- **Protocol number: 156-11-294**
- **Document title: A Phase 3b, Multicenter, Extension Follow-up Trial to Evaluate the Long-term Safety of Children and Adolescent Subjects With Euvolemic or Hypervolemic Hyponatremia Who Have Previously Participated in a Trial of Titrated Oral SAMSCA (Tolvaptan)**
- **Version number: 8.0**
- **Date of the document: 09 November 2015**
- **NCT number: NCT02020278**

Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

SAMSCA®, Tolvaptan (OPC-41061)

REVISED CLINICAL PROTOCOL

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

Protocol No. 156-11-294
IND No. 54,200
NDA No. 22-275
EudraCT No. 2013-002810-11

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3b
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Sponsor Representatives: Medical Director	PPD PPD Phone PPD Fax PPD E-mail: PPD
Clinical Management	PPD Phone: PPD Fax: PPD E-mail: PPD
Immediately Reportable Event	INC Research (see Appendix 1)
Issue Date: Date of Amendment 1: Date of Amendment 2: Date of Amendment 3:	31 October 2013 5 September 2014 26 February 2015 9 November 2015

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Product: SAMSCA®, Tolvaptan (OPC-41061)	Protocol No. 156-11-294 IND No. 54,200 NDA No. 22-275 EudraCT No. 2013-002810-11
Protocol Title:	A Phase 3b, Multicenter, Extension Follow-up Trial to Evaluate the Long-term Safety of Children and Adolescent Subjects With Euvolemic or Hypervolemic Hyponatremia Who Have Previously Participated in a Trial of Titrated Oral SAMSCA® (Tolvaptan)
Clinical Phase/Trial Type:	Phase 3b, safety follow-up with optional open-label tolvaptan treatment component
Treatment Indication:	Dilutional (euvolemic or hypervolemic) hyponatremia
Objectives:	The objective of this trial is to provide 6 months of safety follow-up for children and adolescents with dilutional (euvolemic or hypervolemic) hyponatremia who have previously participated in a tolvaptan hyponatremia trial, and to assess the efficacy of tolvaptan in increasing serum sodium for those subjects who receive optional continuing tolvaptan treatment of variable duration (up to 6 months). **Core Safety Follow-up Component** • For all subjects: To evaluate the post-treatment safety follow-up of children and adolescent subjects with dilutional (euvolemic or hypervolemic) hyponatremia who have previously participated in a tolvaptan hyponatremia trial. **Optional Tolvaptan Treatment Component** • For subjects who receive optional tolvaptan treatment: To demonstrate that tolvaptan safely and effectively achieves and maintains increased serum sodium concentrations in children and adolescent subjects with dilutional (euvolemic or hypervolemic) hyponatremia when used for both multiple short-term treatments, and/or longer chronic treatments.
Trial Design:	**Core Safety Follow-up Component** This is a 6-month safety follow-up trial in children and adolescents with dilutional (euvolemic or hypervolemic) hyponatremia who have previously participated in a tolvaptan hyponatremia trial.

	Enrollment in this trial should follow completion or discontinuation of the previous tolvaptan hyponatremia trial. The subject must have been off investigational medicinal product (IMP) for at least 7 days between trials. A longer lapse between completion of the previous tolvaptan hyponatremia trial and enrollment into this trial is permitted while enrollment is open. Subjects who consent/assent to participate will be followed once a month for 6 months, through telephone calls and/or clinical trial site visits. Subjects will attend the clinic for the baseline visit and a Month 6/end of trial visit. The remainder of the assessments will be conducted through telephone calls. **Optional Tolvaptan Treatment Component** Subjects enrolled in the core safety follow-up component may be eligible for optional tolvaptan treatment. Tolvaptan treatment may be short-term treatment (eg, a few days of treatment needed per episode of hyponatremia) or long-term treatment (eg, treatment for weeks to months). The need for treatment for more than 30 days will be assessed by the investigator on a case-by-case basis. Eligible subjects can be treated with tolvaptan at any time during the 6-month core safety follow-up component. Treatment can be discontinued and reinitiated depending upon the individual subject's need (eg, during chemotherapy treatments). If subjects are off tolvaptan treatment for ≥ 72 hours, reinitiation of treatment (a new treatment cycle) will require reassessment of the eligibility criteria and will begin in a hospital setting. Tolvaptan should be titrated with regular serum sodium assessments.
Subject Population:	Approximately 100 male or female subjects will be enrolled in this trial. Eligible subjects will need to have participated in a previous tolvaptan pediatric trial for dilutional (euvolemic or hypervolemic) hyponatremia.
Inclusion/Exclusion Criteria:	<u>Key inclusion criteria:</u> • Enrollment in one of the previous tolvaptan pediatric trials for hyponatremia. • Willingness to be clinically followed for 6 months. <u>Exclusion criteria:</u> • There are no exclusion criteria for entry into the core safety follow-up component of this trial.

	The optional tolvaptan treatment component has additional eligibility criteria.
Trial Sites:	Subjects may be enrolled at approximately 75 clinical trial sites globally.
Investigational Medicinal Product, Dose, Formulation, Mode of Administration:	Subjects enrolled in this trial may be eligible to receive tolvaptan if they have a clinical need as determined by the investigator and meet the eligibility criteria for optional tolvaptan treatment. Tolvaptan will initially be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets. Upon the availability of an age appropriate formulation, for children who cannot swallow tablets, the protocol will be amended to reflect additional dosing options. Tolvaptan tablets will be administered orally once daily (QD), preferably in the morning hours, with a dose-proportional amount of water. Doses of ≥ 15 mg tolvaptan will be given with 240 mL of water, 7.5 mg of tolvaptan will be given with 120 mL of water, and 3.75 mg of tolvaptan will be given with 60 mL of water. Any initiation or titration of tolvaptan must occur in a hospital setting. If a subject is not expected to receive a higher dose of tolvaptan, ie, if a stable dose is determined, continued administration can be done outside of the hospital setting. Subjects can be treated with optional tolvaptan at any time while participating in the 6-month core safety follow-up component.
Trial Assessments:	• Vital signs • Physical examinations • Body height, weight, and growth percentiles • Tanner Staging • Clinical laboratory tests: Serum sodium assessments and liver function tests (alanine transaminase [ALT], aspartate aminotransferase [AST], total bilirubin [BT]) and creatinine (for subjects on tolvaptan) • Adverse event (AE) reporting • Continued need for tolvaptan treatment after the first 30 days of treatment • Quality of Life (QoL) assessments <u>Pharmacokinetics for optional tolvaptan treatment component:</u> • Sparse blood samples for tolvaptan and plasma

	metabolite concentrations from subjects dosed with tolvaptan for 8 consecutive weeks (one assessment per initiation or reinitiation of therapy at 8 weeks).
Criteria for Evaluation:	**Primary Endpoint:** • Change from baseline in serum sodium while tolvaptan is being administered **Secondary Endpoints:** <u>Efficacy:</u> • Percentage of subjects who require rescue therapy while on tolvaptan treatment • Percentage of subjects who have recurrence of hyponatremia while on tolvaptan • Percentage of subjects requiring continuation of tolvaptan following 30 days of treatment • Change from baseline in QoL assessments (monthly for subjects on tolvaptan) <u>Safety:</u> • Percentage of subjects with overly rapid correction in serum sodium (≥ 12 mEq/L [mmol/L]) in 24 hours after the first dose at introduction or reintroduction of tolvaptan • Changes from baseline in ALT, AST, BT, and creatinine for subjects on tolvaptan • Frequency of AE reports (including cases of dehydration) • Changes from baseline in growth percentiles by visit for body height and weight • Tanner Staging progression score (at 6 months) <u>Pharmacokinetics for tolvaptan treatment:</u> • Plasma concentrations of tolvaptan and metabolites in subjects who have continued tolvaptan therapy for 8 consecutive weeks.
Statistical Methods:	Primary and secondary endpoints will be summarized by descriptive statistics.
Trial Duration:	The core safety follow-up component of the trial will continue until approximately 100 enrolled subjects have either completed or been early terminated from the core safety component.

	Subjects may be eligible to receive optional tolvaptan treatment at any time during their participation in the trial, which will be for 6 months.

Table of Contents

Protocol Synopsis **2**
Table of Contents **7**
List of In-text Tables **13**
List of In-text Figures **14**
List of Appendices **15**
List of Abbreviations and Definitions of Terms **16**
1 Introduction **18**
1.1 Nonclinical Data 20
1.1.1 Juvenile Toxicity Data 22
1.2 Clinical Data 23
1.2.1 Pharmacokinetics/Pharmacodynamics 23
1.2.2 Clinical Efficacy 25
1.3 Known and Potential Risks and Benefits 28
2 Trial Rationale and Objectives **29**
2.1 Trial Rationale 30
2.1.1 Core Safety Follow-up Component 30
2.1.2 Optional Tolvaptan Treatment Component 30
2.2 Dosing Rationale 31
2.3 Trial Objectives 31
3 Trial Design **32**
3.1 Type/Design of Trial 32
3.1.1 Core Safety Follow-up Component 34
3.1.2 Optional Tolvaptan Treatment Component 35
3.1.2.1 Treatment Interruption on Day 30 35
3.2 Trial Treatments 36
3.2.1 Optional Tolvaptan Treatment 36
3.2.1.1 Tablet Formulation 36
3.2.1.2 Titration Guidelines for the Optional Tolvaptan Treatment Component 37
3.2.2 Rescue Therapy 40

3.2.3 Fluid Restriction 41
3.3 Trial Population 41
3.3.1 Core Safety Follow-up Component 41
3.3.2 Optional Tolvaptan Treatment Component 41
3.4 Eligibility Criteria 43
3.4.1 Informed Consent/Assent 43
3.4.2 Inclusion Criteria 44
3.4.3 Exclusion Criteria 44
3.5 Outcome Variables 45
3.5.1 Primary Outcome Variable 45
3.5.2 Secondary Outcome Variables 45
3.5.2.1 Efficacy Variables 45
3.5.2.2 Safety Variables 45
3.5.2.3 Pharmacokinetic Variable: Optional Tolvaptan Treatment Component 46
3.6 Measures to Minimize/Avoid Bias 46
3.7 Trial Procedures 46
3.7.1 Core Safety Follow-up Component 46
3.7.2 Optional Tolvaptan Treatment Component 49
3.7.3 Schedule of Assessments 53
3.7.3.1 Core Safety Follow-up Component 53
3.7.3.1.1 Baseline 53
3.7.3.1.2 Months 1, 2, 3, 4, and 5 54
3.7.3.1.3 Month 6/Early Termination 54
3.7.3.2 Optional Tolvaptan Treatment Component 55
3.7.3.2.1 Pretreatment Baseline Visit 56
3.7.3.2.2 Titration Phase 57
3.7.3.2.2.1 Day 1 57
3.7.3.2.2.2 Day 2 up to Day 4 58
3.7.3.2.3 Days 7, 14, and 21 59
3.7.3.2.4 Day 30 Interruption: 30 (±1) Days Post-first Dose 59
3.7.3.2.4.1 Day 31 60
3.7.3.2.4.2 Day 32 60

3.7.3.2.4.3 Day 33 60
3.7.3.2.4.4 Day 34 61
3.7.3.2.5 Treatment Cycle Month 2: Month 2 Week 2 and Month 2 Week 4 (±2 days) 62
3.7.3.2.6 Maintenance Phase 63
3.7.3.2.6.1 Treatment Cycle Month 3 (and every month thereafter) (±2 days) 63
3.7.3.2.7 Follow-up Phase 64
3.7.3.2.7.1 First Follow-up: 24 (± 4) Hours Post-last Dose 64
3.7.3.2.7.2 Second Follow-up: 7 (± 1) Days Post-last Dose 64
3.7.3.2.7.3 Third Follow-up: 14 (± 2) Days Post-last Dose 65
3.7.4 Efficacy Assessments 65
3.7.4.1 Serum Sodium Concentrations 65
3.7.4.1.1 Serum Sodium Samples for Efficacy 65
3.7.4.1.2 Supplemental Sodium Samples for Safety 65
3.7.4.1.3 Unscheduled Assessments 66
3.7.4.2 Quality of Life Assessments 67
3.7.5 Safety Assessments 67
3.7.5.1 Adverse Events 67
3.7.5.2 Clinical Laboratory Tests: Core Safety Follow-up Component 68
3.7.5.3 Clinical Laboratory Tests: Optional Tolvaptan Treatment Component 68
3.7.5.3.1 Monitoring of Liver Transaminases 68
3.7.5.4 Physical Examination and Vital Sign Assessments 69
3.7.5.5 Neurological Examination 70
3.7.5.6 Tanner Staging 70
3.7.5.7 Hyponatremia History 71
3.7.5.8 Clinical Status Assessment 71
3.7.5.9 Vital Status 71
3.7.6 Pharmacokinetic Assessments 71
3.7.6.1 Blood Collection Times 71
3.7.6.2 Sample Handling and Processing 72
3.7.7 End of Trial 72
3.7.8 Independent Data Monitoring Committee 72
3.8 Stopping Rules, Withdrawal Criteria and Procedures 72

3.8.1 Entire Trial or Treatment Component(s) 72
3.8.2 Individual Site 72
3.8.3 Individual Subject Discontinuation 73
3.9 Screen Failures 74
3.10 Definition of Completed Subjects 74
3.11 Definition of Lost to Follow-up 74
3.12 Subject Compliance 75
3.13 Protocol Deviations 75
4 Restrictions 75
4.1 Prohibited Medications 75
4.2 Other Restrictions 76
5 Reporting of Adverse Events 76
5.1 Definitions 76
5.2 Eliciting and Reporting Adverse Events 78
5.3 Immediately Reportable Events 79
5.3.1 Hyponatremia-related Adverse Events 79
5.3.1.1 Rapid Correction of Serum Sodium 79
5.3.1.2 Other Hyponatremia-related Adverse Events 80
5.4 Potential Drug-induced Liver Injury 80
5.4.1 Liver Transaminase Elevations 80
5.4.1.1 Criteria for Discontinuation from the Optional Tolvaptan Treatment Component of the Trial due to Liver Transaminase Elevations 82
5.5 Pregnancy 82
5.6 Procedure for Breaking the Blind 84
5.7 Follow-up of Adverse Events 84
5.7.1 Follow-up of Non-serious Adverse Events 84
5.7.2 Follow-up of Serious Adverse Events 84
5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring After Last Scheduled Contact 85
6 Pharmacokinetic/Pharmacodynamic Analysis 85
6.1 Pharmacokinetic Analysis 85
7 Statistical Analysis 85
7.1 Sample Size 85

7.2 Datasets for Analysis 85
7.3 Handling of Missing Data 86
7.4 Primary and Secondary Outcome Analysis 86
7.4.1 Primary Outcome Analysis 86
7.4.2 Secondary Outcome Analyses 86
7.4.3 Interim Analysis 87
7.5 Analysis of Demographic and Baseline Characteristics 87
7.6 Safety Analyses 87
7.6.1 Adverse Events 87
7.6.2 Clinical Laboratory Data 87
7.6.3 Physical Examination and Vital Signs Data 87
8 Management of Investigational Medicinal Product 88
8.1 Packaging and Labeling 88
8.2 Storage 88
8.3 Accountability 88
8.4 Returns and Destruction 88
8.5 Reporting of Product Quality Complaints 89
8.5.1 Eliciting and Reporting Product Quality Complaints 89
8.5.2 Information Required for Reporting Purposes 89
8.5.3 Return Process 90
8.5.4 Assessment/Evaluation 90
9 Records Management 90
9.1 Source Documents 90
9.2 Data Collection 90
9.3 File Management at the Trial Site 91
9.4 Records Retention at the Trial Site 92
10 Quality Control and Quality Assurance 92
10.1 Monitoring 92
10.2 Auditing 93
11 Ethics and Responsibility 93
12 Confidentiality 93
13 Amendment Policy 94

15 References.....96

List of In-text Tables

Table 2.2-1	Starting Tolvaptan Tablet Doses as mg/kg of Body Weight	31
Table 3.2.1.2-1	Starting Tolvaptan Doses With or Without Potent or Moderate CYP3A4 Inhibitors	38
Table 3.4.2-1	Inclusion Criteria for Core Safety Follow-up Component	44
Table 3.7.1-1	Core Safety Follow-up Component: Schedule of Assessments for All Subjects	47
Table 3.7.2-1	Schedule of Assessments for Each Treatment Cycle	50
Table 3.7.4.1.2-1	Serum Sodium Assessments During the Optional Tolvaptan Component	66
Table 3.7.5.2-1	Clinical Laboratory Tests During Core Safety Follow-up	68
Table 3.7.5.3-1	Clinical Laboratory Tests During Optional Tolvaptan Treatment	68
Table 4.1-1	List of Cytochrome P450 3A4 Inhibitors (Partial List)	76

List of In-text Figures

Figure 1.2.2-1 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 156-02-238 [SALT 1 and 2] Combined) 27

Figure 1.2.2-2 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) 27

Figure 3.1-1 Trial Design Schematic 33

Figure 3.2.1.2-1 Titration Scheme 39

List of Appendices

Appendix 1	Names of Sponsor Personnel	98
Appendix 2	Institutions Concerned With the Trial	99
Appendix 3	Handling and Shipment of Bioanalytical Samples	101
Appendix 4	Tanner Staging	102
Appendix 5	Optional Tolvaptan Treatment Component: Eligibility Criteria	103
Appendix 6	Optional Tolvaptan Treatment Component: Laboratory Assessment Schedule	105
Appendix 7	Protocol Amendments	106

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
7DFU	7-day follow-up
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
AUC_τ	Area under the concentration-time curve during the dosing interval at steady state
AVP	Arginine vasopressin
BSL	Baseline
BT	Total bilirubin
BW	Body weight
CHF	Congestive heart failure
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent clearance of drug from plasma after extravascular administration
C_{max}	Maximum (peak) plasma concentration
CYP	Cytochrome P450
DDAVP	1-deamino-8-D-arginine vasopressin
DILI	Drug-induced liver injury
eCRF	Electronic case report form
ED_3	Dose required to triple the urine output
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ET	Early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRE	Immediately reportable event
IV	Intravenous
K_i	Inhibition constant

LFT	Liver function test
MHRA	Medicines and Healthcare Products Regulatory
NA	Not applicable
OAPI-EQC	Otsuka America Pharmaceutical, Inc.-Ethics, Quality and Compliance
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PD	Pharmacodynamic(s)
PIP	Pediatric Investigational Plan
PK	Pharmacokinetic(s)
PO	By mouth
POC	Point of care
PQC	Product quality complaint
QD	Once daily
QoL	Quality of Life
SAE	Serious adverse event
SALT	Study of Ascending Levels of Tolvaptan in Hyponatremia
SALTWATER	Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
STAT	Immediately
$t_{1/2,z}$	Terminal-phase elimination half-life
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
WOCBP	Women of child-bearing 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."[1] It is characterized by a subnormal concentration of sodium in the blood (serum sodium < 135 mEq/L [mmol/L]) and is manifested by a range of neurologic 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.[2,3]

Both forms of hyponatremia, dilutional and depletional, impair normal neurologic 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.[4] 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 neurologic damage, respiratory arrest, brainstem herniation, and death if not treated quickly and appropriately.[5] 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, sex, baseline neurologic 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[6] and 15% to 20% of hospitalized patients[6,7,8,9] 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]).[4] Hyponatremia is associated with significant additional hospital morbidity and cost.[10]

Children, especially infants, are particularly vulnerable to sodium and other electrolyte imbalances because of their relatively immature renal function, increased insensible water loss, and 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 dilutional (euvolemic or hypervolemic) hyponatremia are congenital heart failure, 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.[11] 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.[12] 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) and the European Medicines Agency (EMA) have required that pediatric trials be conducted for tolvaptan for the indication of hyponatremia. This trial is an extension trial to follow children and adolescent subjects who participated in a previous tolvaptan pediatric trial for hyponatremia for safety. In addition, this trial will allow continued access to tolvaptan to those subjects with a clinical need per the investigator's discretion for 6 months after enrollment.

