessments will be performed per inpatient standard of care, ie, review patient chart entries (including hyponatremia assessment notes and laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate overall subject eligibility in terms of hyponatremia state.

<sup>f</sup>Urine pregnancy tests will be performed on female subjects  $\geq$  12 years of age and all female subjects  $<$  12 years of age if menstruation has started.

<sup>g</sup>Intervals starting immediately after dosing at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).

<sup>h</sup>Samples within a collection interval are to be refrigerated and pooled. An aliquot for urine chemistry tests will be taken for each collection interval. Uric acid is to be measured at screening only.

<sup>i</sup>Serum sodium assessments are closely tied to neurocognitive assessments, dosing time points and PK blood draws.

- Screening: 2 assessments should be taken, at least 12 hours apart (may be part of medical history). 1 assessment can be combined with the serum chemistry panel.
- Treatment Phase A: Baseline [STAT] assessment will be at 2-4 hours prior to first dose. Post-first dose assessments: 8 and 24 (trough) hours. Then every 12 hours thereafter (alternating 12 hours post-dose and at trough)
- Treatment Phase B: Assessments to be taken every 12 hours (alternating 12 hours post-dose and at trough)
- Treatment Phase C: Assessments to be taken at 72 ( $\pm$  4) hours post-last dose (can be combined with the serum chemistry panel) and at the 7 day post-last dose visit.

<sup>j</sup>Serum chemistry panel includes serum sodium and assessments can be combined for visits where both assessments are indicated.

<sup>k</sup>Results of these tests will further characterize hyponatremia etiology for the Hyponatremia History CRF and are not required to determine eligibility.

Subjects who have clinically relevant TSH or cortisol levels may not respond properly to tolvaptan and will be withdrawn from the trial.

<sup>l</sup>PK samples are closely tied to dosing time points and serum sodium assessments. An ET sample will be collected only if ET is before the last scheduled PK assessment.

- In Treatment Phase A PK samples should be collected at 2 and 8 hours and at trough post-first dose.
- In Treatment Phase B PK will be assessed in subjects continuing treatment with tolvaptan (Late Withdrawal group and nonresponders continuing on tolvaptan) at trough on Days 3, 4 and 5.

<sup>m</sup>The tolvaptan dose will be titrated based on serum sodium levels as described in [Section 3.2.4](#).

**NewText: Table 3.7-1 Schedule of Assessments**

Procedures	Screening	Treatment Phase A			Treatment Phase B			Follow-up Phase C			
	Day -2 and -1	Day 1	Day 2	Day 2a (optional)	Day 3	Day 4	Day 5	72 ( $\pm 4$ ) h post last dose	7 ( $\pm 1$ ) days post-last dose	14 (+2) days post-last dose	Early Termination (ET)
Informed Consent/Assent	X										
Inclusion/exclusion criteria <sup>a</sup>	X	X									
Demographic information	X										
Medical and hyponatremia history	X										
Vital signs <sup>b</sup>	X	X	X	X	X	X	X	X	X		X
12-lead ECG	X										
Height	X										
Body weight <sup>c</sup>	X	X	X	X	X	X	X	X	X		X
Physical examination	X <sup>d</sup>	X	X	X	X	X		X	X		X
Tanner staging	X										
Neurological examination	X	X	X		X	X		X	X		X
Neurocognitive assessment <sup>e</sup>	X	X	X	X	X	X	X	X	X		X
Quality of life assessment	X					X			X		
Clinical status assessment <sup>f</sup>	X	X	X	X	X	X		X	X		X
Alcohol/drug screen	X										
Pregnancy test (if applicable) <sup>g</sup>	X								X		
Fluid intake <sup>h</sup>		X	X								
Urine volume <sup>h</sup>		X	X								
Urinalysis	X							X			X

**Table 3.7-1 Schedule of Assessments**

Procedures	Screening	Treatment Phase A			Treatment Phase B			Follow-up Phase C			
	Day -2 and -1	Day 1	Day 2	Day 2a (optional)	Day 3	Day 4	Day 5	72 (±4) h post last dose	7 (±1) days post-last dose	14 (+2) days post-last dose	Early Termination (ET)
Urine chemistry <sup>h,i</sup>	X	X	X								
Serum sodium <sup>j</sup>	X	X	X	X	X	X	X	X	X		X
Hematology, coagulation, and serum chemistry <sup>k</sup>	X							X			X
Serum osmolality, FENa, and FE urate	X										
TSH and cortisol <sup>l</sup>	X										
PK plasma samples <sup>m</sup>		X	X		X	X	X				X
Tolvaptan dosing <sup>n</sup>		X	X	X	X	X					
Swallow test	X <sup>o</sup>										
Assessment for response to tolvaptan			X	X							
Palatability and acceptability assessment			X								
Randomization					X						
Follow-up phone call or visit										X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

ECG = electrocardiogram; TSH = thyroid-stimulating hormone.

<sup>a</sup>Inclusion/exclusion criteria will be checked at screening and predose on Day 1.<sup>b</sup>Vital signs to be assessed include supine blood pressure, heart rate, respiratory rate, and temperature. Vital signs should be assessed prior to any blood draws.<sup>c</sup>Weight will be taken predose as possible.

<sup>d</sup>The initial physical examination should be a full physical. Subsequent physical examinations can be directed physical examinations that are focused on hyponatremia-related signs and symptoms as well as any major changes from baseline.

<sup>e</sup>Neurocognitive assessments are closely tied to serum sodium assessments and should be done within 1 hour of sodium blood draws.

<sup>f</sup>Clinical status assessments will be performed per inpatient standard of care, ie, review patient chart entries (including hyponatremia assessment notes and laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate overall subject eligibility in terms of hyponatremia state. Volume status will be assessed every 6 hours prior to trial entry and every 6 hours during Treatment Phase A.

<sup>g</sup>Pregnancy tests will be performed on female subjects  $\geq$  12 years of age and all female subjects  $<$  12 years of age if menstruation has started.

<sup>h</sup>Intervals starting immediately after dosing at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).

<sup>i</sup>Samples within a collection interval are to be refrigerated and pooled. An aliquot for urine chemistry tests will be taken for each collection interval. Uric acid is to be measured at screening only.

<sup>j</sup>Serum sodium assessments are closely tied to neurocognitive assessments, dosing time points and PK blood draws.