1.1 Nonclinical Data

Tolvaptan is a vasopressin antagonist that blocks the binding of AVP at the V_2 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_2 and V_{1a} receptors but not V_{1b} receptors. The receptor selectivity potential of tolvaptan for human V_2 receptors (inhibition constant [K_i] = 0.43 nmol/L) is approximately 30 times that for human V_{1a} receptors (K_i = 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_2 or V_{1a} receptors but to a lesser degree than tolvaptan. None of the metabolites appear to have affinity for V_{1b} 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_3) within 2 hours post dosing in rats was estimated to be 0.54 mg/kg and the ED_3 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/hour 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.[13]

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 2×10^{-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 corrected QT 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 3×10^{-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 μg·h/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 μg·h/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).[13]

1.1.1 Juvenile 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.[13]

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 1,000 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.[13]

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 heart failure 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; for the adjunct treatment of chronic renal failure treated with peritoneal dialysis and hematodialysis or hemodiafiltration, for carcinomatous edema in Japan, and for cardiac edema in China and Taiwan. Tolvaptan, under the brand name Jinarc®, is approved to treat ADPKD in Canada and the European Union (EU). As of 31 Mar 2015, the tolvaptan clinical development program consists of 105 trials; 97 trials had been completed worldwide, 4 trials were terminated, and 8 trials were ongoing. More information is available in the IB.[13]

1.2.1 Pharmacokinetics/Pharmacodynamics

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 (0.00005 w/v% at 25°C) 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.[13]

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.[13]

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_{τ}) 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%).

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%.[13]

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_{τ}).

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_t) 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_t 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.[14,15]

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.[13]

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 plasma osmolality, and increased plasma AVP concentrations and renin activity, but no dose-related increases were observed for any other parameter.

Details of the currently available pharmacokinetic (PK)/pharmacodynamic (PD) data for the compound are available in the IB.[13]

1.2.2 Clinical Efficacy

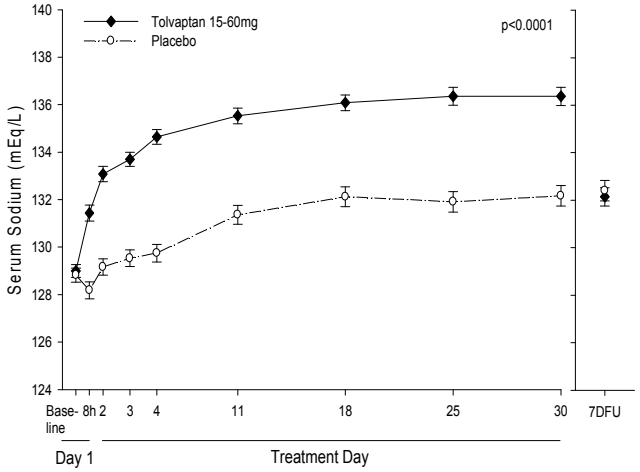
Thirteen trials involving either exclusive evaluation of subjects with hyponatremia (10 trials in which all subjects have hyponatremia and a long-term extension trial) or substantial subpopulations of subjects with hyponatremia (3 CHF trials - not all subjects in these trials had hyponatremia,) have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

Briefly, in clinical trials, tolvaptan has consistently 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.[13]

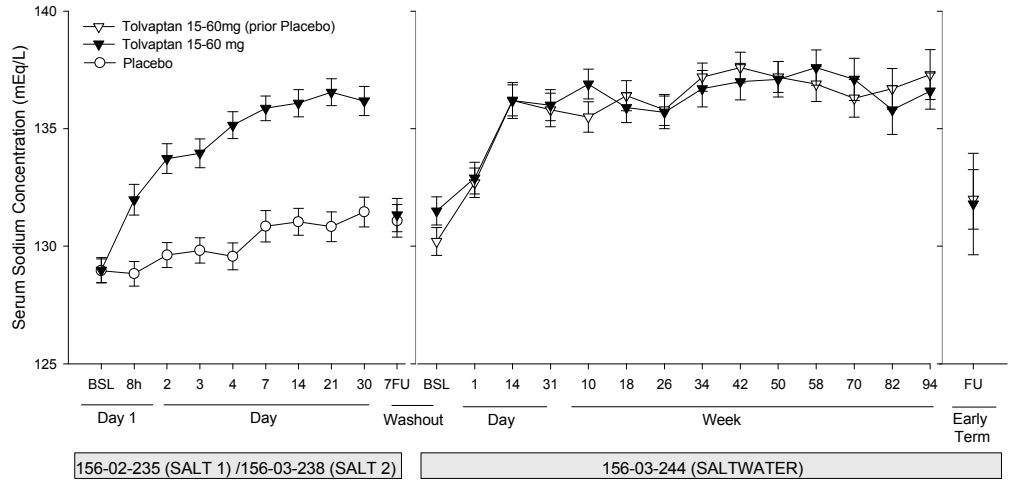
Data from two phase 3, multicenter, randomized, double-blind, placebo-controlled trials evaluating tolvaptan in euvolemic and hypervolemic hyponatremia subjects (Study of Ascending Levels of Tolvaptan in Hyponatremia [SALT] 1 and 2 trials) served as the basis for approval in the US and Europe. A total 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. Patients 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 1.2.2-1) but recovered upon resumption of tolvaptan therapy (Figure 1.2.2-2).



7DFU = 7-day follow-up.

Figure 1.2.2-1 **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)**



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 1.2.2-2 **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.[13]

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 spray-dried tablets. The extent of exposure to oral tolvaptan by dose in the pooled database (N = 7373) comprises 3115 subjects in trials for heart failure, 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.

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 TEAEs (> 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 tolvaptan during clinical trials.[13]

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 subjects with ADPKD 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 1 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 [BT] > 2 × ULN with the elevated BT 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 sex with respect to an increased risk of potential liver injury.

Retrospective evaluation of data from the hyponatremia and heart failure 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 patients treated with tolvaptan are at a potential increased risk for liver injury. Further details regarding this issue can be found in the IB.[13]

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 heart failure, 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 heart failure 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 heart failure 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.[13] To date, no clinical trials in children have been completed with tolvaptan.

2 Trial Rationale and Objectives

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.[16]

Every effort will be made to anticipate and reduce known risks. This trial was designed to minimize the number of participants and minimize the number of procedures, consistent with good study design.[17] Children will be monitored for signs of distress during this trial. The risk threshold for subjects will be monitored by the investigator. A detailed list and description of the safety monitoring to be conducted during this trial can be found in Section 3.7.5.

This trial will consist of a core safety follow-up component and an optional tolvaptan treatment component. The rationale and objectives of the 2 components of the trial are described in Section 2.1.1 (core safety follow-up component) and Section 2.1.2 (optional tolvaptan treatment component).

2.1 Trial Rationale

2.1.1 Core Safety Follow-up Component

The primary purpose of this component of the trial is to follow children and adolescent subjects who have previously participated in a tolvaptan trial for dilutional (euvolemic or hypervolemic) hyponatremia, for safety. The duration of safety follow-up will be 6 months.

Subjects in the core safety follow-up component may either receive no treatment, be treated per the local standard of care for hyponatremia, or if eligible, receive treatment with tolvaptan.

2.1.2 Optional Tolvaptan Treatment Component

While participating in the core safety follow-up component, an enrolled subject may be eligible to receive optional tolvaptan treatment at any time during the 6-month period.

The primary purpose of this component of the trial is to follow children and adolescent subjects who receive optional tolvaptan treatment for dilutional (euvolemic or hypervolemic) hyponatremia, for safety and for efficacy.

Based on the various underlying etiologies contributing to hyponatremia, the need for treatment may differ for each individual subject. This trial is designed to accommodate short-term, long-term, and repeated tolvaptan treatment cycles as necessary within the 6-month core safety component period.

Each tolvaptan treatment cycle will consist of a titration phase and a maintenance phase. Each treatment cycle will have a planned interruption after 30 days of treatment to assess the need for continued treatment. Exceptions to this planned interruption are described in Section 3.1.2.1. Dosing and titration guidelines are detailed in Section 3.2.1.

2.2 Dosing Rationale

In the optional tolvaptan treatment component of the trial, eligible subjects will receive tolvaptan based on age, weight, and the use of CYP3A4 inhibitors.

The doses of tolvaptan used in this trial were selected to be comparable to the doses used in the pivotal phase 3 trials of tolvaptan for hyponatremia in adults (SALT pivotal trials 156-02-235 and 156-03-238).[18,19]

In the pivotal hyponatremia trials,[13,18,19] 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 2.2-1 outlines the mg/kg dose ranges for tolvaptan tablet doses and body weights of 10, 20, 50, 70 (standard adult man), and 100 kg.

It is estimated that subjects 6 years of age weigh approximately 25 kg.[20]

Table 2.2-1 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

Additional dosing and titration guidelines can be found in Section 3.2.1.

2.3 Trial Objectives

The objective of this trial is to provide 6 months of safety follow-up for children and adolescents with dilutional (euvolemic or hypervolemic) hyponatremia who have previously participated in a tolvaptan hyponatremia trial, and to assess the efficacy of

tolvaptan in increasing serum sodium for those subjects who receive optional continuing tolvaptan treatment of variable duration (up to 6 months).

Core Safety Follow-up Component

- For all subjects: To evaluate the post-treatment safety follow-up of children and adolescent subjects with dilutional (euvolemic or hypervolemic) hyponatremia who have previously participated in a tolvaptan hyponatremia trial.

Optional Tolvaptan Treatment Component

- For subjects who receive optional tolvaptan treatment: To demonstrate that tolvaptan safely and effectively achieves and maintains increased serum sodium concentrations in children and adolescent subjects with dilutional (euvolemic or hypervolemic) hyponatremia when used for both multiple short-term treatments, and/or longer chronic treatments.

3 Trial Design

3.1 Type/Design of Trial

This trial consists of 2 components, a 6-month safety follow-up trial, and an embedded optional tolvaptan treatment trial for eligible subjects. The 2 components are described below and illustrated in Figure 3.1-1.

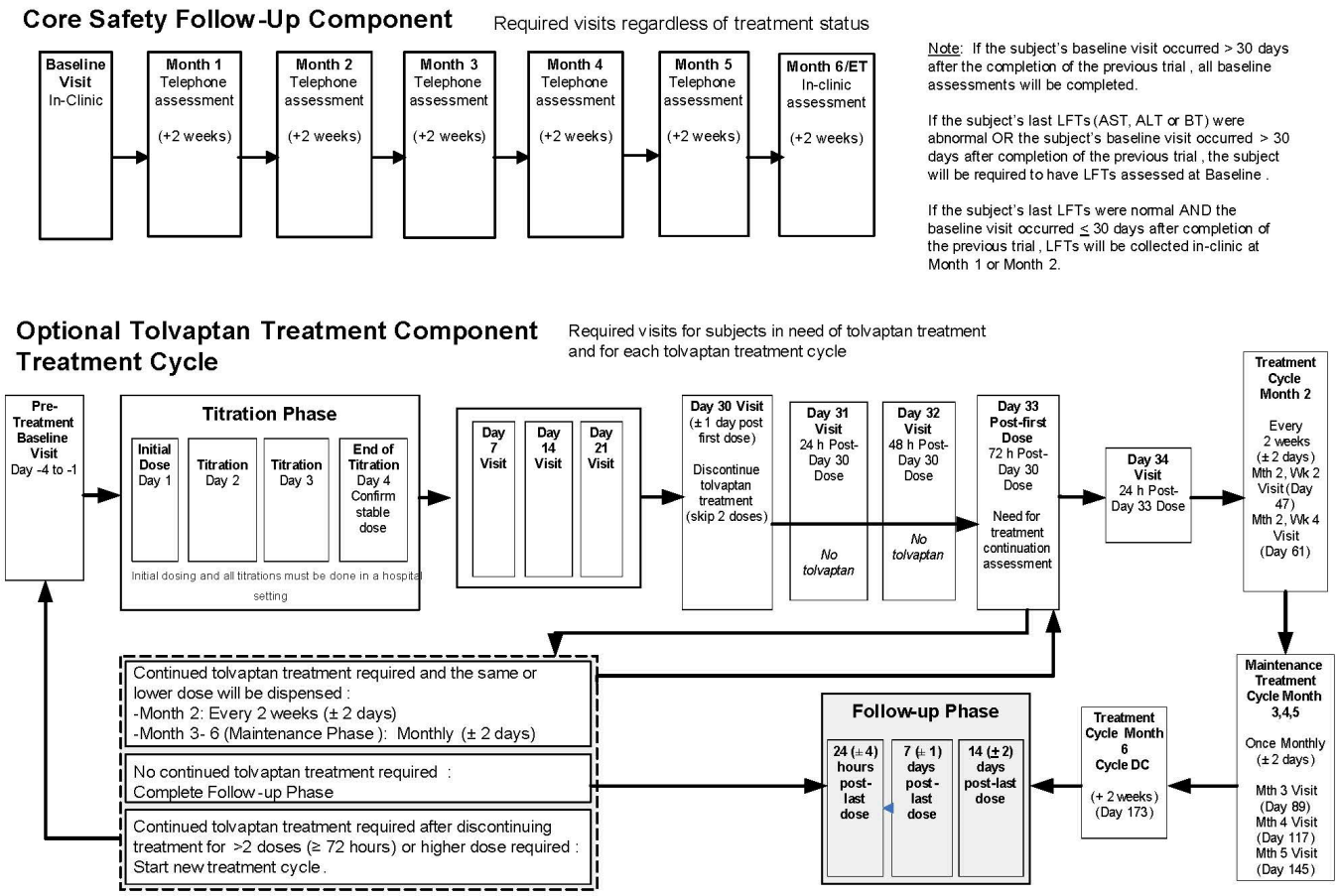


Figure 3.1-1 Trial Design Schematic

3.1.1 Core Safety Follow-up Component

The core safety follow-up component of the trial is a 6-month period in which pediatric subjects (children and adolescents) with dilutional (euvolemic or hypervolemic) hyponatremia who previously participated in a tolvaptan hyponatremia trial will be followed (at a clinical trial site and/or through telephone calls), regardless of the need for treatment for hyponatremia, to assess the long-term safety of tolvaptan. There is no screening phase.

Enrollment into this trial should follow completion or discontinuation from the previous tolvaptan hyponatremia trial; the subject must have been off investigational medicinal product (IMP) for at least 7 days between trials. A longer lapse between completion of the previous tolvaptan hyponatremia trial and enrollment into this trial is permitted while enrollment is open.

The final laboratory assessments for liver function tests (LFTs) from the previous tolvaptan trial can serve as the baseline laboratory assessments for this trial if the values are within the normal range, and collected within 30 days of the baseline visit for this trial. However, LFTs for these subjects will be collected at Month 1 or Month 2 at a clinical site visit or local laboratory. If LFTs from the previous tolvaptan trial are abnormal, or collected > 30 days of the baseline visit of this trial, they will be assessed at baseline.

The last assessments in the previous tolvaptan trial will serve as the baseline assessments if collected within 30 days of enrollment into this trial. Otherwise, assessments will be repeated if > 30 days have lapsed since the previous tolvaptan trial.

Subjects enrolled in this trial will be assessed up to 7 times over the 6 month core safety follow-up component of the trial. The baseline and the Month 6/Early Termination (ET) visits are performed in the clinic, while assessments during Months 1, 2, 3, 4 and 5 will be conducted by telephone, unless LFTs are required at Month 1 or Month 2. During the in-clinic visits, subjects are evaluated for relevant trial information.

Baseline Visit

All subjects will attend the clinic for the baseline visit.

Months 1, 2, 3, 4 and 5

All subjects will receive telephone assessments for Months 1, 2, 3, 4, and 5. If LFTs are required at Month 1 or Month 2, the subject may obtain these results through a clinic visit or from a local laboratory.

Month 6/End of Trial Visit

All subjects will attend the clinic for the Month 6/End of Trial visit.

3.1.2 Optional Tolvaptan Treatment Component

Subjects enrolled in the 6-month core safety follow-up component may be eligible to receive optional tolvaptan treatment for their hyponatremia. Eligibility criteria for optional tolvaptan treatment are outlined in Appendix 5. Eligibility for optional tolvaptan treatment must be determined at the pre-treatment baseline visit (Day −4 to Day -1) of each dosing cycle. Eligible subjects can be treated at any time with optional tolvaptan during the 6-month core safety follow-up component. Optional tolvaptan treatment duration will be case-specific; it can be short-term or long-term, and consist of 1 or more treatment cycles. When a cycle with optional tolvaptan treatment is completed, including the Follow-up Phase visits, subjects will continue in the core safety component to complete the remainder of visits until Month 6. Within this trial, tolvaptan treatment will not extend beyond the 6-month core safety trial period. If the subject completes the 6-month core safety component while on optional tolvaptan treatment, the subject will complete the Month 6 core safety component visit, terminate treatment, and immediately enter the Follow-up Phase.

If a subject simultaneously participates in both core safety and optional tolvaptan treatment components, the visit days will be calculated between both components to ensure the assessments can be overlapped, where applicable.

3.1.2.1 Treatment Interruption on Day 30

Thirty days after the start of optional tolvaptan treatment, subjects will interrupt treatment for up to 2 doses (Days 31-32). The need for continuing treatment after this tolvaptan interruption will be assessed at minimum once daily (or more as needed) during this time.

Subjects who are expected to receive tolvaptan for greater than 30 days duration should demonstrate the need for continued treatment by discontinuing tolvaptan for up to 2 consecutive doses while undergoing close monitoring of serum sodium levels.

However, there is a subgroup of subjects who have an identifiable cause for hyponatremia that has not (or cannot be) changed that will have an option to be excused from this brief interruption of tolvaptan. Examples of such causes include concomitant treatment for refractory seizures with a hyponatremia-inducing medication such as oxcarbazepine (which can increase vasopressin production by the pituitary) that cannot be changed or discontinued, or subjects with a known underlying hyponatremia inducing condition such as volume overload from a failing Fontan repair.

During this treatment interruption, subjects will have serum sodium levels monitored closely. Subjects who demonstrate a decline in serum sodium level will be restarted at the prior dose of tolvaptan as per clinician judgment. Subjects whose serum sodium declines ≥ 4 mEq/L (mmol/L) or who exhibit symptoms of hyponatremia will be immediately placed under direct observation as per clinician judgment and will be restarted at their previous dose of tolvaptan unless there is a compelling reason to reduce the dose. Subjects will be closely monitored until stable.

Investigators should consider the overall clinical status of the subject (including underlying etiology of hyponatremia and volume assessment), prior response to tolvaptan, concomitant medications, age, and weight when determining the appropriate dose at which to restart a subject after a brief discontinuation of tolvaptan to assess the need for further treatment. Investigators should discuss any concerns with the medical monitor.

- Subjects who resume dosing within 72 hours post last dose (either on Day 32 or by the morning of Day 33), can do so at the same dose or a lower dose without having to go through the full titration cycle again.
- Subjects who have a dosing interruption of ≥ 72 hours must enter a new treatment cycle and repeat the full titration cycle in a hospital setting.
- Subjects who do not need to continue treatment with tolvaptan will proceed directly to the Follow-up Phase (Day 7 Follow-up). Subjects will then continue in the core safety follow-up component and complete remaining required visits, as applicable.

The optional tolvaptan treatment component of the trial will be available for the 6-month duration of the core safety component for each subject.

3.2 Trial Treatments

The core safety follow-up component of the trial does not contain any trial specific treatments. However, eligible subjects have the opportunity to receive tolvaptan treatment in the optional tolvaptan treatment component.

3.2.1 Optional Tolvaptan Treatment

3.2.1.1 Tablet Formulation

Tolvaptan tablets will be administered orally once daily (QD), preferably in the morning hours, with a dose- proportional amount of water. Doses of ≥ 15 mg of tolvaptan will be given with 240 mL of water, 7.5 mg of tolvaptan will be given with 120 mL of water, and 3.75 mg of tolvaptan will be given with 60 mL of water. The quantity of water ingested with each dose should be recorded.

3.2.1.2 Titration Guidelines for the Optional Tolvaptan Treatment Component

In the optional tolvaptan treatment component of the trial, eligible subjects will receive tolvaptan based on age, weight, and the use of CYP3A4 inhibitors. Tolvaptan tablets will be administered orally QD, preferably in the morning hours.

Tolvaptan doses can be titrated QD and will be based on serum sodium levels assessed at 24 (± 4) hours following initiation of therapy and each subsequent dose. Titration guidelines are detailed in Figure 3.2.1.2-1. Titration must occur in a hospital setting. Titration may not occur within 24 (± 4) hours of the previous dose and must be based on serum sodium assessment obtained > 20 hours post previous dose. Titration is limited to no more than twice the previous dose, and will be limited to the maximum dose per body weight.

An age-appropriate formulation is not available for this trial. Therefore, the following subjects will be excluded from the optional treatment component of this protocol:

- Subjects < 4 years of age, or weighing < 10 kg,
- Subjects with an inability to swallow tablets, and
- Subjects weighing < 20 kg and taking a moderate or potent CYP3A4 inhibitor

Table 3.2.1.2-1 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.

Table 3.2.1.2-1	**Starting Tolvaptan Doses With or Without Potent or Moderate CYP3A4 Inhibitors**			
Age/Weight	**Can subject swallow a tablet?**	**Starting Dose: No CYP Inhibitor**	**Starting Dose: Moderate CYP Inhibitor**	**Starting Dose: Potent CYP Inhibitor**
≥ 4 y AND ≥ 10 to < 20 kg	Yes	3.75 mg	Not eligible for treatment	Not eligible for treatment
≥ 4 y AND ≥ 20 to ≤ 50 kg	Yes	7.5 mg	3.75 mg	Not eligible for treatment
≥ 4 y AND > 50 kg	Yes	15 mg	7.5 mg	3.75 mg

Based on the weight versus dose information provided in Table 2.2-1 and taking into consideration the concomitant use of a CYP3A4 inhibitor, the starting doses are as follows:

Subjects ≥ 4 years of age and weighing ≥ 10 to < 20 kg:

- Not taking a moderate or potent CYP3A4 inhibitor will receive a QD oral tolvaptan tablet dose of 3.75 mg, with possible up-titration to 7.5 mg and 15 mg
- Taking a moderate or potent CYP3A4 inhibitor are not eligible for optional tolvaptan treatment

Subjects weighing ≥ 20 to ≤ 50 kg:

- Not taking a moderate or potent CYP3A4 inhibitor will receive a QD oral tolvaptan tablet dose of 7.5 mg, with possible up-titration to 15 mg and 30 mg
- Taking a moderate CYP3A4 inhibitor will receive half the starting tolvaptan tablet dose, eg, 3.75 mg tablet, with possible up-titration to 7.5 mg and 15 mg.
- Subjects are not eligible to receive optional tolvaptan treatment if they are taking a potent CYP3A4 inhibitor.

Subjects weighing > 50 kg

- Not taking a moderate or potent CYP3A4 inhibitor will recieve a QD oral tolvaptan tablet dose of 15 mg, with possible up-titration to 30 mg and 60 mg
- Taking a moderate CYP3A4 inhibitor will receive half the starting tolvaptan tablet dose, ie, 7.5 mg, with possible up-titration to 15 mg and 30 mg

- Taking a potent CYP3A4 inhibitor will receive one quarter the starting tolvaptan tablet dose, eg, 3.75 mg, with possible up-titration to 7.5 mg and 15 mg.

Subjects not eligible for the optional tolvaptan treatment component still remain eligible for the core safety follow-up component.

Subjects eligible for the optional tolvaptan treatment component will titrate according to the guidelines listed in Figure 3.2.1.2-1, targeting a final serum sodium concentration between 135 and 140 mEq/L (mmol/L). The clinician-directed target range is also acceptable.

Treatment can be discontinued at any time and cycles may be repeated as needed. If subjects are off tolvaptan treatment for ≥ 72 hours, re-initiation of tolvaptan treatment, starting with the pre-treatment baseline visit will occur. This will require a reassessment of the eligibility criteria, a tolvaptan titration period, and will begin in a hospital setting as part of a new treatment cycle.

The titration scheme is shown in Figure 3.2.1.2-1.

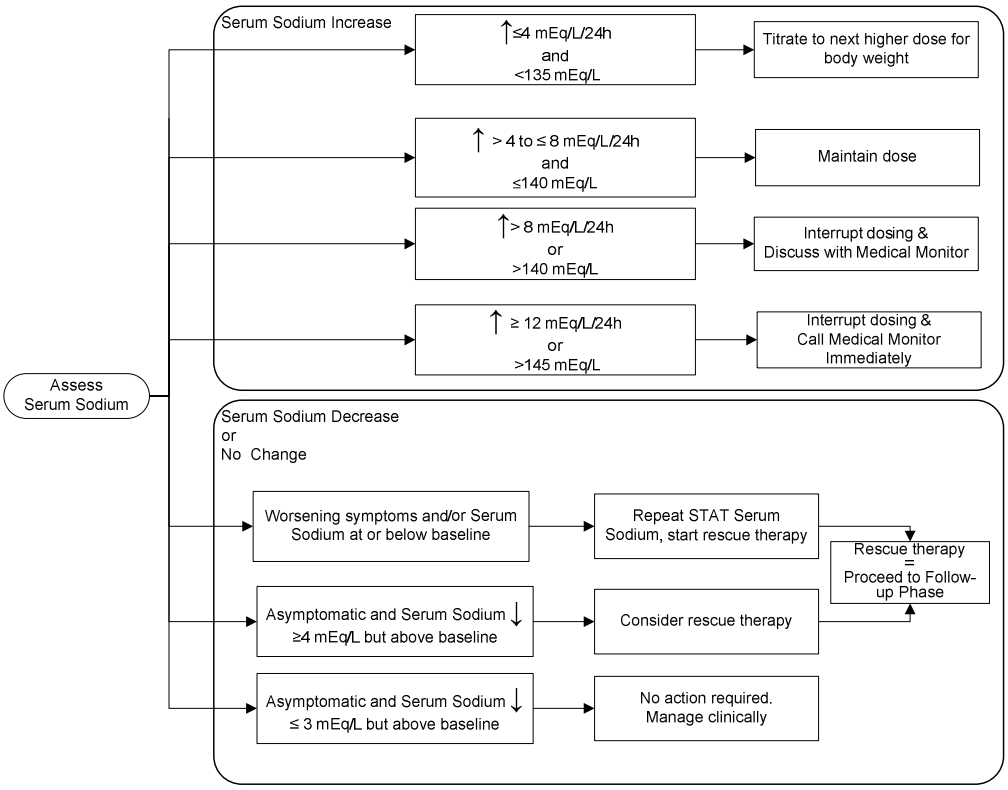


Figure 3.2.1.2-1 Titration Scheme

Titration guidelines are designed to ideally achieve a change in serum sodium concentration of at least 4 to 8 mEq/L (mmol/L) /24 hours but not ≥ 12 mEq/L (mmol/L)/24 hours.

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

- If the serum sodium level increases by ≤ 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.
- If the serum sodium level increases > 4 to ≤ 8 mEq/L (mmol/L)/24 hours in response to tolvaptan treatment and the serum sodium is ≤ 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 discontinuation, concomitant medication adjustment, fluid supplementation and/or withdrawal).
- If serum sodium level increases by ≥ 12 mEq/L (mmol/L) in the 24 hour 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.

3.2.2 Rescue Therapy

Rescue therapy is defined as any treatment, eg, hypertonic saline, isotonic saline (with or without diuretic for the purpose of increasing the serum sodium level), plasmapheresis/dialysis, demeclocycline, urea, lithium, or commercial 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. However, subjects who require rescue therapy during the optional treatment component will be discontinued from tolvaptan prior to receiving rescue therapy.

Subjects will continue to be followed per the schedule of assessments in the optional tolvaptan treatment component (Follow-up Phase visits). Treatment with tolvaptan may be reinitiated only per consultation with the medical monitor. Subjects who have received rescue therapy because of inadequate response to tolvaptan will not be allowed to reinitiate tolvaptan treatment.

For subjects participating in the optional tolvaptan component only, serum sodium values drawn up to, but not after, the initiation of rescue therapy will be included in the

calculation of the efficacy endpoint. Additional guidelines for rescue therapy concerning hyponatremia symptoms and decreasing serum sodium level are as follows:

- If a subject has worsening symptoms and/or has a serum sodium level at or below the baseline value for the current treatment cycle, repeat serum sodium immediately (STAT) to confirm level, and begin rescue therapy.
- If a subject is asymptomatic and serum sodium has decreased by ≥ 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 ≤ 3 mEq/L (mmol/L) but is still above the baseline value, no action is required.

3.2.3 Fluid Restriction

Fluid restriction can be a standard of care in both the core safety follow-up component and the optional tolvaptan treatment component of the trial.

The option of initiating fluid restriction (all fluids) to ≤ 1 liter/day for tolvaptan-treated subjects with serum sodium < 130 mEq/L (mmol/L) is available at the investigator's discretion. Fluid restriction (limit per day) will be recorded (if available and applicable) on the electronic case report form (eCRF).

Fluid restriction must not be initiated for at least the first 24 hours after tolvaptan administration in order to determine the rate and magnitude of serum sodium change. A supplemental serum sodium assessment is scheduled 8 (−1 to + 0.25) hours following the first dose of tolvaptan to provide additional information which may be used to guide the decision to initiate fluid restriction in the future.

3.3 Trial Population

3.3.1 Core Safety Follow-up Component

Approximately 100 male or female subjects will be enrolled in this trial. All subjects must have participated in a previous tolvaptan pediatric hyponatremia trial.

All subjects will be observed for safety for 6 months regardless of treatment status. Subjects enrolled in the core safety component may be eligible to receive optional tolvaptan treatment during the 6-month core safety component (see Appendix 5 for optional tolvaptan treatment component eligibility requirements).

3.3.2 Optional Tolvaptan Treatment Component

Subjects enrolled in the core safety follow-up component of the trial may be eligible for treatment with tolvaptan. These subjects include, but are not limited to, those diagnosed

and admitted to a hospital for treatment of heart failure, hepatocellular disease (including cirrhosis), or SIADH/other. Subjects with acute hyponatremia or hyponatremia expected to resolve spontaneously will be ineligible for tolvaptan treatment. Children with an impaired ability to sense or communicate their thirst will either be required to undergo closer observation, laboratory and urine output monitoring, or will be ineligible for tolvaptan treatment 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 ineligible for tolvaptan treatment.

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/μL 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.[21]

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;[4,22,23] 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

≤ 120 mEq/L (mmol/L), hypernatremia, hypoxemia, severe liver disease, alcoholism, severe burns, severe malnutrition, hypokalemia, diabetes, or renal failure.[4,21]

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 ≥ 130 mEq/L (mmol/L), the subject will be ineligible for tolvaptan administration at that time.

3.4 Eligibility Criteria

3.4.1 Informed Consent/Assent

A written informed consent form (ICF) 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 consent/assent at baseline, and as such must be able to understand that he or she can refuse entry into the trial, or withdraw from the trial at any time without justification, and there will be no consequences to their further care.

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 ICF and written informed assent form. The ICF/assent will be approved by the same IRB/IEC that approves this protocol. Each ICF/assent will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[24] and local regulatory requirements. The investigator will review any written site-specific 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).

Investigators may discuss this trial while the subject is still enrolled in the previous tolvaptan trial, however, consent and assent should not be obtained until the subject is ready to enroll into this trial at the baseline visit. All informed consent/assent procedures must be in accordance with the trial center's IRB/IEC and local regulatory requirements.

Once appropriate essential information has been provided and fully explained in layman's language to the subject and his/her parent or legal guardian by the investigator (or a qualified designee), and it has been documented that the subject and his/her parent or legal guardian has had the opportunity to ask questions, the IRB/IEC-approved written ICF/assent will be signed and dated by both the subject's parent or legal guardian 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 ICF/assent by signing the appropriate form. The subject's parent or legal guardian 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 or legal guardian(s) may be asked to sign additional ICFs if the protocol is amended to significantly add or change procedures. Subjects 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 invited to participate in the core safety follow-up component of the trial must satisfy all ICF/assent requirements, as well as meet all the following inclusion criteria (Table 3.4.2-1):

Table 3.4.2-1 Inclusion Criteria for Core Safety Follow-up Component

1.	Enrollment in a previous tolvaptan pediatric trial for hyponatremia
2.	Trial-specific written informed consent/assent obtained from a parent/guardian or legally acceptable representative, as applicable for local laws, prior to the initiation of any protocol-required procedures. In addition, the subject must provide informed assent at baseline and must be able to understand that he or she can withdraw from the trial at any time
3.	Ability to comply with all requirements of the trial
4.	Willingness to be clinically followed for 6 months

Inclusion criteria for the optional tolvaptan treatment component are outlined in Appendix 5.

3.4.3 Exclusion Criteria

There are no exclusion criteria for entry into the core safety follow-up component of this trial.

Exclusion criteria for the optional tolvaptan treatment component are outlined in Appendix 5.

3.5 Outcome Variables

3.5.1 Primary Outcome Variable

Data for the primary efficacy variable will be collected for all subjects receiving tolvaptan in the optional tolvaptan treatment component of the trial, and will be summarized as follows:

- Change from baseline in serum sodium while tolvaptan is being administered

3.5.2 Secondary Outcome Variables

3.5.2.1 Efficacy Variables

Data for the secondary efficacy variables will be collected for all subjects receiving tolvaptan in the optional tolvaptan treatment component of the trial and will be summarized as follows:

- Percentage of subjects who require rescue therapy while on tolvaptan
- Percentage of subjects who have recurrence of hyponatremia while on tolvaptan
- Percentage of subjects requiring continuation of tolvaptan following 30 days of treatment

Additionally, for all subjects, the following variable will be assessed and summarized:

- Change from baseline in QoL assessments (monthly for subjects on tolvaptan)

3.5.2.2 Safety Variables

Safety variables listed below and their differences from baseline will be summarized.

The safety variables are the following:

- Frequency of AE reports (including cases of dehydration)
- Changes from baseline in growth percentiles by visit for body height and weight
- Tanner Staging progression score (at 6 months)

In addition to the safety variables reported for all subjects, the following variables will be assessed for subjects who enter the optional tolvaptan treatment component of the trial:

- Percentage of subjects with overly rapid correction in serum sodium (≥ 12 mEq/L ([mmol/L]) in 24 hours after the first dose at introduction or reintroduction of tolvaptan)
- Changes from baseline in ALT, AST, BT and creatinine for subjects on tolvaptan

3.5.2.3 Pharmacokinetic Variable: Optional Tolvaptan Treatment Component

- Plasma concentrations of tolvaptan and metabolites in subjects who have continued tolvaptan therapy for 8 consecutive weeks

One PK sample should be taken after 8 weeks of continuous treatment per cycle. This may include a discontinuation of < 72 hours (up to 2 doses) during the Day 30 treatment interruption.

3.6 Measures to Minimize/Avoid Bias

No measures to minimize bias were implemented as this is an observational trial with an option for open-label treatment.

3.7 Trial Procedures

3.7.1 Core Safety Follow-up Component

Enrollment in this trial should follow completion or discontinuation of the previous tolvaptan hyponatremia trial. A lapse between completion of the previous tolvaptan hyponatremia trial and enrollment into this trial is permitted while enrollment is open. Parents or legal guardians will consent and subjects will assent (as applicable) at baseline.

The final laboratory assessments for LFTs from the previous tolvaptan trial can serve as baseline laboratory assessments for this trial if the values are within the normal range, and collected within 30 days of the baseline visit for this trial. The last assessments in the previous tolvaptan trial will serve as the baseline assessments if collected within 30 days of enrollement into this trial. Otherwise, assessments will be repeated if > 30 days have lapsed since the previous tolvaptan trial.

Subjects will be followed for 6 months, (utilizing telephone calls and/or clinical trial site visits). Telephone calls will be conducted with reliable informants, per investigator discretion; either the subject and/or the parent/legal guardian.

Trial assessments and time points for the core safety follow-up component are summarized in Table 3.7.1-1 and described in Section 3.7.3.1.

Table 3.7.1-1 Core Safety Follow-up Component: Schedule of Assessments for All Subjects

Procedures	Baseline	Month 1 (+2 Weeks)	Month 2 (+2 Weeks)	Month 3 (+2 Weeks)	Month 4 (+2 Weeks)	Month 5 (+2 Weeks)	Month 6 or Early Termination (+2 Weeks)
Informed consent and assent	X						
Review inclusion criteria	X						
Demographic information[a]	X						
Telephone assessment[b]		X	X	X	X	X	
In-clinic assessment	X						X
Medical history	X						
Hyponatremia history[a]	X						
Vital signs[a,c]	X						X
Physical examination[a,d]	X						X
Neurological examination	X[h]						
Body height/weight/growth percentiles	X						X
Tanner Staging[a,e]	X						X
ALT, AST, and BT	X[f]	(X)[f]	(X)[f]				
Quality of Life assessments	X						X
Vital status[g]							X
Concomitant medications[a,i]	←	———	———	———	———	———	→
Adverse events[a]	←	———	———	———	———	———	→

[a]The last assessments in the previous tolvaptan trial will serve as the baseline assessments if collected within 30 days of enrollment into this trial. Otherwise, assessments will be repeated if > 30 days has lapsed since the previous tolvaptan trial. For liver function tests, see footnote f.

[b]Telephone calls can be replaced with clinical site visits. Telephone calls will be conducted with reliable informants, per investigator discretion; either the subject and/or the parent/legal guardian.

[c]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.

[d] If the physical examination was performed > 30 days prior to enrollement into this trial, or the baseline visit overlaps with the pretreatment baseline visit in the optional tolvaptan treatment component, a full physical examination will be performed at baseline. A directed physical examination will be done at the core safety baseline visit if < 30 days has elapsed since the previous trial, and should be done at the Month 6/ET visit. Physical examination should include a fontenelle assessment as age appropriate.

[e] A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging.

[f] If the subject's last LFT (AST, ALT or BT) was abnorrmal or the subject's baseline visit occurred > 30 days after completion of the previous trial, the subject will be required to have LFTs assessed at baseline. If the subject's last LFTs were normal and the baseline visit occurred < 30 days after completion of the previous trial, LFTs will be collected at Month 1 or Month 2 (in-clinic visit or local laboratory).

[g] Vital status will be collected through telephone contact at Month 6 (+ 2 weeks) only for subjects who had an early termination and did not withdraw consent.