- Screening: 2 assessments should be taken, at least 12 hours apart (may be part of medical history). One assessment can be combined with the serum chemistry panel.
- Treatment Phase A: Baseline [STAT] assessment will be at 2-4 hours prior to first dose. Post-first dose assessments: 8 and 24 (trough) hours. Then every 12 hours thereafter (alternating 12 hours postdose and at trough)
- Treatment Phase B: Assessments to be taken every 12 hours (alternating 12 hours postdose and at trough)
- Treatment Phase C: Assessments to be taken at 72 ( $\pm$  4) hours post-last dose (can be combined with the serum chemistry panel) and at the 7 day post-last dose visit.

In addition to serum sodium samples obtained for trial qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point of care sodium assessment unit, where available, on Day 1 at 4 to 6 hours postdose and at 18 hours postdose, and on Day 2 (and Day 2a, if applicable) at 6 hours postdose as well as at 18 hours postdose. A point of care assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs).

<sup>k</sup>Serum chemistry panel includes serum sodium and assessments can be combined for visits where both assessments are indicated.

<sup>l</sup>Results of these tests will further characterize hyponatremia etiology for the Hyponatremia History CRF and are not required to determine eligibility.

Subjects who have clinically relevant TSH or cortisol levels may not respond properly to tolvaptan and will be withdrawn from the trial.

<sup>m</sup>PK samples are closely tied to dosing time points and serum sodium assessments. An ET sample will be collected only if ET is before the last scheduled PK assessment.

- In Treatment Phase A PK samples should be collected at 2 and 8 hours and at trough post-first dose.
- In Treatment Phase B PK will be assessed in subjects continuing treatment with tolvaptan (Late Withdrawal group and nonresponders continuing on tolvaptan) at trough (24 hours post last dose, immediately prior to next dose) on Days 3, 4 and 5.

<sup>n</sup>The tolvaptan dose will be titrated based on serum sodium levels as described in [Section 3.2.4](#).

<sup>o</sup>Optional swallow test for subjects who are known or suspected to be unable to swallow tablets, at the investigator's discretion.

Location	Old Text	Updated Text
<b>3.7.1.1 Screening:</b>	<p>A directed physical examination will be performed.</p> <p>Tanner staging will be performed.</p> <p>A neurocognitive assessment will be performed, as appropriate by age and where available.</p> <p>Quality-of-life (QoL) assessment will be performed, as appropriate by age and where available.</p> <p>Clinical status assessments will be performed per inpatient standard of care.</p> <p>Alcohol and drug screens will be performed, as age appropriate.</p> <p>A urine pregnancy test will be performed on all female subjects <math>\geq 12</math> years of age and all female subjects <math>&lt; 12</math> years of age if menstruation has started.</p> <p>Urinalysis and urine chemistry laboratory samples will be collected for analysis.</p> <p>Two blood samples for serum sodium testing will be collected at least 12 hours apart and can be part of the recent medical history to document chronic hyponatremia. (One of these blood draws can be combined with the serum chemistry panel as appropriate to minimize blood draws.)</p> <p>Hematology, coagulation, and serum chemistry laboratory samples will be collected for analysis.</p>	<p>A full physical examination will be performed. The initial physical examination should be a full physical. Subsequent physical examinations can be directed physical examinations that are focused on hyponatremia-related signs and symptoms as well as any major changes from baseline.</p> <p>Tanner staging will be performed.</p> <p>A neurocognitive assessment will be performed, as appropriate by age and where available and should be done within 1 hour of serum sodium blood draw.</p> <p>Quality-of-life (QoL) assessment will be performed, as appropriate by age and where available.</p> <p>Clinical status assessments will be performed per inpatient standard of care.</p> <p>Alcohol and drug screens will be performed, as age appropriate.</p> <p>A pregnancy test will be performed on all female subjects <math>\geq 12</math> years of age and all female subjects <math>&lt; 12</math> years of age if menstruation has started.</p> <p>Urinalysis and urine chemistry laboratory samples will be collected for analysis.</p> <p>Two blood samples for serum sodium testing will be collected at least 12 hours apart and can be part of the recent medical history to document chronic hyponatremia. (One of these blood draws can be</p>

Location	Old Text	Updated Text
	<p>Serum osmolality, FENa, and FE urate will be determined.</p> <p>Thyroid-stimulating hormone (TSH) and cortisol blood samples will be collected to determine possible need for alternate mode of therapy.</p> <p>Concomitant medications will be recorded.</p> <p>Adverse events will be recorded.</p>	<p>combined with the serum chemistry panel as appropriate to minimize blood draws.)</p> <p>Hematology, coagulation, and serum chemistry laboratory samples will be collected for analysis.</p> <p>Serum osmolality, FENa, and FE urate will be determined.</p> <p>Thyroid-stimulating hormone (TSH) and cortisol blood samples will be collected to determine possible need for alternate mode of therapy.</p> <p>Concomitant medications will be recorded.</p> <p>Adverse events will be recorded.</p> <p>Optional swallow test for subjects who are known or suspected to be unable to swallow tablets, at the investigator's discretion.</p> <p>Placebo tablets will be provided for use in performing this test at screening.</p>
<b>3.7.1.2.1 Day 1:</b>	16) A neurological examination will be performed at 8 hours post-first dose.	<p>A neurological examination will be performed at 8 hours post-first dose.</p> <p>In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point of care sodium assessment unit, where available, on Day 1 at 4 to 6 hours postdose and at 18 hours postdose. This sodium safety assessment will be repeated at 6 and 18 hours postdose each day for the remainder of titration. A point of care assessment unit is preferred; however, regular blood draws may be used (especially if</p>

Location	Old Text	Updated Text
3.7.1.2.2 Day 2:	<p>Postdose</p> <p>Assess palatability of tolvaptan tablets for subjects.</p> <p>Fluid intake will be recorded at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).</p> <p>Urine will be collected at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours). Subjects should be asked to void just prior to the end time of each collection interval, as possible.</p> <p>Urine volume will be determined from urine voids made during the 6-hour collection intervals which will be pooled prior to determination of final volume.</p> <p>A urine chemistry sample will be collected and assessed from each 6-hour volume interval starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).</p> <p>Clinical status assessments will be performed per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.</p> <p>A blood sample will be collected for serum sodium testing at 12 hours post-dose.</p>	<p>Postdose</p> <p>Assess palatability and acceptability of tolvaptan dose for subjects.</p> <p>Fluid intake will be recorded at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).</p> <p>Urine will be collected at 6-hour intervals starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours). Subjects should be asked to void just prior to the end time of each collection interval, as possible.</p> <p>Urine volume will be determined from urine voids made during the 6-hour collection intervals which will be pooled prior to determination of final volume.</p> <p>A urine chemistry sample will be collected and assessed from each 6-hour volume interval starting at Hour 0 (0-6, 6-12, 12-18, and 18-24 hours).</p> <p>Clinical status assessments will be performed per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.</p> <p>A blood sample will be collected for serum sodium testing at 12 hours postdose.</p> <p>In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point</p>