[h] A full neurological examination will be completed at the baseline visit only if a full physical examination is performed (see footnote d).

[i] If > 30 days has lapsed since the previous tolvaptan trial, medications taken with 30 days of enrollment will be recorded.

3.7.2 Optional Tolvaptan Treatment Component

If a subject has a clinical need for tolvaptan, the subject may be screened for eligibility to be treated with tolvaptan (see Appendix 5). To assess the subject's eligibility to receive tolvaptan, the subject must have been off treatment with IMP for 7 days following the end of treatment in the previous tolvaptan trial.

Subjects who meet the eligibility criteria for tolvaptan treatment will be administered tolvaptan based on age, weight, and the use of CYP3A4 inhibitors on Day 1 of the cycle. Subsequent dosing adjustments are based on serum sodium response. Refer to Section 3.2.1.2 for dosing guidelines.

Trial assessments and time points for the optional tolvaptan treatment component are summarized in Table 3.7.2-1 and described in Section 3.7.3.2.

	Table 3.7.2-1 Schedule of Assessments for Each Treatment Cycle															
Procedures[a]	**Pre-treatment Baseline[b]**	**Titration Phase[b]**			**Post-titration**						**Treatment Cycle Month 2**	**Treatment Cycle Month 3+ (Maintenance)**	**Month 6 (D173) Cycle DC (+ 2 wk)**	**Follow- up Phase[k]**		
	Days -4 to -1	**Day 1**	**Day 2 and 3**	**Day 4**	**Day 7, 14 and 21**	**Day 30 (±1)**	**Day 31[c]**	**Day 32[c]**	**Day 33[c]**	**Day 34[c]**	**every 2 weeks (±2 days) Mth 2 Wk 2 (D47), Mth 2 Wk 4 (D61)**	**Once monthly (±2 days) Mth 3 (D89), Mth 4 (D117), Mth 5 (D145)**		**24 (±4) hours post-last dose**	**7 (±1) days post-last dose**	**14 (±2) days post-last dose**
Review eligibility criteria for treatment	X															
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[d]	X											X	X			
Body height and weight/ growth percentiles	X											X	X			
Pregnancy test[e]	X								X		X	X		X		
Clinical status assessment	X						X	X	X	X	X	X				
Neurological assessment[f]	X						X	X	X	X	X	X				
Quality of Life assessment	X											X				
Assess ALT, AST, BT, and creatinine	X					X					X[g]	X	X	X		
Assess serum sodium[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Table 3.7.2-1 Schedule of Assessments for Each Treatment Cycle															
Procedures[a]	**Pre-treatment Baseline[b]**	**Titration Phase[b]**			**Post-titration**						**Treatment Cycle Month 2**	**Treatment Cycle Month 3+ (Maintenance)**	**Month 6 (D173) Cycle DC (+ 2 wk)**	**Follow- up Phase[k]**		
	Days -4 to -1	**Day 1**	**Day 2 and 3**	**Day 4**	**Day 7, 14 and 21**	**Day 30 (±1)**	**Day 31[c]**	**Day 32[c]**	**Day 33[c]**	**Day 34[c]**	**every 2 weeks (±2 days) Mth 2 Wk 2 (D47), Mth 2 Wk 4 (D61)**	**Once monthly (±2 days) Mth 3 (D89), Mth 4 (D117), Mth 5 (D145)**		**24 (±4) hours post-last dose**	**7 (±1) days post-last dose**	**14 (±2) days post-last dose**
Tolvaptan dosing		X	X[i]	X[i]	X	X			X	X	X	X				
Confirm stable dose				X												
Dispense tolvaptan drug kit				X	X					X	X	X				
Day 30 treatment interruption							X	X								
Tolvaptan collection/ reconciliation					X	X					X	X		X		
PK sample collection[j]											X	X[j]				
Telephone call																X
Concomitant medications	←															→
Adverse events	←															→

[a] Assessments that are part of a core safety follow-up component trial visit which happens to overlap with a visit in the optional tolvaptan treatment component only need to be performed once.

[b] Titration can be up to 4 days. Cycles can be repeated as needed during the 6-month core safety component. If a subject is off tolvaptan treatment for ≥ 72 hours, titration/reinitiation of tolvaptan will require reassessment of eligibility criteria and will begin in a hospital setting as part of a new treatment cycle.

[c] During the Day 30 treatment interruption, Days 31, 32, 33 and 34 must follow consecutively. Once the Day 30 visit is determined, the subsequent visit days do not have a window.

[d] A full physical examination will be performed at the pretreatment baseline visit if it overlaps the day of the core safety component baseline visit. Otherwise, a directed physical examination will be performed at the required visits. A physical examination should include a fontanelle assessment as age appropriate.

[e] Urine or serum pregnancy tests will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. In Treatment Cycle Month 2 a pregnancy test should be performed a month after the previous assessment at the Month 2, Week 4 visit.

[f] A full neurological examination will be completed at the first pretreatment baseline visit. If the subject has any positive findings on any of the clinical status assessments, a full neurological examination can be performed per investigator judgment.

[g] In Treatment Cycle Month 2, Week 4, liver function tests and serum creatinine should be collected and assessed.

[h] Serum sodium will be assessed for efficacy and safety (supplemental draws) according to Table 3.7.4.1.2-1.

[i] The dose will be titrated based on serum sodium results assessed at a minimum of 24-hour intervals (± 4 hours). See Section 3.2.1.2 for dosing information.

[j] One PK sample should be taken after 8 weeks of continuous treatment per cycle. This may include a discontinuation of < 72 hours during the Day 30 treatment interruption. A sample will only be collected at Month 3 if missed at the Month 2 visit.

[k] Subjects who discontinue or complete the treatment cycle should immediately proceed to the Follow-up Phase.

3.7.3 Schedule of Assessments

3.7.3.1 Core Safety Follow-up Component

3.7.3.1.1 Baseline

Participation in this trial should follow completion or discontinuation of the previous tolvaptan trial. The last assessments in the previous tolvalptan trial will serve as the baseline assessments if collected within 30 days of enrollment into this trial. Otherwise, assessments will be repeated if > 30 days has lapsed since the previous tolvaptan trial.

The following procedures will be performed during the baseline visit:

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) ICF and assent will be obtained from each subject's parent or legal guardian prior to any trial procedures being conducted.
   b) Each subject will indicate willingness to participate in the trial by signing or marking an assent form (as applicable) supplied for this purpose.
   c) Informed consent/assent needs to be obtained each time a subject matriculates into the next age group.
2) Inclusion criteria for entry into the core safety follow-up component will be reviewed and documented.
3) Demographic information will be collected or transferred from the previous trial.
4) Medical and hyponatremia history will be recorded separately. Medical history should include the subject's current list of medical problems in addition to the history recorded for the prior trial. The hyponatremia medical history should include the etiology of subject's hyponatremia (see Section 3.3.2) and what treatment was administered before trial enrollment. A detailed history specific to etiology of hyponatremia will also be recorded.
5) Any observable symptoms of hyponatremia will be assessed and recorded separately.
6) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be transferred from the last assessments from the previous trial or assessed after the subject has been supine for ≥ 3 minutes, as appropriate. Vital signs should be performed prior to the blood draws.
7) Physical examination information will be transferred from the last assessments from the previous trial or performed, as appropriate. Physical examination should include a fontenelle assessment as age appropriate.
8) A neurological examination will be conducted. A full neurological examination will be completed if a full physical examination is performed.
9) Body height and body weight will be measured.
10) Growth percentile will be calculated. Prior growth development information should also be collected, if available.

11) Tanner Staging will be transferred from the last assessments from the previous trial or completed as part of the physical examination, as appropriate. Historical staging information should also be collected, if available. A subject who has reached Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging.
12) If the subject's last LFT (AST, ALT or BT) was abnormal or the subject's baseline visit occurred > 30 days after completion of the previous trial, the subject will be required to have LFTs assessed at baseline. If the subject's last LFTs were normal and the baseline visit occurred < 30 days after completion of the previous trial, LFTs will be collected at Month 1 or Month 2.
13) Quality of Life assessment will be performed, as appropriate by age and where available.
14) Concomitant medications will be recorded. If > 30 days have lapsed since the previous tolvaptan trial, medications taken within 30 days of enrollment will be recorded.
15) Adverse events will be assessed.

3.7.3.1.2 Months 1, 2, 3, 4, and 5

Subjects and/or their parents or legal guardians will be contacted by telephone at the end of Months 1, 2, 3, 4, and 5 (+ 2 weeks) to assess any new or ongoing AEs and to collect information on any medications administered since the last visit.

If the subject's last LFTs were normal and the baseline visit occurred < 30 days after completion of the previous trial, LFTs will be collected at Month 1 or Month 2 (in-clinic visit or local laboratory).

3.7.3.1.3 Month 6/Early Termination

Subjects will return to the clinical trial site at the end of Month 6 (+ 2 weeks) or at early termination (ET) and the following assessments will be performed:

1) Any observable symptoms of hyponatremia will be assessed and recorded separately.
2) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be performed prior to any blood draws.
3) A directed physical examination will be performed. Physical examination should include a fontenelle assessment as age appropriate.
4) Body height will be measured.
5) Body weight will be measured.
6) Growth percentile will be calculated.

7) Tanner Staging will be completed at the Month 6 clinical trial site visit or at ET according to the instructions specified in Section 3.7.5.6 and Appendix 4. A subject who has reached Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging.
8) Quality of Life assessment will be performed, as appropriate by age and where available.
9) Concomitant medications will be recorded.
10) Adverse events will be assessed.

Month 6 is the completion visit, and subjects will no longer be eligible for optional tolvaptan treatment under this protocol at this time.

If a subject terminates early from the trial and agrees to continued telephone contact, the subject or parent/legal guardian will be contacted by telephone at Month 6 to assess vital status.

3.7.3.2 Optional Tolvaptan Treatment Component

Subjects may become eligible for tolvaptan treatment at any time while participating in the 6-month core safety follow-up component if they have dilutional (euvolemic or hypervolemic) hyponatremia (serum sodium < 130 mEq/L [mmol/L]). The investigator is required to call the medical monitor to discuss the appropriateness of tolvaptan treatment for subjects who discontinued from the previous trial of titrated oral IMP early or demonstrated a lack of response to tolvaptan, but have a demonstrated clinical need for tolvaptan. Subjects participating in the optional tolvaptan treatment component will concurrently maintain visit assessments in the core safety follow up component up to and including the Month 6 final visit. Core safety follow-up assessments can be scheduled per the defined windows and at the convenience of the subject's optional tolvaptan treatment visit schedule.

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 exclude such cases from the optional tolvaptan treatment component of the trial. To be eligible for the optional tolvaptan treatment component of this protocol, subjects must have persistent dilutional (euvolemic or hypervolemic) hyponatremia, defined as serum sodium assessments < 130 mEq/L (mmol/L) that are documented for at least 48 hours after the final dose of IMP in the previous trial and prior to the planned initiation of tolvaptan titration in this trial. These values can be documented using historical values previously obtained per standard of care. A third (immediate [STAT]) serum sodium assessment < 130 mEq/L (mmol/L), which will serve as the final treatment qualification, management strategy, and baseline

value for efficacy endpoints, is to be obtained within 2 to 4 hours prior to the first dose of tolvaptan. Additional qualification assessments will be performed per etiology of hyponatremia (Section 3.3.2).

The procedures to be performed at the required visits for subjects in need of tolvaptan treatment and for each tolvaptan treatment cycle are summarized in this section.

If possible, all assessments while subjects are treated with tolvaptan should be synchronized with those performed as part of the core safety follow-up component of the trial (ie, assessments should not be performed twice at the same time point).

3.7.3.2.1 Pretreatment Baseline Visit

The following procedures will be performed during the pretreatment baseline visit (Days −4 to −1) to ensure the subject qualifies for each tolvaptan treatment cycle:

1) Eligibility criteria (see Appendix 5) will be reviewed.
2) A clinical status assessment including a full neurological examination will be performed. If the subject has any positive findings on the clinical status assessment at the second or subsequent pretreatment baseline visits, a full neurological examination can be performed per investigator judgment.
3) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed at each visit after the subject has been supine for ≥ 3 minutes. Vital signs should be performed prior to the blood draws.
4) A full physical examination will be performed if it overlaps with the same assessment at the core safety baseline visit. Otherwise, a directed physical examination will be performed. Physical examination should include a fontenelle assessment as age appropriate.
5) Body height will be measured.
6) Body weight will be measured.
7) Growth percentile will be calculated.
8) A blood sample for ALT, AST, BT and creatinine will be collected.
9) A urine or serum pregnancy test will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started.
10) Within 48 hours prior to tolvaptan administration, 2 samples for serum sodium testing will be collected at least 12 hours apart.
11) Quality of Life assessment will be performed, as appropriate by age and where available.
12) Concomitant medications will be recorded.
13) Adverse events will be assessed.

3.7.3.2.2 Titration Phase

A subject who requires tolvaptan treatment can be treated for as many cycles as deemed necessary by the investigator within the 6 month trial period. The duration of treatment cycles may vary per the investigator's assessment of clinical need. Regardless of the number of treatment cycles and the duration of tolvaptan treatment in each cycle, optional tolvaptan treatment cycles will consist of a titration phase, a maintenance phase, and a follow-up phase. The schedule of assessments for the optional tolvaptan treatment component is shown in Table 3.7.2-1.

The first dose of tolvaptan will be administered upon successful completion of all pretreatment baseline procedures. Subjects will enter a titration phase and follow the titration schedule outlined in Section 3.2.1.2. Subjects will be required to be in a hospital setting during initiation and titration of tolvaptan.

During the Titration Phase on Day 1 up to Day 4 of treatment, in addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment will be obtained using a point of care (POC) sodium assessment unit, where available, at 4 to 6 (+0.25) hours postdose and at 18 (± 1) hours postdose. A POC assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs). A schedule of blood samples required for serum sodium assessments can be found in Table 3.7.4.1.2-1.

3.7.3.2.2.1 Day 1

All titration of tolvaptan will be done in a hospital setting. Please see Section 3.2.1 for details on titration and dosing.

The following procedures will be performed on Day 1:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A blood sample for STAT serum sodium testing will be collected within 2 to 4 hours prior to the first dose. Results need to be reviewed prior to dosing to confirm continued treatment eligibility of the subject.
3) In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only will be obtained using a POC sodium assessment unit, where available, on Day 1 at 4 to 6 (+0.25) hours postdose and at 18 (± 1) hours postdose. A POC assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs).
4) Tolvaptan will be administered.

5) A blood sample for serum sodium testing will be collected 8 (-1 to +0.25) hours post-first dose.
6) Concomitant medications will be recorded.
7) Adverse events will be assessed.

Table 3.7.4.1.2-1 presents the efficacy and safety serum sodium samples required during Day 1 of the titration period.

3.7.3.2.2.2 Day 2 up to Day 4

The investigator should schedule evaluations daily while the subject remains in a hospital setting per the schedule of assessments. The following procedures will be performed during the titration period:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-dose (trough) on Days 2, 3, and 4. The results must be reviewed prior to tolvaptan dosing.
3) In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment will be obtained using a POC sodium assessment unit, where available, at 6 (-1 to +0.25) hours postdose and at 18 (± 1) hours postdose on Days 2, 3, and 4 during the titration period. A POC assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs).
4) Administer tolvaptan. Tolvaptan will be titrated per the titration guidelines (see Section 3.2.1.2).
4) On Day 4, if a stable dose of tolvaptan has been confirmed, the initial titration phase will conclude, and sufficient tolvaptan will be dispensed for subjects that are outpatients for QD dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation.
6) Concomitant medications will be recorded.
7) Adverse events will be assessed.
8) Instruct subjects not to take a tolvaptan dose before coming to the clinic for their Day 7 visit.

Table 3.7.4.1.2-1 presents the efficacy and safety serum sodium samples required during Days 2, 3, and 4 of the titration period.

3.7.3.2.3 Days 7, 14, and 21

Subjects should arrive to the clinic prior to taking the morning dose of tolvaptan. The following assessments will be performed during each in-clinic visit during the first month of the treatment cycle:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-last dose with the results reviewed prior to subsequent tolvaptan dosing.
3) Tolvaptan will be administered.
4) Tolvaptan dispensed at each visit will be returned for accountability.
5) Sufficient tolvaptan will be dispensed for subjects that are outpatients for QD dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation.
6) Concomitant medications will be recorded.
7) Adverse events will be assessed.
8) Instruct subjects not to take a tolvaptan dose before coming to the clinic for their Day 14, 21, and 30 visits.

Once the Day 30 visit is scheduled, the next visits (Days 31 to 34) must occur consecutively.

3.7.3.2.4 Day 30 Interruption: 30 (±1) Days Post-first Dose

After 30 days of tolvaptan treatment, all subjects (exceptions explained in Section 3.1.2.1) should discontinue treatment for up to 2 doses to assess the continued need for tolvaptan treatment. Subjects should arrive to the clinic prior to taking the morning dose of tolvaptan.

The following assessments will be performed during the Day 30 visit:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-last dose with the results reviewed prior to subsequent tolvaptan dosing.
3) A blood sample for ALT, AST, BT, and creatinine will be collected.
4) Tolvaptan dispensed the previous week will be returned for accountability.
5) Tolvaptan will be administered during the clinic visit.
6) Concomitant medications will be recorded.
7) Adverse events will be assessed.

8) Instruct subjects to return to the clinic for visits on Day 31 and 32.

3.7.3.2.4.1 Day 31

The following assessments will be performed:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A clinical status assessment will be performed. If the subject has any positive findings on the clinical status assessment, a full neurological examination can be performed per investigator judgment.
3) A blood sample will be collected for serum sodium testing at 24 hours (± 4 hours) post the Day 30 dose. Refer to Figure 3.1-1 for a trial schematic, and Section 3.2.1 for a description of the treatment continuation decision.
4) Concomitant medications will be recorded.
5) Adverse events will be assessed.

3.7.3.2.4.2 Day 32

The following assessments will be performed:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A clinical status assessment will be performed. If the subject has any positive findings on the clinical status assessment, a full neurological examination can be performed per investigator judgment.
3) A blood sample will be collected for serum sodium testing at 48 hours (± 4 hours) post the Day 30 dose. Refer to Figure 3.1-1 for a trial schematic and Section 3.2.1 for a description of the treatment continuation decision.
4) Concomitant medications will be recorded.
5) Adverse events will be assessed.

3.7.3.2.4.3 Day 33

The following assessments will be performed:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A clinical status assessment will be performed. If the subject has any positive findings on the clinical status assessment, a full neurological examination can be performed per investigator judgment.

3) A urine or serum pregnancy test will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started.
4) A blood sample will be collected for serum sodium testing at 72 hours (± 4 hours) post the Day 30 dose. Refer to Figure 3.1-1 for a trial schematic and Section 3.2.1 for a description of the treatment continuation decision.
5) Confirm need for continuing treatment.
   a) If continuing treatment is needed and subjects have been off drug for < 72 hours:
      - Tolvaptan will be administered.
        Subjects who reinitiate treatment at the same dose or a lower dose of tolvaptan after discontinuation for < 72 hours will not be required to reinitiate treatment in a hospital setting. However, tolvaptan will not be dispensed until subjects have a 24 hour postdose serum sodium assessment on Day 34.
   b) If continuing treatment is needed and subjects have been off drug for ≥ 72 hours:
      - Subjects will reinitiate treatment, starting with titration (Section 3.2.1.2), which will require reassessment of the eligibility criteria. Titration will begin in a hospital setting as part of a new treatment cycle starting at the pretreatment baseline visit (Section 3.7.3.2.1). In these cases, the subject will re-start the schedule of assessments at the pretreatment baseline visit.
   c) If no continuing treatment is needed:
      - The subject will move to the Follow-up Phase visit schedule and complete the assessments for the 7-day and 14-day post-last dose visits (Section 3.7.3.2.7.2).
6) Concomitant medications will be recorded.
7) Adverse events will be assessed.

3.7.3.2.4.4 Day 34

The following assessments will be performed:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A clinical status assessment will be performed. If the subject has any positive findings on the clinical status assessment, a full neurological examination can be performed per investigator judgment.
3) A blood sample will be collected for serum sodium testing at 24-hours (± 4 hours) post last dose (trough) with the results reviewed prior to a subsequent tolvaptan dose.
4) Tolvaptan will be administered.
5) Sufficient tolvaptan will be dispensed for subjects that are outpatients for QD dosing until their next scheduled visit. Subjects and their parents/legal guardians

will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation.

6) Concomitant medications will be recorded.
7) Adverse events will be assessed.
8) Instruct subjects not to take a tolvaptan dose on the day of the next scheduled visit.

3.7.3.2.5 Treatment Cycle Month 2: Month 2 Week 2 and Month 2 Week 4 (±2 days)

The next clinic visit should occur 2 weeks after the decision to continue treatment is made (Month 2 Week 2, Day 47 [± 2 days]), and then 2 weeks thereafter if treatment is continued (Month 2 Week 4, Day 61 [± 2 days]). Subjects should arrive to the clinic prior to taking the morning dose of tolvaptan.

The following assessments will be performed during each visit during the second month of each treatment cycle:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-last dose (trough) with the results reviewed prior to subsequent tolvaptan dosing.
3) A blood sample for ALT, AST, BT and creatinine will be collected (Month 2 Week 4 visit only).
4) For each treatment cycle, a single PK blood sample will be collected after 8 consecutive weeks of tolvaptan dosing for the determination of tolvaptan and metabolites plasma concentrations.
5) A clinical status assessment will be performed. If the subject has any positive findings on the clinical status assessment, a full neurological examination can be performed per investigator judgment.
6) A urine or serum pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started (Month 2 Week 4 visit only).
7) Tolvaptan dispensed the previous visit will be returned for accountability.
8) Tolvaptan will be administered in clinic.
9) Sufficient tolvaptan will be dispensed for subjects that are outpatients for QD dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation.
10) Concomitant medications will be recorded.
11) Adverse events will be assessed.

12) Instruct subjects not to take a tolvaptan dose on the day of the next scheduled visit.

3.7.3.2.6 Maintenance Phase

3.7.3.2.6.1 Treatment Cycle Month 3 (and every month thereafter) (±2 days)

Subjects will return to the clinical trial site for assessment once monthly for Month 3 (Day 89 [± 2 days]), Month 4 (Day 117 [± 2 days]), Month 5 (Day 145 [± 2 days]) and Month 6 (Day 173[± 2 days]). Subjects should arrive to the clinic prior to taking the morning dose of tolvaptan. The following procedures will be performed:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A urine or serum pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started (Months 3, 4, and 5).
3) A directed physical examination will be performed. Physical examination should include a fontenelle assessment as age appropriate.
4) Body height will be measured (Months 3, 4, and 5).
5) Body weight will be measured (Months 3, 4, and 5).
6) Growth percentile will be calculated (Months 3, 4, and 5).
7) A clinical status assessment will be performed. If the subject has any positive findings on the clinical status assessment, a full neurological examination can be performed per investigator judgment (Months 3, 4, and 5).
8) A blood sample for ALT, AST, BT, and creatinine will be collected.
9) A blood sample for serum sodium testing will be collected at 24 hours (± 4 hours) post-last dose (trough).
10) Tolvaptan dispensed the previous month will be returned for accountability.
11) Tolvaptan will be administered in the clinic (Months 3, 4, and 5).
12) Sufficient tolvaptan will be dispensed for subjects that are outpatients for QD dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation.
13) A single PK blood sample will be collected if missed at Month 2 and there have been 8 weeks of consecutive tolvaptan treatment.
14) Quality of Life assessments will be performed, as appropriate by age and where available (Months 3, 4, and 5).
15) Concomitant medications will be recorded.
16) Adverse events will be assessed.

17) Instruct subjects not to take a tolvaptan dose on the day of the next scheduled visit (Months 3, 4, and 5).

Tolvaptan treatment cycles may be repeated at the discretion of the investigator during subject's participation in the 6-month core safety period. After discontinuation of tolvaptan for any reason, subjects will proceed to the Follow-up Phase as noted in Section 3.7.3.2.7.

3.7.3.2.7 Follow-up Phase

After discontinuation from tolvaptan treatment, the subject must return to the site for follow-up assessments at 24 (± 4) hours post-last dose (if applicable) and/or at 7 (±1) days post-last dose. A follow-up telephone contact will occur at 14 (±2) days post-last dose.

If a subject starts a new treatment cycle during the Follow-up Phase, the remaining follow-up visits will not be done and the subject will restart at the pretreatment baseline visit.

3.7.3.2.7.1 First Follow-up: 24 (± 4) Hours Post-last Dose

The following procedures will be performed:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A blood sample for ALT, AST, BT, and creatinine will be collected.
3) A urine or serum pregnancy test will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started (if not done within the last 30 days).
4) A blood sample for serum sodium testing will be collected at 24 (± 4) hours post-last dose.
5) Any remaining tolvaptan will be collected from the subjects and returned for accountability.
6) Concomitant medications will be recorded.
7) Adverse events will be assessed.

3.7.3.2.7.2 Second Follow-up: 7 (± 1) Days Post-last Dose

An additional follow-up visit will occur 7 (± 1) days post-last dose. The following assessments will be performed:

1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws.
2) A blood sample for serum sodium testing will be collected.
3) Concomitant medications will be recorded.
4) Adverse events will be assessed.

3.7.3.2.7.3 Third Follow-up: 14 (± 2) Days Post-last Dose

A follow-up telephone contact will occur at 14 (± 2) days post-last dose for assessment of AEs and concomitant medications.

1) Concomitant medications will be recorded.
2) Adverse events will be assessed.

Subjects will complete the remaining visits in the core safety follow-up component up to Month 6.

3.7.4 Efficacy Assessments

3.7.4.1 Serum Sodium Concentrations

3.7.4.1.1 Serum Sodium Samples for Efficacy

Serum sodium samples for assessment of efficacy will be collected during the optional tolvaptan treatment component of the trial according to Table 3.7.4.1.2-1.

Additional details can be found in Section 3.7.3.2.

3.7.4.1.2 Supplemental Sodium Samples for Safety

In addition to serum sodium samples obtained for treatment qualification and efficacy endpoints, supplemental samples for the purposes of safety assessment only will be obtained using a POC sodium assessment unit, where available. A POC assessment unit is preferred; however, regular blood draws may be used (especially if they can be combined with standard of care labs). The supplemental sodium samples for safety assessments are found in Table 3.7.4.1.2-1.

Table 3.7.4.1.2-1 Serum Sodium Assessments During the Optional Tolvaptan Component

			Blood Draws for Serum Sodium	
Treatment Cycle	**Phase**	**Day**	**Efficacy**	**Supplemental Safety**
Month 1	Pretreatment baseline	-4 to -1	Within 48 hours prior to tolvaptan administration, 2 blood samples, 12 hours apart	-
	Titration	1	2 to 4 hours prior to the first dose	-
			8 (-1 to + 0.25) hours postdose	4 to 6 (+ 0.25) hours postdose
			-	18 (± 1) hours postdose
		2, 3, and 4	24 (± 4) hours post previous dose (trough)	6 (-1 to +0.25) hours and 18 (±1) hours postdose
	Posttitration treatment	7, 14 and 21	24 (± 4) hours post previous dose	-
	Day 30 interruption	30	24 (± 4) hours post previous dose	-
		31	24 (± 4) hours post previous dose	
		32	48 (± 4) hours post previous dose	-
		33	72 (± 4) hours post previous dose	-
		34	24 (± 4) hours post previous dose	-
Month 2	Treatment	Every 14 (± 2) days	24 (± 4) hours post previous dose	-
Months 3, 4 and 5	Treatment (Maintanence)	Every month (± 2 days)	24 (± 4) hours post previous dose	-
Month 6/ET	Trial termination	-	Month 6 or trial termination	-
Follow-up	Follow-up	-	24 (± 4) hours post-previous dose	-
		-	7 (±1) days post last dose	-

Additional details can be found in Section 3.7.3.2.

3.7.4.1.3 Unscheduled Assessments

Additional unscheduled serum sodium assessments or supplemental sodium assessments (POC) 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. Unscheduled sodium assessments will only be collected if associated with an AE.

3.7.4.2 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 ≥ 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 or the parent/caregiver, as appropriate.

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

3.7.5 Safety Assessments

Safety will be assessed through the monitoring of AEs, clinical laboratory tests, vital signs, body weight, physical examinations, neurological examinations, rescue therapy, fluid restriction, and Tanner Staging. See Table 3.7.1-1 and Table 3.7.2-1.

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 3.7.5.2.

3.7.5.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

In addition, for subjects on tolvaptan treatment, active monitoring is required for:

- Absolute serum sodium level ≥ 145 mEq/L (mmol/L)
- An overly rapid correction of the serum sodium level (an increase in serum sodium of > 8 mEq/L [mEq/L (mmol/L)] over a 10-hour period, ≥ 12 mEq/L [mEq/L (mmol/L)] over a 24-hour period, or a rate of correction in serum sodium concentration that the investigator deems too rapid)
- Neurologic symptoms, or other signs or symptoms suggestive of osmotic demyelination (see Section 5.3.1 for more details)
- Elevations in AST or ALT that are ≥ 2 × ULN or levels that increase ≥ 2 times their previously observed level. If this occurs, a BT level should also be

evaluated. See Section 3.7.5.3.1 for more information and Section 5.4 for detailed instructions on how this type of event should be captured

- Worsening symptoms of hyponatremia
- Hypovolemia or hypotension requiring intervention.
- Clinical signs and symptoms of dehydration

3.7.5.2 Clinical Laboratory Tests: Core Safety Follow-up Component

Table 3.7.5.2-1 presents the protocol-required clinical laboratory tests for all subjects enrolled in the core safety follow-up component. No further laboratory assessments are required per protocol except as needed for the follow-up of AEs.

Table 3.7.5.2-1	**Clinical Laboratory Tests During Core Safety Follow-up**
AST **ALT** **BT**	

3.7.5.3 Clinical Laboratory Tests: Optional Tolvaptan Treatment Component

Table 3.7.5.3-1 presents the protocol-required clinical laboratory tests for all subjects in the optional tolvaptan treatment component. If these laboratory tests are to be obtained as part of the standard of care for the subject, the timing should be coordinated per the schedule of assessments (Section 3.7.3), whenever possible, to minimize the number of blood draws for the subject. All clinical laboratory tests required during optional tolvaptan treatment will be performed by local laboratories. For the schedule of laboratory assessments, please refer to Appendix 6.

Table 3.7.5.3-1	**Clinical Laboratory Tests During Optional Tolvaptan Treatment**
ALT AST BT Creatinine	<u>Efficacy:</u> Serum Sodium <u>Additional Tests:</u> Serum or urine pregnancy test (if applicable) Supplemental sodium samples for safety

3.7.5.3.1 Monitoring of Liver Transaminases

Long-term use of tolvaptan has demonstrated the potential to cause a clinically significant elevation in liver function test values. 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 ≥ 2 × ULN or whose levels increase ≥ 2 times their previous observed value, a total bilirubin (BT) level should also be evaluated. These elevated values should be confirmed by retesting. If BT is ≥ 2× ULN or ≥ 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.

3.7.5.4 Physical Examination and Vital Sign Assessments

Full and directed physical examinations will be performed and documented according to the Schedule of Assessments (Section 3.7.3). If the physical examination was performed > 30 days prior to enrollment into this trial or the core safety baseline visit overlaps with the pretreatment baseline visit in the optional tolvaptan treatment component, a full physical examination will be performed. A directed physical examination will be done at the core safety baseline visit if < 30 days have elapsed since the previous trial. A directed physical examination will also be performed at the Month 6/ET visit.

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. Any condition present at the posttreatment directed physical examination that was not present at baseline 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.

Body weight will be measured (see Schedule of Assessments Section 3.7.3). Every effort should be made to ensure that body weight measurements will be performed in a reproducible and consistent manner. Body weight measurements should be performed at the clinical trial 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.

Vital sign data will include supine blood pressure, heart rate, respiratory rate, and temperature. Vital signs will be taken when the subject has been lying down (bed positioned < 45 degree angle) for at least 3 minutes. All vital sign assessments should be performed prior to the blood draw at the nominal time point.

3.7.5.5 Neurological Examination

A neurological examination will be performed as part of the directed physical examination per the Schedule of Assessments in Table 3.7.1-1 and Table 3.7.2-1. 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.

A full neurological examination will be completed at the core safety baseline visit only if a full physical examination is being performed, or at the first pretreatment baseline visit. If the subject has any positive findings on any of the clinical status assessments, a full neurological examination can be performed per investigator judgment.

The principal investigator or his/her appointed designee is primarily responsible to perform the full neurological examination. If the appointed designee is to perform the full neurological examination, he/she must be permitted by local regulations.

3.7.5.6 Tanner Staging

The collection of Tanner Staging data is required for all subjects in the core safety follow-up component at the baseline and the Month 6 Visit. Every attempt should be made to collect this information.

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 may be completed by the trial affiliated pediatrician or family practitioner (additionally physician's assistant or nurse practitioner where licensing permits). A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging, and the same stage will be carried forward to any subsequent visits. 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 clinician will arrive at a single score summarizing the domains (not individual domain scores) when evaluating the subject.

3.7.5.7 Hyponatremia History

Each subject's hyponatremia medical history will be recorded at the baseline visit of the core safety follow-up component. The hyponatremia history should include the etiology of subject's hyponatremia and what treatment was administered before trial enrollment. Symptoms potentially attributable to hyponatremia should be specifically assessed for in prior history. The hyponatremia assessment at baseline will consist of documentation of hyponatremia etiology (eg, SIADH, hepatocellular disease [including cirrhosis], heart failure, or other) and prior hyponatremia treatment, ie, fluid restriction, if applicable. A detailed history specific to etiology of hyponatremia will also be recorded.

3.7.5.8 Clinical Status Assessment

Clinical status assessments will be performed per inpatient standard of care and should include review of patient 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.

3.7.5.9 Vital Status

An assessment of vital status will be conducted on subjects who terminate prior to the Month 6 core safety visit, and do not withdraw consent for continued telephone contact. The telephone contact will be made on the date at which the subject would have reached the core safety follow-up component Month 6 visit (+ 2 weeks), and will be conducted with a reliable informant; either the subject and/or the parent/legal guardian, per investigator discretion. Vital status collected and recorded will be:

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

3.7.6 Pharmacokinetic Assessments

3.7.6.1 Blood Collection Times

For subjects undergoing treatment with tolvaptan for at least 8 consecutive weeks (short interruptions of < 72 hours are still considered consecutive treatment), a single blood sample to measure tolvaptan and metabolite concentrations at steady state will be

obtained for each treatment cycle. The date and time of the PK sample and the date and time of the dose given immediately prior to the PK sample will be documented and recorded on the eCRF.

For each subject all samples will be collected according to local guidelines and best practices for pediatric care.

3.7.6.2 Sample Handling and Processing

All blood samples will be shipped to the testing facility for analysis. Specific information regarding sample handling and processing is provided in Appendix 3.

3.7.7 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 Month 6 visit or early termination visit for the last subject completing or withdrawing from the trial.

3.7.8 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) has been 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 Component(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

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB/IEC if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). 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 the trial 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 must be withdrawn from tolvaptan treatment:

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 of tolvaptan treatment;
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 (see Section 3.12, Subject Compliance);
d) At the request of the subject, investigator, Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) or designee, or regulatory authority;
e) Subject becomes pregnant; or
f) Subject is lost to follow-up.

In addition, subjects on tolvaptan treatment who meet the following criteria should have results confirmed with a repeat test. Sodium tests should be done either STAT or through bedside monitoring.

- The subject's serum sodium increases by > 8 mEq/L (mmol/L) in any 10-hour period following dosing on Day 1 of a cycle
- The subject's serum sodium increases by ≥ 12 mEq/L (mmol/L) in the 24-hour period following dosing
- At any time after dosing, the subject's serum sodium is ≥ 145 mEq/L (mmol/L).
- Evidence of dehydration
- Abnormal liver function tests (see Section 5.4)

If the result is confirmed, the medical monitor should be contacted to consider options of down-titration, dose discontinuation, concomitant medication adjustment, fluid supplementation, and/or withdrawal.

The sponsor and the medical monitor should be notified promptly when a subject requires IV normal saline or other rescue therapy. Subjects receiving rescue therapy are to continue to be monitored per protocol (to discharge or death). Subjects who have received rescue therapy secondary to inadequate response to tolvaptan will not be allowed to reinitiate tolvaptan treatment.

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 at Month 6 for vital status (Section 3.7.5.9).

3.9 Screen Failures

Since the core component of this trial is a 6-month safety follow-up trial, no subject will be considered a screen failure.

3.10 Definition of Completed Subjects

The core safety follow-up component of the trial is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial regardless of whether or not the subject was on tolvaptan treatment. For purposes of this trial, subjects who complete the Month 6 visit in the core safety component will be defined as trial completers.

The opportunity to participate in the optional tolvaptan treatment component is open to subjects during their 6-month participation in the core safety component.

3.11 Definition of Lost to Follow-up

Subjects or subjects' parents/guardians who cannot be contacted on or before their final visit 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 call with the subject, statement by a family member or primary care physician, or public records). It is expected that 3 documented attempts will be made to determine a subject's current health status before assigning a "lost to follow-up" status.

3.12 Subject Compliance

For the core safety follow-up component compliance is defined as completion of all visits.

For the optional tolvaptan treatment component 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 because of an emergency, accident, or mistake (eg, violation of informed consent/assent process, tolvaptan dispensing or subject dosing error, treatment assignment error, or 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 sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the site monitor.

4 Restrictions

4.1 Prohibited Medications

During tolvaptan treatment, 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, subject dosing will be determined based on weight, age and use of CYP3A4 inhibitors. Refer to Section 3.2.1 for dosing guidelines. A partial list of CYP3A4 inhibitors is provided in Table 4.1-1.

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

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 with tolvaptan until 24 hours post-last dose of tolvaptan. In addition, the use of alcohol within 72 hours prior to dosing and during tolvaptan treatment is prohibited.

The use of saline in this population should be closely monitored. The use of hypertonic saline (3% or greater) within 8 hours of the initial screening laboratory collection prior to tolvaptan treatment 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. Please see Section 4.1 for the partial list of prohibited medications during tolvaptan treatment. The use of normal saline (0.9%) is allowed during the Pretreatment baseline Period until the beginning of treatment; normal saline use can resume during the follow-up period. 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 inintended 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.

A serious adverse event (SAE) includes any event that results in any of the following outcomes:

1) Death
2) Life-threatening, ie, the subject was, in the opinion of the investigator or sponsor, 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.
3) Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions
4) Requires in-patient hospitalization or prolongs hospitalization
   - Hospitalization itself should not be reported as an SAE; wherever possible the reason for hospitalization should be reported
   - Hospitalization or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs
5) Congenital anomaly/birth defect
6) 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.