Location	Old Text	Updated Text
		of care sodium assessment unit, where available, at 6 and 18 hours postdose. A point of care assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs).
<b>3.7.1.2.3 Day 2a (optional):</b>	<p><u>Postdose</u></p> <p>7) Clinical status assessments will be performed per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.</p> <p>8) A blood sample will be collected for serum sodium testing at 12 hours postdose.</p>	<p><u>Postdose</u></p> <p>Clinical status assessments will be performed per inpatient standard of care, ie, patient chart entries will be reviewed (including hyponatremia assessment notes, including laboratory results [trial and nontrial specific], any examination findings, medical problem list changes, and fluid intake and output) to evaluate the subject's hyponatremia state.</p> <p>A blood sample will be collected for serum sodium testing at 12 hours postdose.</p> <p>In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point of care sodium assessment unit, where available, at 6 and 18 hours postdose. A point of care assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs).</p>
<b>3.7.1.4.2 7 Days Post-last Dose:</b>	<p>1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq</math> 3 minutes. Vital signs should be performed prior to blood draws.</p> <p>2) A blood sample for serum sodium testing will be collected.</p>	<p>11) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for <math>\geq</math> 3 minutes. Vital signs should be performed prior to blood draws.</p> <p>12) A blood sample for serum sodium testing will be collected.</p> <p>13) A pregnancy test will be performed on all female subjects</p>

Location	Old Text	Updated Text
	<p>3) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</p>	<p><math>\geq 12</math> years of age and all female subjects <math>&lt; 12</math> years of age if menstruation has started.</p> <p>14) A neurocognitive assessment will be performed within 1 hour of the serum sodium sample.</p>
<b>3.7.2.1 Serum Sodium Concentrations:</b>	<p>Monitoring frequency of serum sodium is at the discretion of the clinical investigator; however, the minimum sample collection required for all subjects is described in <a href="#">Section 3.7.1</a>.</p> <p>In order to qualify for this trial, subjects must have documentation of chronic dilutional hyponatremia (serum sodium <math>&lt; 130</math> mEq/L [mmol/L]) that is present for <math>\geq 48</math> hours. Specifically, each subject must have 2 blood samples collected at least 12 hours apart over a minimum of 48 hours for assessment of baseline serum sodium level to determine subject eligibility. These can be either part of the recent medical history concerning the current hospital stay or prospectively collected as part of this trial.</p> <p>On Day 1, a third (STAT) serum sodium sample should be drawn within 2-4 hours prior to dosing; the results must be verified to be <math>&lt; 130</math> mmol/L prior to the first dose. Serum sodium assessments should be performed at 8 hours post-first dose and at trough 24 hours post-first dose (this assessment will fall on Day 2 predose).</p> <p>On Day 2 (or 2a), Day 3, and Day 4 (through the following morning on Day 5):</p> <p>For all subjects receiving tolvaptan (Late Withdrawal and Nonresponders continuing on tolvaptan) serum sodium assessments will be performed at trough and 12 hours post-dose each day during Treatment Phase A and Treatment Phase B.</p>	<p>Monitoring frequency of serum sodium is at the discretion of the clinical investigator; however, the minimum sample collection required for all subjects is described in <a href="#">Section 3.7.1</a> and <a href="#">Section 3.7.4.2.1</a>.</p> <p>In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point of care sodium assessment unit, where available, on Day 1 at 4 to 6 hours postdose and at 18 hours postdose. This sodium safety assessment will be repeated at 6 and 18 hours postdose each day for the remainder of titration. A point of care assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs).</p> <p>In order to qualify for this trial, subjects must have documentation of chronic dilutional hyponatremia (serum sodium <math>&lt; 130</math> mEq/L [mmol/L]) that is present for <math>\geq 48</math> hours. Specifically, each subject must have 2 blood samples collected at least 12 hours apart over a minimum of 48 hours for assessment of baseline serum sodium level to determine subject eligibility. These can be either part of the recent medical history concerning the current hospital stay or prospectively collected as part of this trial.</p> <p>On Day 1, a third (STAT) serum sodium sample should be drawn within 2-4 hours prior to dosing; the results must be verified to be <math>&lt; 130</math> mmol/L prior to the first dose. Serum sodium assessments</p>

Location	Old Text	Updated Text
	<p>For all subjects not receiving tolvaptan (Early Withdrawal and Nonresponders on standard of care) serum sodium assessments will be performed every 12 hours throughout Treatment Phase A and Treatment Phase B.</p> <p>For all subjects final serum sodium assessments will be taken at 24 (<math>\pm 4</math>) and 72 (<math>\pm 4</math>) hours post-last dose as well as at 7 days post-last dose.</p> <p>Additional unscheduled serum sodium assessments may be performed at the discretion of the clinical investigator and other physicians of record, depending on the local standards and subject's clinical condition. All serum sodium concentrations collected as part of standard of care will be reported as unscheduled sodium assessments in the electronic CRF through the follow-up sodium assessments.</p>	<p>should be performed at 8 hours post-first dose and at trough 24 hours post-first dose (this assessment will fall on Day 2 predose).</p> <p>On Day 2 (or 2a), Day 3, and Day 4 (through the following morning on Day 5):</p> <ul style="list-style-type: none"> <li>– For all subjects receiving tolvaptan (Late Withdrawal and Nonresponders continuing on tolvaptan) serum sodium assessments will be performed at trough and 12 hours postdose each day during Treatment Phase A and Treatment Phase B.</li> <li>– For all subjects not receiving tolvaptan (Early Withdrawal and Nonresponders on standard of care) serum sodium assessments will be performed every 12 hours throughout Treatment Phase A and Treatment Phase B.</li> </ul> <p>For all subjects final serum sodium assessments will be taken at 24 (<math>\pm 4</math>) and 72 (<math>\pm 4</math>) hours post-last dose as well as at 7 days post-last dose.</p>
3.7.3.1 Blood Collection Times:	<p>Blood samples will be taken so that tolvaptan and metabolite concentrations can be determined. Samples will be taken on Day 1 at 2 hours (<math>\pm 5</math> minutes) and 8 hours (concurrent with 8 h serum sodium sample) post-first dose. On Days 2, 3, 4 and 5 samples will be taken at trough (24 hours post previous dose but prior to the subsequent dose), concurrent with serum sodium samples, for subjects dosed with tolvaptan on Days 1, 2, 3, and/or 4, respectively, regardless of status as responder/non-responder. An early termination (ET) sample will be taken if ET occurs prior to the last planned PK sample. No ET sample is required if ET</p>	<p>Blood samples will be taken so that tolvaptan and metabolite concentrations can be determined. Samples will be taken at the following times:</p> <p>On Day 1 at 2 hours (<math>\pm 5</math> minutes) and 8 hours (concurrent with 8 h serum sodium sample) post-first dose.</p> <p>On Days 2, 3, 4 and 5 samples will be taken at trough (prior to the subsequent dose), concurrent with serum sodium samples, for subjects dosed with tolvaptan on Days 1, 2, 3, and/or 4, respectively, regardless of status as responder/non-responder.</p>

Location	Old Text	Updated Text
	<p>occurs at the same visit where a PK sample has already been obtained.</p> <p>For each PK blood sample collected volumes are not expected to exceed 1.2 mL. Total volume per sample may be lower depending on finalization of blood collection supplies.</p> <p>Serum sodium assessments and other clinically necessary blood samples take priority, therefore, due to restrictions in allowable total daily blood volumes based on local guidelines and subject age, it may not be possible to take more than one PK sample per day. If so, the PK sampling should be changed to:</p> <p>Day 1: 2 hours post dose (<math>\pm</math> 5 minutes)</p> <p>Day 2: 8 (<math>\pm</math> 2) hours post dose (may be concurrent with serum sodium or other blood sampling)</p> <p>Day 3 at trough, ie, pre-dose/24 hours post prior dose (concurrent with serum sodium sample)</p>	<p>An early termination (ET) sample will be taken if ET occurs prior to the last planned PK sample. No ET sample is required if ET occurs at the same visit where a PK sample has already been obtained.</p> <p>For each PK blood sample collected volumes are not expected to exceed 1.2 mL. Total volume per sample may be lower depending on finalization of blood collection supplies.</p> <p>Serum sodium assessments and other clinically necessary blood samples take priority, therefore, due to restrictions in allowable total daily blood volumes based on local guidelines and subject age, it may not be possible to take more than one PK sample per day. If so, the PK sampling should be changed to:</p> <p>Day 1: 2 hours postdose (<math>\pm</math> 5 minutes)</p> <p>Day 2: 8 (<math>\pm</math> 2) hours postdose (may be concurrent with serum sodium or other blood sampling)</p> <p>Day 3 at trough, ie, predose/24 hours post prior dose (concurrent with serum sodium sample)</p>
<b>3.7.3.2.4 Palatability and Acceptability Assessment:</b>	<p>New section for this amendment</p>	<p>A questionnaire will be administered once to assess palatability to rate flavor/taste, smell, sweetnees, and overall liking of the study medication immediately after dosing. Subjects will also be asked about the ease of swallowing the study medication. Between 15 to 20 minutes after dosing, subjects will be asked again about overall liking of the study medication. This assessment will only be done in subjects aged 3 years to 18 years.</p>
<b>3.7.4 Safety Assessments:</b>	<p>The monitoring frequency of safety assessments is at the</p>	<p>The monitoring frequency of safety assessments is at the discretion</p>

Location	Old Text	Updated Text
	discretion of the clinical investigator; however, the trial requires the minimum sample collection for all subjects noted in <a href="#">Section 3.7.1</a> .	of the clinical investigator; however, the trial requires the minimum sample collection for all subjects noted in <a href="#">Section 3.7.1</a> and <a href="#">Section 3.7.4.2.1</a> .
<b>3.7.4.2.1 Serum Sodium:</b>	New section for this amendment	<p>In addition to serum sodium samples obtained for trial qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only can be obtained using a point of care sodium assessment unit, where available, on Day 1 at 4 to 6 hours postdose and at 18 hours postdose. This sodium safety assessment will be repeated at 6 and 18 hours postdose each day for the remainder of Treatment Phase A. A point of care assessment unit is preferred since it is expected to reduce overall daily blood volume needed for assessments (expected 0.5 mL for regular blood draws versus up to several drops for a point of care assessment, depending on the device used); however, regular blood draws may be used (especially if they can be combined with standard of care labs).</p> <p>Additional unscheduled serum sodium assessments may be performed at the discretion of the clinical investigator and other physicians of record, depending on the local standards and subject's clinical condition. All unscheduled serum sodium concentrations collected as part of standard of care will be reported as unscheduled sodium assessments in the electronic CRF through the follow-up sodium assessments.</p>
3.7.4.2.3 Clinical Lab Tests:	<p><a href="#">Table 3.7.4.2-1</a> presents required clinical laboratory assessments (serum chemistry, hematology, coagulation, urinalysis, and urine chemistry). All clinical laboratory tests will be performed by local laboratories. Serum cortisol and TSH will be measured during screening using the remaining blood sample obtained for</p>	<p><a href="#">Table 3.7.4.2-1</a> presents required clinical laboratory assessments (serum chemistry, hematology, coagulation, urinalysis, and urine chemistry). All clinical laboratory tests will be performed by local laboratories. Serum cortisol and TSH will be measured during screening using the remaining blood sample obtained for serum</p>