Non-serious adverse events are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event:

- 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 OPDC. Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication.

Clinical Laboratory Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. 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 AE is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

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

Related: There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.

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

5.2 Eliciting and Reporting Adverse Events

The investigator 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 INC Research. Serious AE collection is to begin after a subject has signed the ICF/assent.

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, INC Research must be notified immediately by telephone or fax of any Immediately Reported Events (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 within 24 hours after either the investigator or site personnel become aware of any SAE, DILI, or confirmed pregnancy, by telephone or by fax to INC Research as outlined in Appendix 1. An IRE form must be completed and sent by 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 overly rapid correction does not occur in this pediatric population.

Rapid correction of hyponatremia is defined as any increase in serum sodium $\geq$ 12 mEq/L (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.

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 ≥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 ≥ 2 × ULN or whose levels increase ≥ 2 times their initial baseline value, a BT level should also be evaluated. Elevated values should be confirmed via retest. If the BT is ≥ 2 × ULN or ≥ 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 × 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 ≥ 2 × ULN or whose levels increase ≥ 2 times their initial baseline value in subjects with an elevated baseline value, a BT level should also be evaluated. If the BT is ≥ 2 × ULN or ≥ 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 ≥ 2 × ULN:

1) ALT, AST, alkaline phosphatase, and BT 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 ≥ 3 × 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 DILI 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 from the Optional Tolvaptan Treatment Component of the Trial due to Liver Transaminase Elevations

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

1) ALT or AST ≥ 8 × ULN
2) ALT or AST ≥ 5 × ULN for more than 2 weeks
3) ALT or AST ≥ 3 × ULN AND (BT ≥ 2 × ULN or INR > 1.5)
4) ALT or AST ≥ 3 × 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 treatment options. 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.[25,26]

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 optional tolvaptan treatment component of this 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, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. 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 the optional tolvaptan treatment component of 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 in the optional tolvaptan treatment component, 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 or legal guardian must sign an ICF/assent stating that the above-mentioned risk factors and the consequences were discussed with the subject and/or the parent/guardian.

For WOCBP who are participating in the optional tolvaptan treatment component, a urine and/or serum pregnancy test for human chorionic gonadotropin (hCG) will be performed at pretreatment baseline on all WOCBP (and female subjects ≥12 years of age and all female subjects < 12 years of age, if menstruation has started). Urine and/or serum pregnancy tests will also be conducted at Day 33 and monthly thereafter. 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 optional tolvaptan treatment component of this 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 the 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 subjects in the core safety follow-up component of this trial, information on AEs will be followed for 2 weeks after the Month 6 Visit.

5.7.1 Follow-up of Non-serious Adverse Events

Non-serious 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 not recovered from the AE at the last scheduled contact, follow-up contacts will be scheduled at least every 4 weeks until reolution of the AE is confirmed or the condition is considered clinically stable. All non-serious 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 after the last dose of IMP is administered, or 14 days after the Month 6/ET visit, whichever is later.

Serious adverse events that are **identified or ongoing on 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 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 tolvaptan, should be reported to INC Research. This may include SAEs that are captured on follow-up telephone call 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, stabilized, 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 or stabilized.

6 Pharmacokinetic/Pharmacodynamic Analysis

6.1 Pharmacokinetic Analysis

For those subjects undergoing chronic treatment with tolvaptan for at least 8 consecutive weeks for each initiation or reinitiation of therapy, the concentration of tolvaptan and metabolites will be obtained and summarized using descriptive statistics.

7 Statistical Analysis

7.1 Sample Size

Sample size was not determined by a formal computation to achieve a target power. It is expected that approximately 100 subjects may enroll from previous tolvaptan pediatric trials for hyponatremia.

7.2 Datasets for Analysis

The following datasets are defined for this trial:

- Enrolled Subjects (core safety follow-up component)

  - Core Dataset: comprises all subjects for whom an ICF is signed for the trial.
- Treated Subjects (optional tolvaptan treatment component)
  - Safety Dataset: comprises those subjects who receive at least one dose of tolvaptan.
  - Efficacy Dataset: comprises those subjects in the safety dataset who have at least one post-baseline efficacy evaluation for serum sodium concentration.

7.3 Handling of Missing Data

The primary dataset for efficacy analyses will be in the tolvaptan treated subjects - efficacy dataset. The efficacy dataset will consist of the actual observations recorded at each visit so that no imputation of missing values will be made.

7.4 Primary and Secondary Outcome Analysis

7.4.1 Primary Outcome Analysis

The primary endpoint for all tolvaptan treated subjects is:

- Change from baseline in serum sodium while tolvaptan is being administered

7.4.2 Secondary Outcome Analyses

The secondary endpoints for all tolvaptan treated subjects include the following:

- Percentage of subjects who require rescue therapy while on tolvaptan
- Percentage of subjects who have recurrence of hyponatremia while on tolvaptan
- Percentage of subjects requiring continuation of tolvaptan following 30 days of treatment
- Percentage of subjects with overly rapid correction in serum sodium (≥ 12 mEq/L [mmol/L]) in 24 hours after the first dose at introduction or reintroduction of tolvaptan
- Changes from baseline in ALT, AST, BT and creatinine for subjects on tolvaptan

In addition, the secondary endpoints for all enrolled subjects include:

- Frequency of AE reports
- Change from baseline in QoL assessments
- Change from baseline in growth percentiles by visit for body height and weight
- Tanner Staging progression score (at 6 months)

All secondary endpoints will be summarized using descriptive statistics.

7.4.3 Interim Analysis

No interim analysis is planned.

7.5 Analysis of Demographic and Baseline Characteristics

Demographic characteristics and medical history at baseline will be summarized by descriptive statistics, eg, proportion, mean, median, standard deviation, minimum, and maximum values.

7.6 Safety Analyses

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 for all subjects (AEs), and all subjects receiving tolvaptan (treatment-emergent AEs [TEAEs]):

- AEs and TEAEs
- AEs and TEAEs by severity
- TEAEs potentially causally related to the IMP
- AEs and TEAEs with an outcome of death
- Serious AEs and TEAEs
- AEs and TEAEs leading to discontinuation

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

7.6.2 Clinical Laboratory 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. Where baseline values are unavailable, summary statistics of available data at each visit will be presented.

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

For full details on tolvaptan management, please refer to the tolvaptan IB.

8.1 Packaging and Labeling

Trial medication will be provided to the investigator(s) by the sponsor (or designated agent). Tolvaptan will be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets. Each package used in the dosing period will be labeled to clearly disclose the subject identification (ID), 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 current tolvaptan tablet formulation intended for use in the optional tolvaptan component of this trial is limited to administration to those who can easily swallow a 3.75-mg tablet (6 mm) and weigh ≥ 10 kg.

8.2 Storage

Tolvaptan 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 tolvaptan to any subject not participating in this protocol.

Tolvaptan will be stored at 25°C (77°F) or below, with excursions allowed from 15°C to 30°C (59°F to 86°F). The clinical trial site staff or designated personnel will maintain a temperature log in the drug storage area recording the temperature at least once each working day.

8.3 Accountability

The investigator, or designee, must maintain an inventory record of tolvaptan received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused and/or partially used tolvaptan must be returned to OPDC (or a designated contractor).

All tolvaptan 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 tolvaptan.

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 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 PPD
- Phone - Rocky Mountain Call Center at PPD

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

- 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

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, return it in the product retrieval package, which will be provided by Otsuka America Pharmaceutical, Inc.-Ethics, Quality and Compliance (OAPI-EQC).

It must 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 clinical trial site, 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 tolvaptan 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 tolvaptan 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 initialed 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 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 tolvaptan 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, because of 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 limited to, tolvaptan 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 site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, the ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Sciences (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. The IRB/IEC will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling CRFs, 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 supplies of tolvaptan, 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 the tolvaptan tablets 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.

15 References

1 Totapally BR, Raszynski A. Hyponatremia in pediatric practice. Int Pediatrics. 2006;21(1):37-50.

2 Eulmesekian PG, Perez A, Minces, PG, Bohn D. Hospital-acquired hyponatremia in postoperative pediatric patients: Prospective observational study. Pediatr Crit Care Med. 2010;11(4):479-83.

3 Hanna M, Saberi MS. Incidence of hyponatremia in children with gastroenteritis treated with hypotonic intravenous fluids. Pediatr Nephrol. 2010;25:1471-5.

4 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.

5 Adrogue HJ. Consequences of inadequate management of hyponatremia. Am J Nephrol. 2005;25:240-9.

6 Miller M, Morley JE, Rubenstein LZ. Hyponatremia in a nursing home population. J Am Geriatr Soc. 1995;43(12):1410-3.

7 Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy. (Second of two parts). N Engl J Med. 1988;319(17):1127-34.

8 Chen L-K, Lin M-H, Hwang S-J, Chen T-W. Hyponatremia among the institutionalized elderly in two long-term care facilities in Taipei. J Chin Med Assoc. 2006;69(3):115-9.

9 Huda MSB, Boyd A, Skagen K, Wile D, Van Heyningen C, Watson I, et al. Investigation and management of severe hyponatraemia in a hospital setting. Postgrad Med J. 2006;82:216-9.

10 Wald R, Jaber BL, Price LL, Updahyay A, Madias N. Impact of hospital-associated hyponatremia on selected outcomes. Arch Int Med. 2010;170(3):294-302.

11 Androgue JA, Madias NE. Hyponatremia. N Engl J Med. 2000;342:1581-9.

12 Hasegawa H, Okubo S, Ikezumi Y, Uchiyama K, Hirokawa T, Hirano H, et al. Hyponatremia due to an excess of arginine vasopressin is common in children with febrile disease. Pediatr Nephrol. 2009;24(3):507-11.

13 Otsuka Pharmaceutical Development & Commercialization, Inc. OPC-41061 Investigator's Brochure. Edition 21, Otsuka Report, issued 25 Aug 2015.

14 PPD An open-label, randomized, three-period crossover study of the pharmacokinetics and pharmacodynamics of oral tolvaptan tablets under fasting and non-fasting conditions in subjects of Caucasian and Japanese descent. Otsuka Clinical Study Report for Protocol 156-03-242, issued 23 Jul 2004.

15 PPD An open-label, randomized, crossover study of the effect of food (standard FDA high-fat breakfast) on tolvaptan pharmacokinetics in normal subjects following administration of 60-mg oral tolvaptan tablets. Otsuka Clinical Study Report for Study 156-05-256, issued 24 Jul 2006.

16 U.S. Food and Drug Administration. Guidance for Industry. Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans [report on the internet]. 2013 Jul [cited 05 Jul 2013].

17 US Department of Health and Human Services: Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population. ICH December 2000.

18 PPD Multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia. Otsuka Clinical Study Report for Protocol 156-02-235, issued 07 Aug 2006.

19 PPD International, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia. Otsuka Clinical Study Report for Protocol 156-03-238, issued 25 Jul 2006.

20 National Center for Health Statistics, National Center for Chronic Disease Prevention and Health Promotion. Clinical Growth Charts. Last updated Nov 2000. Available from: http://www.cdc.gov/growthcharts Accessed Oct 1, 2010.

21 Moritz ML, Ayus JC. Preventing neurological complications from dysnatremias in children. Pediatr Nephrol. 2005;20:1687-700.

22 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):S1-21.

23 Karp BI, Laureno R. Pontine and extrapontine myelinolysis; a neurologic disorder following rapid correction of hyponatremia. Medicine. 1993;72:359-73.

24 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].

25 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].

26 U.S. Food and Drug Administration. [available on the internet, last updated 22 Jan 2014; cited 14 Feb 2014].

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	PPD
Canada	PPD (primary) or PPD (alternative)
Czech Republic	PPD
Germany	PPD
Italy	PPD
Poland	PPD
Romania	PPD
Spain	PPD
Turkey	No toll free number available; please dial PPD (primary) or PPD (alternative)
United Kingdom	PPD
United States	PPD (primary) or PPD (alternative)

Project Leader/Medical Director:

PPD

PPD

Phone PPD Fax PPD

Clinical Management:

PPD

Phone: PPD Fax: PPD

PPD

Phone PPD Fax PPD

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: PPD

Trial Management & Clinical Monitoring
INC Research
3201 Beechleaf Court, Suite 600
Raleigh, North Carolina 27604-1547, USA
Phone: PPD

Investigational Materials
Almac Clinical Services Limited
Seagoe Industrial Estate
9 Charlestown Road
Craigavon
County Armagh
BT63 5PW
United Kingdom
Phone: PPD
Fax: PPD

IRT Systems (treatment assignment)
S-CLINICA
1500 Market Street
12th Floor East Tower
Philadelphia, Pennsylvania 19102, USA
Phone: PPD

Clinical Laboratory Supplies
Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, Indiana 46214, USA
Phone: PPD

Medical Monitoring
INC Research
3201 Beechleaf Court, Suite 600
Raleigh, North Carolina 27604-1547, USA
Phone: PPD
Fax: PPD

Medical Monitor:
PPD
PPD
3210 Beechleaf Ct., Suite 600
Raleigh, North Carolina 27604, USA
Phone PPD Mobile PPD
Fax: PPD
E-Mail:
PPD

Electronic Data Capture
MediData Solutions
79 Fifth Avenue, 8th Floor
New York, New York 10003, USA
Phone: PPD
Fax: PPD

Study Communications & Patient/Site Support
Matthews Media Group
700 King Farm Boulevard, Suite 500
Rockville, MD 20850, USA
Phone: PPD

Central Laboratory (PK)
ICON Development Solutions, Inc.
8282 Halsey Road
Whitesboro, New York 13492, USA
Phone: PPD

IDMC Support

Chiltern (formerly Theorem Clinical Research)
1016 West Ninth Avenue
King of Prussia, PA, 19406, USA
Phone: PPD
Fax: PPD

Appendix 3 Handling and Shipment of Bioanalytical Samples

All tubes must be labeled using the central laboratory's bar code labels provided with the sample collection kits. The central laboratory's requisition form must be completely filled out in regards to all the sample information. In addition, the subject ID number and date of collection must be hand-written on the sample tube. It is important to note the exact time of the blood collection on the eCRF.

Each specimen must be labeled using a waterproof pen. A label suitable for the storage conditions must contain the subject ID number and date of collection, must correspond to the requisition form, and must be firmly attached. The requisition form must contain the name, address, and telephone number of the contact person from the trial site.

Plasma Samples for Tolvaptan

Blood (1 mL) will be collected into plastic Vacutainer 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 at −20°C or on dry ice. Samples should be shipped monthly.

Shipment of Plasma

Plasma samples must be neatly packed in the kits provided by the central laboratory and restrained in a Styrofoam container that is completely filled with dry ice to avoid air spaces that allow evaporation of the dry ice. The Styrofoam container should be sealed with tape and placed in a cardboard box. The central laboratory must be alerted of sample shipment. Packages must not be shipped on Thursday, Fridays, Saturdays, or any day prior to a holiday without the expressed consent of OPDC or the central laboratory. Shipments from clinical trial sites will be via an overnight carrier to the central laboratory (Clinical Laboratory Supplies, Covance Central).

Appendix 4 Tanner Staging

Classification of Sex Maturity Stages in Girls

Stage	Pubic Hair	Breasts
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

Stage	Pubic Hair	Penis	Testes
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 Optional Tolvaptan Treatment Component: Eligibility Criteria

Subjects will be eligible for tolvaptan treatment if they meet the criteria outlined in the table below.

Eligibility Criteria for Optional Tolvaptan Treatment	
1.	Male or female subjects ≥ 4 years of age (or per local Health Authority age restrictions) and ≥ 10 kg
2.	The subject must have been off treatment with the investigational medicinal product (IMP) for at least 7 days following the end of treatment in the previous tolvaptan trial for hyponatremia (euvolemic or hypervolemic)
3.	Persistent dilutional (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 to 4 hours prior to the first dose of tolvaptan
4.	Ability to swallow tablets
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 the pretreatment baseline for this trial 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 tolvaptan for sexually active females of childbearing potential

Subjects will be ineligible for tolvaptan treatment if they meet any of the following criteria:

Ineligibility Criteria for Tolvaptan Treatment	
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.	Use of potent CYP3A4 inhibitors in subjects ≤ 50 kg or moderate CYP3A4 inhibitors in subjects < 20 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

Ineligibility Criteria for Tolvaptan Treatment	
8.	Has eGFR < 30 mL/min/1.73 m^2 calculated by the following equation: eGFR (mL/min/1.73 m^2) = 0.413 × height (cm)/serum creatinine (mg/dL)
9.	Has acute kidney injury defined as: • Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours; or • Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or • Urine volume < 0.5 mL/kg/h for 6 hours
10.	Has severe or acute neurological symptoms requiring other intervention (eg, hyperemesis, obtundation, seizures)
11.	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
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 the pretreatment visit 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.	Patient who has cirrhosis and meets 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 an investigational drug trial (other than a previous tolvaptan hyponatremia trial) within the past 30 days, without prior approval from the medical monitor
25.	Subjects < 4 years of age (or per local Health Authority age restrictions), weight < 10 kg, or who are unable to swallow tablets

AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; ICU = intensive care unit; IRE = Immediately Reportable Event; ULN = upper limit of normal

Appendix 6 Optional Tolvaptan Treatment Component: Laboratory Assessment Schedule

Frequency of Recurring Laboratory Assessments			
Treatment Phase	**Serum Sodium**	**LFTs (ALT, AST, BT) and creatinine**	**PK[a]**
Pretreatment Baseline doses	Day -1 to Day -4: assessments ≤ 130 mEqL (mmol/L) ≥ 12 hours apart	Required at baseline if not done within the previous month	
Month 1: Titration[b]	Once daily efficacy assessment and additional safety assessments 4 to 6 hours and 18 hours postdose		
Month 1: Post-titration[c]	Once weekly	Once monthly	
Month 2: Post-titration (steady dose)	Every 2 weeks	Once monthly	Once post 8 weeks of continuous treatment
Month 3+ post-titration (steady dose): Maintenance (Months 3, 4, and 5)	Once monthly	Once monthly[d,e]	
Month 6	24 (±4) hours postdose	Once	
Post-last dose Follow-up each cycle	24 (±4) hours and 7 (±1) days		

[a] Once post 8 weeks for every new cycle of treatment

[b] Day 1 up to Day 4

[c] Days 7, 14, and 21

[d] AST, ALT, and BT will be assessed if more than 1 month has elapsed since LFTs were performed

[e] See Section 3.7.5.3.1 for more information and Section 5.4 for detailed instructions on follow-up of subjects with elevations in AST, ALT, or BT that are ≥ 2 × ULN or levels that increase ≥ 2 x from baseline.

NA = Not applicable.