Location	Old Text	Updated Text
	<p>serum chemistry. If these results are obtained as part of the standard of care for the subject, a trial-specific sample should be obtained and sent to the local laboratory for analysis per the schedule of assessments (<a href="#">Section 3.7.1</a>). Uric acid will be measured during screening for calculation of FENa and FE urate.</p>	<p>chemistry. If these results are obtained as part of the standard of care for the subject, a trial-specific sample should be obtained and sent to the local laboratory for analysis per the schedule of assessments (<a href="#">Section 3.7.1</a>). Uric acid will be measured during screening for calculation of FENa and FE urate.</p> <p>It is recognized that there may be limitations based on age and weight of children for the amount of blood that can be drawn at a single time point, per day, and the overall conduct of the trial. Wherever possible, it is encouraged to combine standard of care samples that would be taken regardless of trial participation with those samples required for the trial.</p> <p>In case of limited blood or urine volume availability, the bolded assessments in <a href="#">Table 3.7.4.2.3-1</a> take priority. Serum sodium and liver function tests are essential to the conduct of the trial.</p>
<p><b>Table 3.7.4.2.3-1</b>  <b>Clinical</b>  <b>Laboratory Tests</b>  <b>to be Performed</b>  <b>Locally:</b></p>	<p><b>Urobilinogen</b>  <u><b>Additional Test:</b></u>  <b>Urine pregnancy</b> (if applicable)</p>	<p>Urobilinogen  <u><b>Additional Test:</b></u>  <b>Serum or urine pregnancy test</b> (if applicable)</p>
<p><b>3.7.4.3 Physical Examination:</b></p>	<p>Directed physical examinations will be performed and documented according to the schedule of assessments (<a href="#">Section 3.7.1</a>).</p> <p>The principal investigator or his/her appointed designee is primarily responsible to perform the physical examination. If the appointed designee is to perform the physical examination, he/she must be permitted by local regulations. Whenever</p>	<p>Directed physical examinations will be performed and documented according to the schedule of assessments (<a href="#">Section 3.7.1</a>). The initial physical examination should be a full physical. Subsequent physical examinations can be directed physical examinations that are focused on hyponatremia-related signs and symptoms as well as any major changes from baseline.</p> <p>The principal investigator or his/her appointed designee is primarily</p>

Location	Old Text	Updated Text
	<p>possible, the same individual should perform all physical examinations for a given subject. Any condition present at the post-treatment directed physical examination that was not present at Screening should be documented as an AE and followed to a satisfactory conclusion.</p> <p>All physical examination assessments should include assessments of all major body systems, including but not limited to, ears, nose, and throat, the thorax area, abdomen, urogenital, extremities, and skin and mucosae. Neurological examinations will be performed in an age-appropriate manner per <a href="#">Section 3.7.4.3.1</a>.</p>	<p>responsible to perform the physical examination. If the appointed designee is to perform the physical examination, he/she must be permitted by local regulations. Whenever possible, the same individual should perform all physical examinations for a given subject. Any condition present at the post-treatment directed physical examination that was not present at Screening should be documented as an AE and followed to a satisfactory conclusion.</p> <p>All full physical examination assessments should include assessments of all major body systems, including but not limited to, ears, nose, and throat, the thorax area, abdomen, urogenital, extremities, and skin and mucosae. Neurological examinations will be performed in an age-appropriate manner per <a href="#">Section 3.7.4.3.1</a>.</p>
3.7.4.8 Volume Status Assessment:	New section for this amendment	Volume status will be assessed every 6 hours prior to trial entry and every 6 hours during Treatment Phase A.
<b>3.9 Screen Failures:</b>	...Subjects who are deemed screen failures may be rescreened for possible participation at a later date if no randomization number has been assigned. Subjects who receive a randomization number may not be rescreened regardless of whether they receive trial medication.	...Subjects who are deemed screen failures may be rescreened for possible participation if they have not taken a dose of IMP.
<b>4.1 Prohibited Medications:</b>	Continuous or short term use of other medications, while not prohibited, may be restricted by the investigator because of their potential for interference with tolvaptan metabolism. Since tolvaptan is a sensitive CYP3A4 substrate, subjects weighing $\geq$ 20 kg and taking moderate inhibitors of CYP3A4 will be administered half of their regular dose of tolvaptan. For subjects weighing $>$ 50 kg and taking potent CYP3A4 inhibitors, with the	Continuous or short term use of other medications, while not prohibited, may be restricted by the investigator because of their potential for interference with tolvaptan metabolism. Tolvaptan is a sensitive CYP3A4 substrate; plasma concentrations increased approximately 4-fold when tolvaptan was administered with the potent CYP3A4 inhibitor ketoconazole. <sup>16,24</sup> Where appropriate dose reductions are possible, tolvaptan doses may be

Location	Old Text	Updated Text
	<p>exception of amiodarone, which was previously found to have no effect on tolvaptan, a one-quarter dose will be used (3.75 mg). Moderate and potent CYP3A4 inhibitors are not allowed for subjects weighing &lt; 20 and <math>\leq</math> 50 kg, respectively.<sup>16,24</sup> A partial list of CYP3A4 inhibitors is provided in <a href="#">Table 4.1-1</a>.</p>	<p>coadministered with potent or moderate CYP3A4 inhibitors (see Section <a href="#">2.1.1</a> and Table <a href="#">2.2.2-1</a>).</p> <p>A partial list of CYP3A4 inhibitors is provided in <a href="#">Table 4.1-1</a>.</p>
4.2 Other Restrictions:	<p>The use of saline in this population should be closely monitored. The use of hypertonic saline (3%), including normal saline challenge) within 8 hours of the qualifying screening serum sodium laboratory assessment is prohibited.</p>	<p>The use of saline in this population should be closely monitored. The use of hypertonic saline (3%), including normal saline challenge within 8 hours of the qualifying screening serum sodium laboratory assessment is prohibited. The use of hypertonic saline (3% or greater) is prohibited during tolvaptan treatment. Routine use of hypertonic saline, while prohibited, may be considered only if used emergently (ie, with a severe symptomatic episode) and with the understanding that free water clearance may be stimulated if tolvaptan had been administered in the prior 24 hours, based on the medical judgment of the investigator.</p>
5.5 Pregnancy:	<p>Female subjects of childbearing potential who are sexually active must use an effective method of birth control during the course of the trial and for 14 days after the last dose of IMP in a manner such that risk of failure is minimized. Unless the subject or her partner(s) is sterile (ie, female subjects who have had an oophorectomy and/or hysterectomy; or male partners who have had orchiectomy) or remain abstinent, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom, or sponge with spermicide. Any single method of birth control, including</p>	<p>Women of childbearing potential (WOCBP) are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months).</p> <p>For WOCBP who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been</p>

Location	Old Text	Updated Text
	<p>vasectomy and tubal ligation, may fail, leading to pregnancy.</p> <p>Before enrolling female subjects of childbearing potential in this clinical trial, investigators must review guidelines about trial participation for female subjects of childbearing potential. The topics should generally include:</p> <ul style="list-style-type: none"> <li>General information</li> <li>ICF/assent form, as applicable</li> <li>Pregnancy prevention information</li> <li>Drug interactions with hormonal contraceptives</li> <li>Contraceptives in current use</li> <li>Guidelines for the follow-up of a reported pregnancy</li> </ul> <p>Prior to trial enrollment, female subjects of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject's parent or legal guardian must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed with the subject and parent/guardian.</p> <p>During the trial, all female subjects of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).</p> <p>If a subject or investigator suspects that the subject may be</p>	<p>postmenopausal for at least 12 consecutive months) or remains fully abstinent (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] or withdrawal are not acceptable methods of contraception), two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, condom with spermicide, or sponge with spermicide. The following 3 contraceptive methods are not allowed in this trial: birth control pills, birth control depot injection, and birth control implant. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.</p> <p>Before enrolling WOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all WOCBP. The topics should generally include:</p> <ul style="list-style-type: none"> <li>General information</li> <li>ICF/assent form, as applicable</li> <li>Pregnancy prevention information</li> <li>Drug interactions with hormonal contraceptives</li> <li>Contraceptives in current use</li> <li>Guidelines for the follow-up of a reported pregnancy</li> </ul> <p>Before trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject or the</p>

Location	Old Text	Updated Text
	<p>pregnant prior to IMP administration, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must be withdrawn from the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial.</p> <p>(Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the trial medical monitor.)</p> <p>The investigator must immediately notify INC Research of any pregnancy associated with IMP exposure, including 14 days after the last dose of IMP and record the event on the IRE form and forward it to INC Research. INC Research will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.</p> <p>Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray trials). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to INC Research, on appropriate Pregnancy Surveillance form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months.</p>	<p>subject's parent or legal guardian must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed with the subject and/or the parent/guardian.</p> <p>A urine and/or serum pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening on all WOCBP and female subjects <math>\geq</math>12 years of age and all female subjects <math>&lt;</math>12 years of age, if menstruation has started. If a urine test is performed and is positive, the investigator will follow up with a confirmatory serum test.</p> <p>During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).</p> <p>If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. (Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the Clinical Safety and Pharmacovigilance department [see <a href="#">Appendix 1</a> for contact information])</p> <p>The investigator must immediately notify the sponsor of any</p>

Location	Old Text	Updated Text
		<p>pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.</p> <p>Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray trials). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator must report to the sponsor, on appropriate Pregnancy Surveillance form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.</p>
<b>7.1.1 Sample Size for Efficacy:</b>	...Sample size re-estimation will be conducted when 90% of the subjects finish (complete or discontinue) the trial.	...Sample size re-estimation will be conducted when 90% of the subjects finish (complete or discontinue) the trial. The trial must include no fewer than 60 subjects on IMP for the assessment of safety based on regulatory feedback.
<b>8.1 Packaging and Labeling:</b>	The IMP will be provided to the investigator(s) by the sponsor (or designated agent). The IMP will be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets in blister packs. Each blister pack used in the dosing period will be labeled to clearly disclose the, compound ID, trial number, the sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements, and other information required by local regulatory authorities.	The IMP will be provided to the investigator(s) by the sponsor (or designated agent). The IMP will be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets in blister packs or as 60 mL bottles containing 1 mg/mL (0.1% w/v) tolvaptan suspension. Each blister pack and suspension bottle used in the dosing period will be labeled to clearly disclose the compound ID, trial number, the sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements, and other information required by local regulatory authorities. Each site will

Location	Old Text	Updated Text
	<p>The current tolvaptan tablet formulation intended for use in this trial is limited to administration to those who can easily swallow a 3.75-mg tablet (6 mm) and weigh <math>\geq 10</math> kg. A suspension formulation is in development that will be suitable for children who cannot swallow tablets (eg, <math>&lt; 4</math> years) and will also allow dosage adjustment for children with body weight <math>&lt; 20</math> or <math>\leq 50</math> kg who are taking moderate or potent inhibitors of CYP3A4, respectively. Once available, the protocol will be amended to include the details of this formulation and will include information on the packaging and labeling for that formulation</p>	<p>be supplied with bottle(s) containing placebo tablets to use for subject screening purposes. Each placebo bottle will be labeled to clearly disclose the compound ID, trial number, instruction for use, route of administration, appropriate precautionary statement, and other information required by the local regulatory authorities. For dosing suspension, syringes and bottle adaptors will be made available to the sites.</p>
<b>8.2 Storage:</b>	<p>The IMP will be stored at 25°C (77°F) or below, with excursions allowed from 15 to 30°C (59 to 86°F). The clinical site staff or designated personnel will maintain a temperature log in the drug storage area recording the temperature at least once each working day.</p>	<p>The IMP blister packs will be stored at 25°C (77°F) or below, with excursions allowed from 15 to 30°C (59 to 86°F). The IMP suspension bottles will be stored at 2 to 8°C (35.6 to 46.4°F) and protected from light. The clinical site staff or designated personnel will maintain a temperature log in the drug storage area recording the temperature at least once each working day.</p>
<b>9.1 Source Documents:</b>	<p>...Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF.</p>	<p>...Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, 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.</p>
<b>9.2 Data Collection:</b>	<ul style="list-style-type: none"> <li>• Documentation of the informed consent process, including any revised consents;</li> <li>• The date of the visit and the corresponding visit or day in the trial schedule;</li> <li>• General subject status remarks, including any <i>significant</i> medical findings. The severity, frequency, and duration</li> </ul>	<ul style="list-style-type: none"> <li>• Documentation of the informed consent process, including any revised consents;</li> <li>• Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;</li> </ul>