Appendix 7 Protocol Amendments

Amendment Number: 1
Issue Date: 5 Sep 2014

PURPOSE:

- To increase the consistency of this protocol with other tolvaptan pediatric hyponatremia protocols
- To revise trial endpoints in accordance with the Pediatric Investigation Plan
- To clarify study design, procedures, and assessments
- To incorporate revised definitions of IMP causality

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 more consistency in data collection and to allow for data to be generated that could be synthesized and analyzed across trials. This protocol amendment also aligns the trial endpoints with the Pediatric Investigation Plan.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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 PPD PPD Issue Date: 31 Oct 2013	Clinical Management PPD PPD Issue Date: 31 October 2013 Date of Amendment 1: 5 September 2014
Synopsis - Clinical Phase/Trial Type	Phase 3b, safety follow-up with optional open-label extension	Phase 3b, safety follow-up with optional open-label tolvaptan treatment component
Synopsis - Treatment Indication	Euvolemic or hypervolemic hyponatremia	Dilutional (euvolemic or hypervolemic) hyponatremia
Synopsis - Objectives	For all subjects: • To evaluate the post-treatment safety follow-up of children and adolescent subjects with euvolemic or hypervolemic hyponatremia who have previously participated in a trial of titrated oral tolvaptan For subjects who receive tolvaptan: • To demonstrate that tolvaptan safely and effectively achieves and maintains increased serum sodium concentrations in children and adolescent subjects with euvolemic or hypervolemic hyponatremia when used for both multiple short-term treatments and/or longer chronic treatments	This trial will consist of a core safety follow-up component (duration: 6 months) and an optional tolvaptan treatment component (duration: variable, depending on the subjects' continuing need for tolvaptan treatment). The objectives of this trial are: **Core Safety Follow-up Component** • For all subjects: To evaluate the post-treatment safety follow-up of children and adolescent subjects with dilutional (euvolemic or hypervolemic) hyponatremia who have previously participated in a trial of titrated oral investigational medicinal product (IMP [tolvaptan in Trial 156 08 276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205]). **Optional Tolvaptan Treatment Component** • For subjects who receive tolvaptan: To demonstrate that tolvaptan safely and effectively achieves and maintains increased serum sodium concentrations in children and adolescent subjects with dilutional (euvolemic or hypervolemic) hyponatremia when used for both multiple short-term treatments and/or longer chronic treatments.
Synopsis - Trial Design	This is an observational, follow-up trial in children and adolescents who have previously participated in a trial of titrated oral tolvaptan	**Core Safety Follow-up Component** This is a 6-month safety follow-up trial in children and adolescents

Location	Old Text	Updated Text
	for euvolemic or hypervolemic hyponatremia. Subjects who were enrolled in one of the tolvaptan pediatric efficacy, safety, pharmacokinetic (PK), and pharmacodynamic trials for hyponatremia (ie, Trials 156-08-276, 156-12-205, or 156-13-207) are eligible for participation in this trial. Enrollment in this trial should directly follow completion or discontinuation of the previous trial. The end of trial visit in the previous trial will serve as the Baseline Visit in this trial. Subjects will be followed once a month for 6 months, alternating between telephone contact and in-clinic visits, to clinically evaluate children and adolescent subjects with hyponatremia, regardless of the need for treatment. If a subject has a clinical need for treatment with tolvaptan, the subject may be screened for eligibility to be dosed with tolvaptan. The subject must have been off of treatment with the investigational medicinal product (IMP) for a minimum of 7 days following the end of treatment in the previous trial to assess the subject's clinical need for dosing. Subjects can be treated with tolvaptan during and/or after the initial 6-month follow-up period. Since hyponatremia in this patient population can often be transient and/or may be secondary to hypovolemic states, subjects will be screened for hyponatremic histories as well as clinically evaluated to rule out such cases before being dosed with tolvaptan. For the purpose of determining eligibility for treatment with tolvaptan within this protocol, persistent hyponatremia will be defined as serum sodium assessments < 130 mmol/L documented as present for at least 48 hours. Specifically, subjects must have at least 2 documented serum sodium assessments < 130 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) serum sodium assessment < 130 mmol/L, which will serve as the baseline value for efficacy endpoints, is to be obtained within 3 (± 1) hours of the first dose of trial medication. Additional qualification assessments will be performed as per etiology of hyponatremia. The first dose of trial medication will be	who have previously participated in a trial of titrated IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) for dilutional (euvolemic or hypervolemic) hyponatremia. Enrollment in this trial should directly follow completion or discontinuation of the previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205). Subjects who consent/assent to participate will be followed once a month for 6 months, alternating between telephone calls and clinical trial site visits, to clinically evaluate children and adolescent subjects with dilutional (euvolemic or hypervolemic) hyponatremia, regardless of the need for treatment. **Optional Tolvaptan Treatment Component** Any subject enrolled in the core safety follow-up component who has a medical need for tolvaptan per the investigator's assessment, may have short-term treatment (ie, a few days of treatment needed per episode of hyponatremia) or long-term treatment (ie, treatment for weeks to months with concomitant medication). The need for treatment beyond 30 days will be determined by a scheduled treatment discontinuation. The subject must have been off treatment with the IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) for 7 days following the end of treatment in the previous trial of titrated oral IMP to assess the subject's clinical need for dosing. Subjects can be treated with tolvaptan during and/or after the 6-month follow-up period (core safety follow-up component). Treatment can be discontinued and reinitiated depending upon the individual subject's need (eg, during chemotherapy treatments). If subjects are off tolvaptan treatment for >72 hours, reinitiation of

Location	Old Text	Updated Text
	administered upon successful completion of all pretreatment baseline procedures. Eligible subjects will initially be administered tolvaptan once daily and subsequently titrated in a hospital setting. Follow-up 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. Treatment with tolvaptan can continue per clinical need as determined by the investigator in consultation with the sponsor's medical monitor. The treatment should be tailored to the needs of an individual subject. Serum sodium concentrations will be assessed during the treatment cycle and at 48 (± 4) hours and 7 (+ 1) days post-last dose. Up-titration of tolvaptan doses can occur once daily and will be based on serum sodium levels at > 20 hours following initiation of therapy and each subsequent dose; up-titration may not occur within 20 hours of the previous dose. Treatment can be discontinued and reinitiated as needed per individual subject's need (eg, during chemotherapy treatments). If subjects are off of tolvaptan treatment for ≥ 48 hours, reinitiation of treatment will require reassessment of the eligibility criteria and should begin in a hospital setting. Tolvaptan should be titrated with regular serum sodium assessments. After discontinuation of trial medication, serum sodium should be assessed at 48 (± 4) hours and 7 (+ 1) days post-last dose.	treatment will require reassessment of the eligibility criteria and will begin in a hospital setting. Tolvaptan should be titrated with regular serum sodium assessments.
Synopsis - Subject Population	Up to 140 male and female subjects may be eligible for this trial; subjects will need to have completed at least one of the previous tolvaptan pediatric trials for hyponatremia (ie, Trials 156-08-276, 156-12-205, or 156-13-207). Subjects with euvolemic or hypervolemic hyponatremia eligible to be screened for treatment with tolvaptan 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	Up to 140 male or female subjects may be eligible for this trial; subjects will need to have participated in one of the previous tolvaptan pediatric trials for dilutional (euvolemic or hypervolemic) hyponatremia (ie, Trials 156-08-276, 156-13-207, or 156-12-205).

Location	Old Text	Updated Text
	inappropriate secretion of antidiuretic hormone (SIADH). Subjects with acute hyponatremia or hyponatremia expected to resolve spontaneously will be ineligible for tolvaptan treatment. 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 ineligible for tolvaptan treatment if this is not possible. The eligibility criteria for tolvaptan treatment have been designed to ensure careful selection of subjects with chronic (≥ 48 hours) dilutional hyponatremia (euvolemic or hypervolemic) associated with heart failure, hepatocellular disease (including cirrhosis), or SIADH 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.	
Synopsis - Inclusion/ Exclusion Criteria	Key inclusion criteria: • Enrollment in at least one of the previous tolvaptan pediatric trials for hyponatremia (ie, Trials 156-08-276, 156-12-205, or 156-13-207) • Willing to be clinically followed for 6 months Exclusion criteria: There are no exclusion criteria for entry into this trial.	Key inclusion criteria: • Participation in one of the previous tolvaptan pediatric trials for hyponatremia (ie, Trials 156-08-276, 156-13-207, or 156-12-205). • Willingness to be clinically followed for 6 months. Exclusion criteria: • There are no exclusion criteria for entry into the core safety follow-up component of this trial.
Synopsis - Trial Sites	Subjects may be enrolled at up to 65 centers globally.	Subjects may be enrolled at up to 65 clinical trial sites globally.
Synopsis - Investigational Medicinal Product, Dose, Formulation, Mode of	Subjects enrolled in this trial will not receive IMP unless they demonstrate a clinical need as determined by the investigator and meet the eligibility criteria for treatment. Tolvaptan will initially be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets. Upon the availability of a liquid formulation,	Subjects enrolled in this trial will not receive tolvaptan unless they demonstrate a clinical need as determined by the investigator and meet the eligibility criteria for treatment. Tolvaptan will initially be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets. Upon the availability of an oral liquid

Location	Old Text	Updated Text
Administration	the protocol will be amended to reflect additional dosing options. 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 tolvaptan will be given with 60 mL of water. The duration of administration of tolvaptan will be per medical need as determined by the principal investigator. Eligible subjects may have short-term treatment (ie, a few days of treatment needed per episode of hyponatremia) or long-term treatment (ie, treatment for weeks to months with concomitant medication). 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 > 20 hours following initiation of therapy; a change in serum sodium ≤ 4 mmol/L from baseline should warrant up-titration, which is limited to no more than twice the previous dose. • Subjects < 2 years of age or weighing < 10 kg will be excluded until the availability of a liquid formulation. Tolvaptan metabolism is primarily mediated by cytochrome P450 (CYP) 3A4 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. • Subjects ≥ 2 years of age and weighing ≥ 10 to < 20 kg will be given a 3.75-mg tablet on Day 1 with possible up-titration to 7.5- and 15-mg doses. • 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. • Subjects weighing > 50 kg will be given a 15-mg tablet on	formulation, the protocol will be amended to reflect additional dosing options. Tolvaptan tablets will be administered orally once daily (QD), preferably in the morning hours, with a dose-proportional amount of water. Doses of ≥ 15 mg tolvaptan will be given with 240 mL of water, 7.5 mg of tolvaptan will be given with 120 mL of water, and 3.75 mg of tolvaptan will be given with 60 mL of water. Any initiation or titration of tolvaptan must occur in a hospital setting. If a subject is not expected to receive a higher dose of tolvaptan, ie, if a stable dose is determined, continued administration can be done outside of the hospital setting. Subjects can be treated with tolvaptan during and/or after the 6-month core safety follow-up component.

Location	Old Text	Updated Text
	Day 1 with possible up-titration to 30- and 60-mg doses. 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 ≥ 12 mmol/L/24 hours. Subjects will receive daily doses of oral tolvaptan based on individual titration results and clinical need. Treatment can continue or be discontinued and reinitiated per clinical need as determined by the investigator in consultation with the sponsor's medical monitor. Reinitiation of treatment after a subject is off of tolvaptan for ≥ 48 hours will require reassessment of the eligibility criteria. Subjects will be required to be in a hospital setting during initiation or up-titration of tolvaptan. If a subject is not expected to receive a higher dose of tolvaptan, continued administration can be done outside of the hospital setting.	
Synopsis - Trial Assessments	Safety: • Adverse event reporting • Vital signs • Clinical laboratory tests • Physical examinations • Body height and weight • Tanner Staging Efficacy for tolvaptan treatment: • Serum sodium concentration Pharmacokinetics for tolvaptan treatment: • Sparse blood samples for tolvaptan and plasma metabolite concentrations from subjects dosed with tolvaptan for 8 consecutive weeks (one assessment per initiation or	Safety: • Vital signs • Physical examinations • Body height and weight/Growth percentiles • Tanner Staging • Clinical laboratory tests: Serum sodium assessments and liver function tests (alanine transaminase [ALT], aspartate aminotransferase [AST], and total bilirubin [BT]) • Adverse event reporting Efficacy for tolvaptan treatment: • Serum sodium concentration • Continued need for tolvaptan treatment after the first 30 days of treatment.

Location	Old Text	Updated Text
	reinitiation of therapy at 8 weeks) Baseline: • Medical and hyponatremia history • Urine pregnancy tests (subjects eligible for tolvaptan treatment only) • Clinical laboratory tests	Pharmacokinetics for tolvaptan treatment: Sparse blood samples for tolvaptan and plasma metabolite concentrations from subjects dosed with tolvaptan for 8 consecutive weeks (one assessment per initiation or reinitiation of therapy at 8 weeks).
Synopsis - Criteria for Evaluation	**Primary Endpoints:** Safety: • Adverse events, including cases of dehydration • Vital signs • Body weight, height, and growth percentiles • Tanner Stages Safety for tolvaptan treatment: In addition to the safety variables reported for all subjects, the following variables will be assessed for subjects on tolvaptan: • Percentage of subjects with overly rapid improvement in serum sodium (≥ 12 mmol/L in 24 hours after the first dose at introduction or reintroduction of IMP) • Percentage of subjects who experience recurrence of hyponatremia while on IMP • Clinical laboratory abnormalities: – Serum sodium, overly rapid changes in serum sodium – Changes from baseline in alanine transaminase and aspartate transaminase **Secondary Endpoints:** Efficacy for tolvaptan treatment: • Change in serum sodium from baseline at each visit while the IMP is being administered. Serum sodium will be assessed daily during titration. Then, it will be assessed at each visit, at a minimum monthly once a subject has reached the optimal dose.	**Primary Endpoint:** • Change from baseline in serum sodium while tolvaptan is being administered **Secondary Endpoints:** Efficacy: • Percentage of subjects who require rescue therapy while on tolvaptan treatment • Percentage of subjects requiring continuation of tolvaptan following 30 days of treatment • Change from baseline in QoL assessments for all subjects Safety: • Percentage of subjects with overly rapid correction in serum sodium (≥ 12 mEq/L [mmol/L]) in 24 hours after the first dose at introduction or reintroduction of tolvaptan) • Changes from baseline in ALT, AST, and BT for subjects on tolvaptan • Frequency of AE reports for all subjects • Changes from baseline in growth percentiles (weight and height) for all subjects • Tanner Staging progression for all subjects Pharmacokinetics for tolvaptan treatment: • Plasma concentrations of tolvaptan and metabolites in subjects who have continued tolvaptan therapy for 8 consecutive weeks.

Location	Old Text	Updated Text
	Pharmacokinetics for tolvaptan treatment: • Plasma concentrations of tolvaptan and metabolites in subjects who have continued tolvaptan therapy for 8 consecutive weeks **Exploratory Endpoint:** Safety: • Quality of Life assessments	
Synopsis - Statistical Methods	The primary and secondary analyses will use descriptive statistics.	Primary and secondary endpoints will be summarized by descriptive statistics. A paired Student's t-test will be used to evaluate growth data, eg, height, body weight, and growth percentiles. Tanner Staging will be analyzed using the Cochran-Mantel-Haenszel row mean scores differ test controlling for subjects.
Synopsis - Trial Duration	The trial duration is expected to continue until tolvaptan becomes approved for the pediatric population. All enrolled subjects will be followed for a minimum of 6 months. For subjects on active treatment with tolvaptan, the length of participation for each individual subject will vary depending on the duration of treatment required and if repeat treatments are necessary.	The core safety follow-up component of the trial is expected to continue until all enrolled subjects from Trials 156-08-276, 156-13-207, or 156-12-205 have been followed for a minimum of 6 months. For subjects in the optional tolvaptan treatment component, the length of participation for each individual subject will vary depending on duration of treatment required and the need for repeated treatments. The opportunity to participate in the Optional Tolvaptan Treatment Component is planned to remain open until the last subject completes the Core Safety Follow-up Component.
List of Abbreviations	Abbreviations removed: CRF Case report form FENa Fractional excretion of sodium FE urate Fractional excretion of urate	Abbreviations added: BT Total bilirubin cAMP Cyclic adenosine monophosphate CKD Chronic kidney disease CrCL Creatinine clearance eCRF Electronic case report form EMA European Medicines Agency MHLW Ministry of Health, Labour, and Welfare (Japan) NA Not applicable NOAEL No observed adverse effects level QD Once daily

Location	Old Text	Updated Text
		QoL Quality of Life SALT Study of Ascending Levels of Tolvaptan in Hyponatremia SALTWATER Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions
Section 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 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." It is characterized by a subnormal concentration of sodium in the blood (serum sodium < 135 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. Both forms of hyponatremia, dilutional and depletional, 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. Various clinical and nonclinical experiments and case studies have documented the role of sodium in maintaining extracellular osmolality and transmembrane electrical and chemical	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." It is characterized by a subnormal concentration of sodium in the blood (serum sodium < 135 mEq/L [mmol/L]) and is manifested by a range of neurologic 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. Both forms of hyponatremia, dilutional and depletional, impair normal neurologic 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. Various clinical and nonclinical experiments and case studies have documented the role of sodium in maintaining extracellular osmolality and transmembrane electrical and chemical

Location	Old Text	Updated Text
	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. 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 and 15% to 20% of hospitalized patients, 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 mmol/L) and approximately 1% were found to have moderate hyponatremia (serum sodium < 130 mmol/L). Hyponatremia is associated with significant additional hospital morbidity and cost. 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	potentials. Sudden decreases in the concentration of extracellular sodium lead to influx of water into cells, often resulting in cerebral edema, irreversible neurologic damage, respiratory arrest, brainstem herniation, and death if not treated quickly and appropriately. 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, sex, baseline neurologic 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[6] and 15% to 20% of hospitalized patients,[6,7,8,9] 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]).[4] Hyponatremia is associated with significant additional hospital morbidity and cost.[10] Children, especially infants, are particularly vulnerable to sodium and other electrolyte imbalances because of their relatively immature renal function, increased insensible water loss, and limited ability to communicate thirst. Hence, hyponatremia is not

Location	Old Text	Updated Text
	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 congenital heart failure, 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. 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. 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 is an extension trial to follow children and adolescent subjects who were enrolled in a previous tolvaptan pediatric trial for hyponatremia. In addition, this trial will allow continued access to tolvaptan to those subjects with a clinical need per the investigator's discretion.	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 dilutional (euvolemic or hypervolemic) hyponatremia are congenital heart failure, 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. 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. 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) and the European Medicines Agency (EMA) have required that pediatric trials be conducted for tolvaptan for the indication of hyponatremia. This trial is an extension trial to follow children and adolescent subjects who participated in a previous tolvaptan pediatric trial for hyponatremia. In addition, this trial will allow continued access to tolvaptan to those subjects with a clinical need per the investigator's discretion.
Section 1.2 Clinical Data	Tolvaptan was approved in adults by the US FDA, 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 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.	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 11 other countries for the treatment of specific forms of hyponatremia. Tolvaptan was approved by the Japanese Ministry of Health, Labour, and Welfare (MHLW) on 27 Oct 2010 for the adjunct treatment of volume overload in heart failure 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

Location	Old Text	Updated Text
		(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 hematodialysis or hemodiafiltration, and for carcinomatous edema in Japan; and for cardiac edema in China and Taiwan. As of 31 Mar 2014, 87 trials had been completed, 4 trials were terminated because of slow enrollment, and 10 trials were ongoing. More information is available in the IB.
Section 1.2.1 Pharmacokinetics /Pharmacodynamics	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 Japan, the United Kingdom, China, Korea, Argentina, and the US.	Since inception of the program, a total of 46 phase 1 trials have been completed with tolvaptan (as of 31 Mar 2014) in healthy subjects or special populations in Japan, the United Kingdom, China, Korea, Argentina, and the US. One phase 1 trial is ongoing.
Section 1.2.2 Clinical Efficacy	Eleven trials involving either exclusive evaluation of adult subjects with hyponatremia (8 trials in which all subjects had hyponatremia) or substantial subpopulations of subjects with hyponatremia (3 CHF trials - not all subjects in these trials had hyponatremia) have been completed. These 11 trials have included a total of 804 hyponatremic subjects exposed to tolvaptan in doses ranging from 5 to 90 mg (4 subjects randomized to tolvaptan did not receive trial medication, 2 subjects in Trial 156-02-235 [SALT 1] and 2 subjects in Trial 156-97-204); 480 subjects were from the 8 trials in which all subjects had hyponatremia and 324 subjects were from the 3 CHF trials who also had hyponatremia. Two trials in subjects with hyponatremia are ongoing as of the IB cutoff date. The hyponatremia-specific population for these trials was subjects with nonhypovolemic, nonacute hyponatremia arising from a variety of etiologies including heart failure, cirrhosis, SIADH, and others. Efficacy results from these completed trials can be found in the IB. 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	Thirteen trials involving either exclusive evaluation of 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 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. ... 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