Location	Old Text	Updated Text
	<p>of any AEs and the investigator's assessment of relationship to the IMP must also be recorded;</p> <ul style="list-style-type: none"> <li>• Any changes in concomitant medications or dosages;</li> <li>• A general reference to the procedures completed;</li> <li>• The signature (or initials) and date of all clinicians who made an entry in the progress notes.</li> </ul> <p>...Changes will be made by striking a single line through erroneous data, and clearly entering the correct data (eg, <del>wrong data</del>-right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.</p>	<ul style="list-style-type: none"> <li>• The date of the visit and the corresponding Visit or Day in the trial schedule;</li> <li>• General subject status remarks, including any <i>significant</i> medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;</li> <li>• Any changes in concomitant medications or dosages;</li> <li>• A general reference to the procedures completed;</li> <li>• The signature (or initials) and date of each clinician (or designee) who made an entry in the progress notes.</li> </ul> <p>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, <del>wrong data</del>-right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician. If electronic data systems are being utilized, a full audit trail of changes must be maintained.</p>
<b>9.3 File Management at the Trial Site:</b>	The investigator will ensure that the trial center file is maintained in accordance with Section 8 of the ICH Guideline for GCP <sup>29</sup> and as required by applicable local regulations	The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 <sup>29</sup> and as required by applicable local regulations
<b>9.4 Records Retention at the Trial Site:</b>	<ul style="list-style-type: none"> <li>• A period of at least 2 years following the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date of discontinuation); OR</li> </ul> <p>...The investigator will be responsible to maintain adequate and</p>	<ul style="list-style-type: none"> <li>• A period of at least 2 years following the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR</li> </ul> <p>...The investigator will be responsible to maintain adequate and</p>

Location	Old Text	Updated Text
	accurate electronic or hard copy source documents of all observations and data generated during this trial.	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.
<b>10.1 Monitoring:</b>	The sponsor has ethical, legal, and scientific obligations to follow this trial in a detailed and orderly manner in accordance with established research principles, the ICH GCP Guideline, 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 site during the trial, as well as communicate frequently via telephone and written communications.	The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and 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 site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.
<b>10.2 Auditing:</b>	The sponsor's Quality Management Unit (or representative) may conduct trial site audits. Audits will include, but are not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents.	The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not be limited to, IMP supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents.
<b>11 Ethics and Responsibility:</b>	This trial must be conducted in compliance with the protocol, the ICH GCP Guideline, and applicable local laws and regulatory requirements. Each trial site will seek approval by an IRB or IEC according to regional requirements.	This trial must be conducted in compliance with the protocol, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB or IEC according to regional requirements, and the investigator will provide that documentation to the sponsor.

Location	Old Text	Updated Text
<b>12 Confidentiality:</b>	<p>...However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. 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.</p> <p>Subjects will be identified only by initials and unique subject numbers in CRFs. Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary.</p>	<p>...However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy 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.</p> <p>Subjects will be identified only by unique subject numbers in CRFs. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.</p>
<b>13 Amendment Policy:</b>	<p>The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it be 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/IEC. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB/IEC approval of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, followed by IRB/IEC notification within 5 working days. The sponsor will submit protocol amendments to the applicable regulatory agencies.</p>	<p>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/IEC. 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/IEC, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB/IEC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB/IEC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local</p>

Location	Old Text	Updated Text
	<p>When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the trial before expecting continued participation.</p>	<p>applicable timelines.</p> <p>When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB/IEC, 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.</p>
<b>14 Publication Authorship Requirements:</b>	New section for this amendment	
<b>Appendix 2:</b>	<p>Phone: [REDACTED]        Mobile: [REDACTED]        E-Mail: [REDACTED]</p> <p><b>Study Communications &amp; Patient/Site Support</b></p> <p>Phone: [REDACTED]</p>	<p>Phone: [REDACTED]; Mobile: [REDACTED]</p> <p>Fax: [REDACTED]</p> <p>E-Mail: [REDACTED]</p> <p><b>Study Communications &amp; Patient/Site Support</b></p> <p>Phone: [REDACTED]</p> <p><b>IDMC Support</b></p> <p>Phone: [REDACTED]</p> <p>Fax: [REDACTED]</p>

Location	Old Text	Updated Text
<b>Agreement:</b>	<p>...and in the sponsor's (or designee's) Clinical Research Agreement.</p> <p>...I am aware that this protocol must be approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where tolvaptan 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 Paragraph I of the sponsor's Clinical Research Agreement, at which time I agree to adhere strictly to the protocol as amended).</p> <p>...I agree to await IRB/IEC approval before implementation of any protocol 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/IEC within 5 working days. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only.</p> <p>...I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Research 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 sub-investigators 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 prior to publication of efficacy and safety results on an individual basis.</p>	<p>...and in the sponsor's (or designee's) Clinical Trial Agreement.</p> <p>...I am aware that this protocol must be approved by the Institutional Review Board (IRB) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where tolvaptan 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).</p> <p>...I agree to await IRB/IEC 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/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only, if required by local regulations.</p> <p>...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 sub-investigators 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.</p>

Location	Old Text	Updated Text
	<p>Principal or Coordinating Investigator Signature and Date</p> <hr/> <p>Sponsor Representative Signature and Date</p>	<p>Principal Investigator</p> <hr/> <p>Print Name</p> <hr/> <p>Signature</p> <hr/> <p>Date</p>

**ADDITIONAL RISK TO THE SUBJECT:** There is no additional risk to the subjects.

**Amendment Number:** 4

**Issue Date:** 07 May 2015

**PURPOSE:**

- Correction of typographical errors in the dosing table (Table 2.1.1-2) for the suspension for subjects taking a CYP3A inhibitor.
- Removed the word “Tablet” from the title of Table 2.1.1-2 as the table includes dosing information for tolvaptan tablets and for the suspension formulation of tolvaptan.
- Updated the Clinical Management contact information on the title page and in Appendix 1.
- Correction of typographical error in Section 2.1.1 Dosing Rationale.

**BACKGROUND:**

Table 2.1.1-2 was added to this protocol with Amendment Number 3. Subsequent to the approval of Amendment Number 3, typographical errors were discovered in Table 2.1.1-2. The errors are being corrected with this protocol amendment (Amendment Number 4).

The Clinical Management contact information has been updated.

A typographical error in Section 2.1.1 Dosing Rationale has been corrected. The word “staring” has been corrected to “starting”.

**MODIFICATIONS TO PROTOCOL:**

**Sectional Revisions:** changes made to specific sections of the protocol are listed in the table below.

Location	Old Text	Updated Text
Title Page:	Clinical Management [REDACTED] Phone [REDACTED]; Fax [REDACTED]; E-mail: [REDACTED]	Clinical Management [REDACTED] Phone [REDACTED]; Fax [REDACTED]; E-mail: [REDACTED]
	Issue Date: 03 Jul 2013 Date of Amendment 1: 04 Nov 201 Date of Amendment 2: 19 May 2014 Date of Amendment 3: 26 February 2015	Issue Date: 03 Jul 2013 Date of Amendment 1: 04 Nov 201 Date of Amendment 2: 19 May 2014 Date of Amendment 3: 26 February 2015 <b>Date of Amendment 4: 07 May 2015</b>
<b>2.1.1 Dosing Rationale:</b>	... Subjects $\geq$ 2 years of age, weighing $\leq$ 30 kg and who cannot safely swallow a tablet, will receive an oral, once daily dose of tolvaptan suspension starting at 0.15 mg/kg.	... Subjects $\geq$ 2 years of age, weighing $\leq$ 30 kg and who cannot safely swallow a tablet, will receive an oral, once daily dose of tolvaptan suspension starting at 0.15 mg/kg.

### Old Text: Table 2.1.1-2

**Table 2.1.1-2 Starting Tolvaptan Tablet Doses in the Presence of Potent or Moderate CYP3A Inhibitors**

Tolvaptan Dose	Age/Body Weight (as applicable)	Potent Inhibitor	Moderate Inhibitor
0.1 mg/kg suspension <sup>a</sup>	44 wk to $<$ 2 y or $<$ 10 kg	-	0.05 mg/kg suspension
0.15 mg/kg suspension	$\geq$ 2 y, $\leq$ 30 kg	0.04 mg/kg suspension	0.8 mg/kg suspension
3.75 mg tablet	$\geq$ 10 kg to $<$ 20 kg	0.94 mL suspension	0.19 mL suspension
7.5 mg tablet	20 kg to 50 kg	1.90 mL suspension	3.75 mg tablet
15 mg tablet	$\geq$ 50 kg	3.75 mg tablet	7.5 mg tablet

<sup>a</sup>The smallest volume of suspension that may be administered is 0.3 mL (0.3 mg), therefore dose reductions for potent inhibitors cannot be accommodated and for moderate inhibitors children weighing  $<$  6 kg cannot be accommodated.

**Updated Text: Table 2.1.1-2****Table 2.1.1-2 Starting Tolvaptan Doses in the Presence of Potent or Moderate CYP3A Inhibitors**

Tolvaptan Dose	Age/Body Weight (as applicable)	Potent Inhibitor	Moderate Inhibitor
0.1 mg/kg suspension <sup>a</sup>	44 wk to < 2 y or < 10 kg	-	0.05 mg/kg suspension
0.15 mg/kg suspension	≥ 2 y, ≤ 30 kg	0.04 mg/kg suspension	<b>0.08 mg/kg suspension</b>
3.75 mg tablet	≥ 10 kg to < 20 kg	0.94 mL suspension	<b>1.90 mL suspension</b>
7.5 mg tablet	20 kg to 50 kg	1.90 mL suspension	3.75 mg tablet
15 mg tablet	≥ 50 kg	3.75 mg tablet	7.5 mg tablet

<sup>a</sup>The smallest volume of suspension that may be administered is 0.3 mL (0.3 mg), therefore dose reductions for potent inhibitors cannot be accommodated and for moderate inhibitors children weighing < 6 kg cannot be accommodated.

Location	Old Text	Updated Text
Appendix 1:	Phone [REDACTED]; Fax [REDACTED]	Phone [REDACTED]; Fax [REDACTED]

**ADDITIONAL RISK TO THE SUBJECT:** There is no additional risk to the subjects.

**Amendment Number:** 5

**Issue Date:** 17 Nov 2015

**PURPOSE:**

The main intent of the Amendment is to clarify administrative sections, align with current protocol templates, and incorporate recent requests from Regulatory Authorities (Food and Drug Administration [FDA]).

**BACKGROUND:**

This protocol serves as the single trial for the Pediatric Written Request with the FDA and the Pediatric Research Equity Act (PREA) requirement for the US. The FDA has agreed to the current version of the protocol and updates have been made to address further comments from the FDA, and other regulatory agencies.

**MODIFICATIONS TO PROTOCOL:**

**General Revisions:**

- Removed the neurocognition test battery. This was an exploratory endpoint and the removal of the neurocognition test battery has no impact on the safety aspects of the trial.
- Clarified dosing as dual formulations are employed: tablet and suspension.
- Alignment within the protocol descriptor sections of time points for pharmacokinetic assessments and serum sodium assessments; no change to requirement of time points or assessments.
- Clarification of Exclusion Criteria and added an exclusion criterion to reflect the suspension use and protocol template update.
- Removed reference to the extension study, 156-11-294.
- Standard Protocol template updates made to reflect Investigator's Brochure (IB) Edition 21 issuance.
- Clarified requirements for a full versus directed physical examination and neurological examination. Added a fontanelle assessment as age appropriate.
- Clarified urine vs. serum pregnancy test requirements.
- FE urate changed to FE urea throughout the protocol.
- Urine uric acid changed to urine urea throughout the protocol.
- Provided additional information related to the Tanner Staging Assessment, including an Appendix for classification reference.
- Updated the protocol template to make consistent with changes in the Phase 3 global protocol template (ie. revised definition of AE, SAE definition related to hospitalization, IRE definition, including potential DILI, Clinical lab test value changes, IMP Causality, Eliciting and Reporting AEs).
- Clarified pregnancies to be reported to INC Research instead of the sponsor.

- Clarified the time points in which nonserious and serious AEs will be followed.
- Updated list of abbreviations and references.

**ADDITIONAL RISK TO THE SUBJECT:** There is no additional risk to the subjects.

A complete redline version of this amendment showing all changes from the previous version will be produced and available upon final approval of this amendment.

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, 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) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where tolvaptan 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- or IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms 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 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/IEC 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/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC 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 sub-investigators 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.

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Principal Investigator Print Name

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Signature

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Date

**Otsuka Pharmaceutical Development & Commercialization, Inc.**

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OPC-41061

**SIGNATURE PAGE**

**Document Name: 156-08-276 Protocol Amendment 5**

**Document Number: 0001027730**

**Document Version: 9.0**

<b>Signed by</b>	<b>Meaning of Signature</b>	<b>Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)</b>
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[REDACTED]	Clinical Pharmacology	17-Nov-2015 21:46 GMT+00
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