Location	Old Text	Updated Text
	greater decreases in body weight as compared to placebo. ... 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 ($p < 0.001$). On stopping tolvaptan therapy, sodium concentrations fell to the level of placebo concentrations (see Figure 1.2.2-1).	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 1.2.2-1) but recovered upon resumption of tolvaptan therapy (Figure 1.2.2-2).
Figure 1.2.2-2		New figure added
Section 1.3 Known and Potential Risks and Benefits	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. The most commonly reported treatment-emergent adverse events (TEAEs; > 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 > 5% incidence) in hyponatremia trials for subjects treated with placebo were peripheral edema, diarrhea, dyspnea, vomiting, fatigue, headache, diarrhea, and nausea. The IB provides a thorough review of the adverse events (AEs) experienced with this compound during	As of 31 Mar 2014, pooled exposure data are available from 88 trials, including 7201 subjects worldwide who were exposed to oral doses of tolvaptan. The extent of exposure to oral tolvaptan by dose in the pooled database (N = 7201) comprises 3115 subjects in trials for heart failure, 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, 391 subjects in trials for cardiac edema, 855 subjects in trials for hepatic edema, 37 subjects with renal impairment in a phase 1 trial, and 1061 healthy subjects in clinical pharmacology trials. The most commonly reported 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

Location	Old Text	Updated Text
	clinical trials. 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. ... 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 heart failure, 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	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 TEAEs (> 5% incidence) in the placebo subjects were peripheral oedema, diarrhoea, headache, ascites, vomiting, dyspnoea, nausea, and hypotension. The IB provides a thorough review of the adverse events (AEs) experienced with this compound during clinical trials. 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 subjects with ADPKD 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 1 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 [BT] > 2 × ULN with the elevated BT 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 sex with respect to an increased risk of potential liver

Location	Old Text	Updated Text
	receiving optimal standard heart failure 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 heart failure 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 and prescribing information can be found in the product label, which is attached to the IB. To date, no clinical trials in children have been conducted with tolvaptan.	injury. ... 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 heart failure, 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 heart failure 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 heart failure 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. To date, no clinical trials in children have been conducted with tolvaptan.
Section 2 Trial Rationale and Objectives	No text in this section.	This trial will consist of a core safety follow-up component and an optional tolvaptan treatment component. The rationale and objectives of the 2 components of the trial are described in Section 2.1.1 (core safety follow-up component) and Section 2.1.2 (optional tolvaptan treatment component).
Section 2.1 Trial Rationale	The purpose of this trial is to follow children and adolescent subjects who have previously participated in a trial of titrated oral tolvaptan for euvolemic or hypervolemic hyponatremia and to examine the safety and efficacy of tolvaptan when used for both multiple short-term treatments and longer chronic treatments in children and adolescents with euvolemic or hypervolemic hyponatremia secondary to various underlying etiologies. Up to 140 potential subjects are to be enrolled in the tolvaptan pediatric trials for hyponatremia (ie, Trials 156-08-276, 156-12-205,	No text in this section.

Location	Old Text	Updated Text
	and 156-13-207). This trial will follow subjects for 6 months following treatment in the previous trial. Based on the information from Otsuka's pediatric hyponatremia advisory board, although short-term treatment is expected, repeat treatments over time may be necessary. Therefore, some of the subjects may require a regimen with tolvaptan to supplement treatment following the completion of the earlier short-term efficacy, safety, PK, and PD trials (ie, Trials 156-08-276, 156-12-205, or 156-13-207). Recruitment for this proposed trial will be exclusively from Trials 156-08-276, 156-12-205, or 156-13-207 after subjects meet the entry criteria.	
Section 2.1.1 Core Safety Follow-up Component	New section in this amendment.	The primary purpose of this component of this trial is to follow children and adolescent subjects who have previously participated in a trial of titrated oral IMP (tolvaptan in Trial 156-08-276; tolvaptan or placebo in Trial 156-13-207 or Trial 156-12-205) for dilutional (euvolemic or hypervolemic) hyponatremia regardless of their treatment status with tolvaptan. The minimum duration of safety follow-up will be 6 months.
Section 2.1.2 Optional Tolvaptan Treatment Component	New section in this amendment.	Children and adolescent subjects who have previously participated in a tolvaptan hyponatremia trial (Trials 156-08-276, 156-13-207, or 156-12-205) who meet the eligibility criteria for treatment with tolvaptan may be eligible for one or more additional cycles of tolvaptan treatment. Depending upon clinical need and the investigator's discretion, subjects in the core safety follow-up component may receive no treatment, be treated per the local standard of care for hyponatremia, or start treatment with tolvaptan. Based on the various underlying etiologies contributing to hyponatremia, the need for treatment may differ per individual subject. Therefore, some of the subjects may require a regimen with tolvaptan to supplement treatment following the completion of the earlier short-term efficacy, safety, PK, and PD

Location	Old Text	Updated Text
		trials (Trials 156-08-276, 156-13-207, or 156-12-205), and this protocol is designed to accommodate short-term, long-term, and repeated tolvaptan treatment cycles as necessary. Each tolvaptan treatment cycle will consist of a titration phase and a maintenance phase, with a planned discontinuation of treatment on Day 30 for assessment of the need for continued treatment. After demonstrating the need for continued tolvaptan treatment beyond the first 30 days, subjects taking concomitant medications, with underlying conditions, or receiving treatments that contraindicate the discontinuation of tolvaptan treatment may be exempted from treatment discontinuation.
Section 2.2 Dosing Rationale	Eligible subjects with a demonstrated clinical need will be dosed with tolvaptan 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 ≥ 2 years of age and weighing ≥ 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 ≥ 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. 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 optional tolvaptan treatment component of the trial, eligible subjects with a demonstrated clinical need will be dosed with tolvaptan based on age, weight, and the use of CYP3A4 inhibitors. Subjects < 2 years of age, or < 10 kg, or those who cannot swallow a tablet, will be excluded until an oral liquid formulation becomes available. Subjects ≥ 2 years of age and weighing ≥ 10 to < 20 kg will receive an oral QD dose of tolvaptan starting as a 3.75-mg spray-dried tablet. Subjects weighing 20 to 50 kg, inclusive, will receive an oral QD dose of tolvaptan starting as a 7.5-mg spray-dried tablet. Subjects weighing > 50 kg will receive an oral QD dose of tolvaptan starting as a 15-mg spray-dried tablet. For subjects weighing ≥ 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 oral liquid formulation is available. It is estimated that subjects 6 years of age weigh approximately 25 kg. Starting tolvaptan tablet doses as mg/kg of body weight are shown in Table 2.2-1.
Table 2.2-1 Starting Tolvaptan Tablet	New table in this amendment.	

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr><td>Doses as mg/kg Body Weight</td><td></td><td>Table 2.2-1 Starting Tolvaptan Tablet Doses as mg/kg of Body Weight
<table>
<tr><th rowspan="2">Tolvaptan Tablets</th><th colspan="5">Tolvaptan Doses as mg/kg</th></tr>
<tr><th>BW of 10 kg</th><th>BW of 20 kg</th><th>BW of 50 kg</th><th>BW of 70 kg</th><th>BW of 100 kg</th></tr>
<tr><td>3.75 mg</td><td>0.375</td><td>0.19</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>7.5 mg</td><td>-</td><td>0.375</td><td>0.15</td><td>-</td><td>-</td></tr>
<tr><td>15 mg</td><td>-</td><td>-</td><td>0.30</td><td>0.21</td><td>0.15</td></tr>
</table>
BW = body weight</td></tr>
<tr><td>Section 2.3 Objectives</td><td>The objectives of this trial are:
For all subjects: To evaluate the post-treatment safety follow-up of children and adolescent subjects with euvolemic or hypervolemic hyponatremia who have previously participated in a trial of titrated oral tolvaptan.
For subjects who receive tolvaptan: To demonstrate that tolvaptan safely and effectively achieves and maintains increased serum sodium concentrations in children and adolescent subjects with euvolemic or hypervolemic hyponatremia when used for both multiple short-term treatments and/or longer chronic treatments.</td><td>The objectives of this trial are:
For all subjects (core safety follow-up component): To evaluate the post-treatment safety follow-up of children and adolescent subjects with dilutional (euvolemic or hypervolemic) hyponatremia who have previously participated in a trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 or 156-12-205).
For subjects who receive tolvaptan (optional tolvaptan treatment component): To demonstrate that tolvaptan safely and effectively achieves and maintains increased serum sodium concentrations in children and adolescent subjects with dilutional (euvolemic or hypervolemic) hyponatremia when used for both multiple short-term treatments and/or longer chronic treatments.</td></tr>
<tr><td>Section 3.1 Type/Design of Trial</td><td>See Figure 3.1-1 for a schematic of the trial design.

This is an observational follow-up trial in children and adolescents who have previously participated in a trial of titrated oral tolvaptan for euvolemic or hypervolemic hyponatremia. Subjects who were enrolled in at least one of the tolvaptan pediatric efficacy, safety, PK, and PD trials for hyponatremia (ie, Trials 156-08-276, 156 -12-205, or 156-13-207) are eligible for enrollment in this trial. Enrollment in this trial should directly follow completion or</td><td>This trial consists of 2 components, a 6 month safety follow-up study and an embedded optional tolvaptan treatment study for subjects. The 2 components are described below and illustrated in Figure 3.1-1.</td></tr>
</table>

Location	Old Text	Updated Text
	discontinuation of the previous trial. The end of trial visit in the previous trial will serve as the Baseline Visit in this trial. Subjects will be followed once a month for 6 months, alternating between telephone contact and in-clinic visits, to clinically evaluate children and adolescent subjects with hyponatremia, regardless of the need for treatment. If a subject has a clinical need for treatment with tolvaptan, the subject may be screened for eligibility to be dosed within this trial. The subject must have been off of treatment with the investigational medicinal product (IMP) for a minimum of 7 days following the end of treatment in the previous trial to assess the subject's clinical need for dosing. Subjects can be treated with tolvaptan during and/or after the initial 6-month follow-up period.	

Old Text: Figure 3.1-1

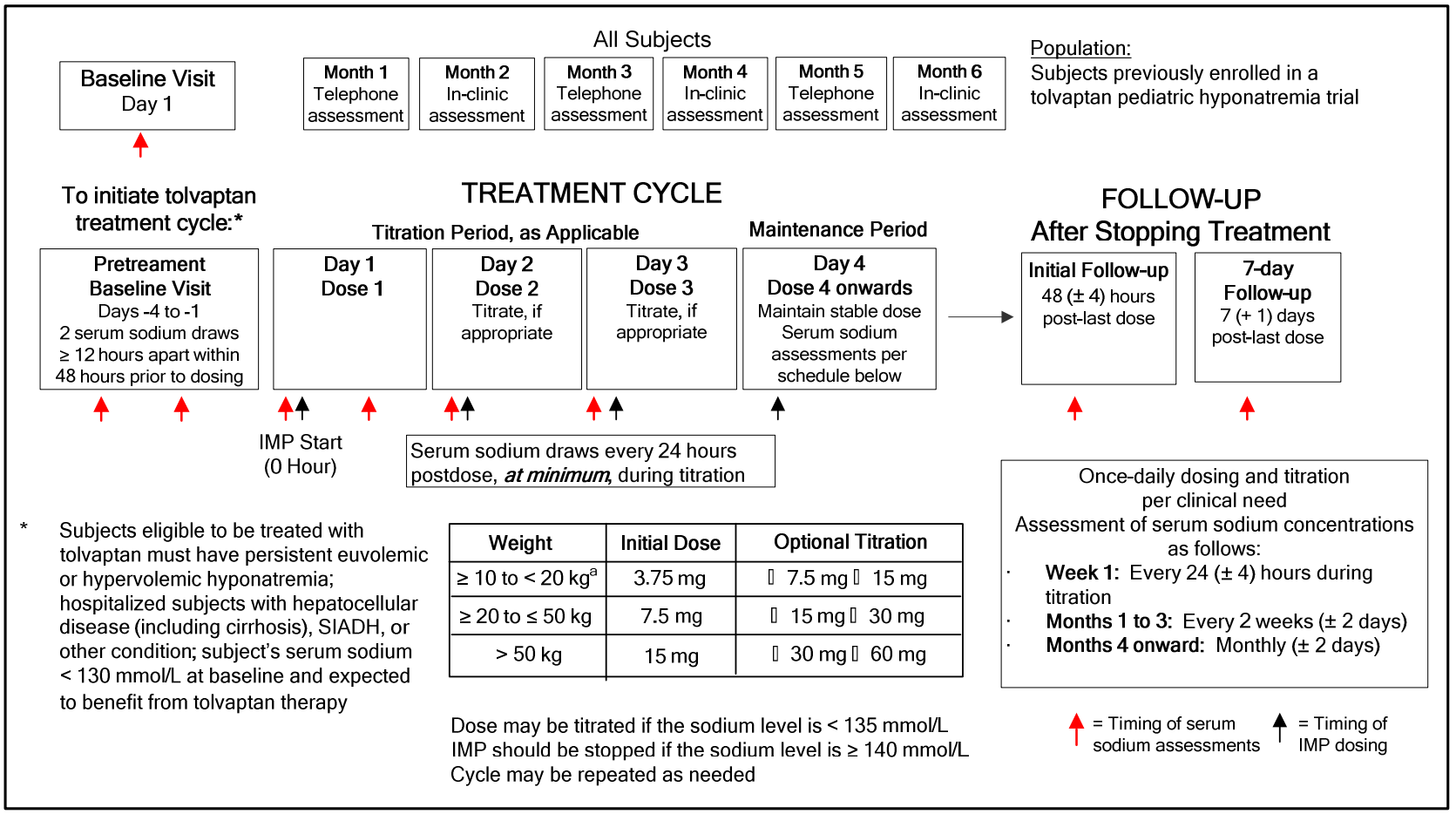


Figure 3.1-1 Trial Design Schematic

[a]Subjects must be ≥ 2 years of age and weigh ≥ 10 kg until development of a liquid formulation is complete.

New Text: Figure 3.1-1

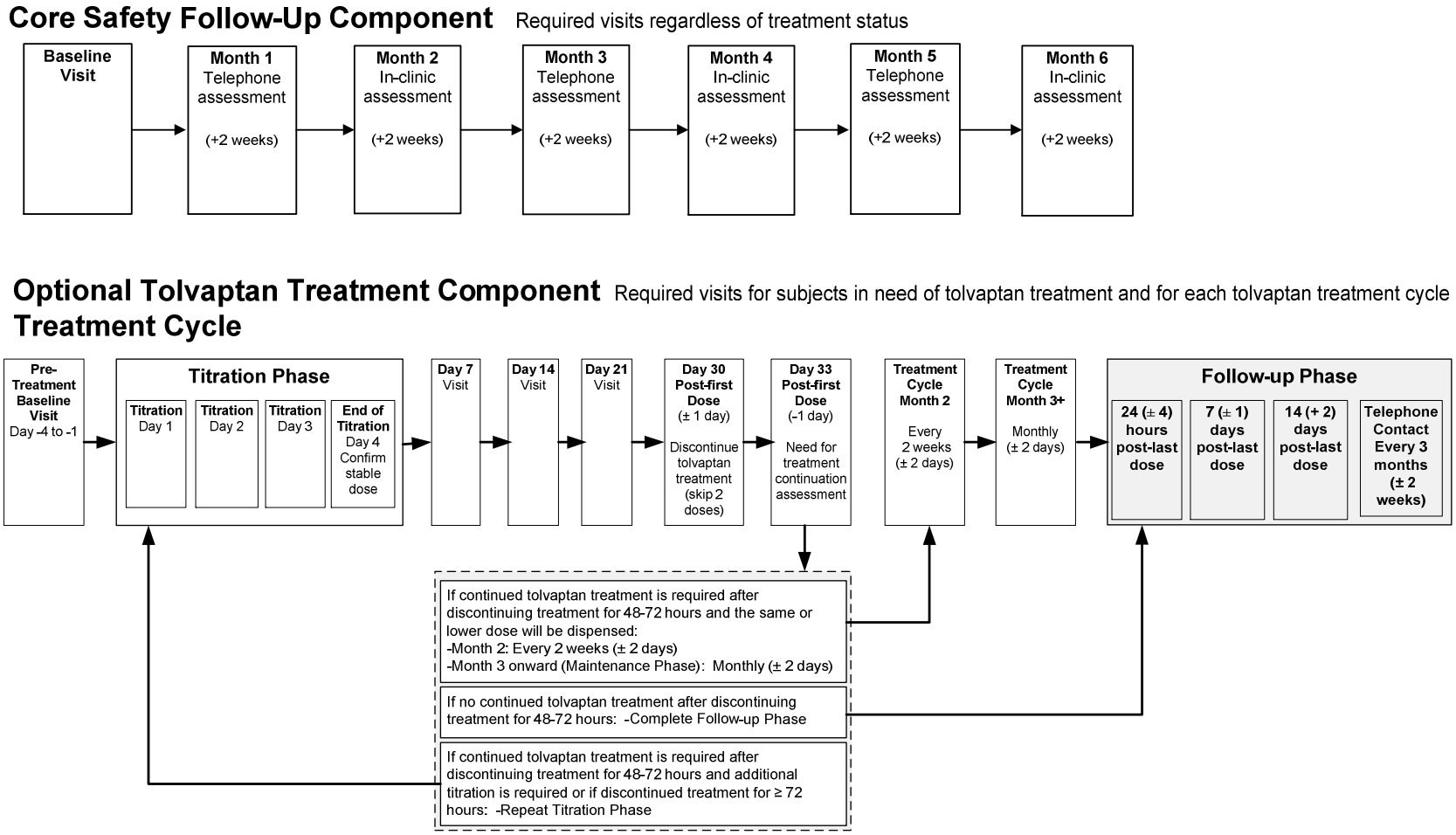


Figure 3.1-1 Trial Design Schematic

Location	Old Text	Updated Text
Section 3.1.1 Core Safety Follow-up Component	**Section 3.1.1 Tolvaptan Treatment** Pediatric and adolescent subjects who are diagnosed with euvolemic or hypervolemic hyponatremia (serum sodium < 130 mmol/L) that persists despite initial standard background therapy (eg, including fluid restriction) are eligible to be screened for dosing with tolvaptan. All potential subjects must also be deemed by the investigator as likely to benefit from a therapy that raises serum sodium levels. The investigator is required to call the medical monitor to discuss the appropriateness of dosing for subjects who discontinued from the previous trial early or demonstrated a lack of response, but have a clinical need for tolvaptan. 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 determining eligibility for treatment with tolvaptan within this protocol, persistent hyponatremia will be defined as serum sodium assessments < 130 mmol/L documented as present for at least 48 hours. Specifically, subjects must have at least 2 serum sodium assessments < 130 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 mmol/L, which will serve as the baseline value for efficacy endpoints, is to be obtained within 3 (± 1) hours of the first dose of trial medication. Additional qualification assessments will be performed as per etiology of hyponatremia. The first dose of trial medication will be administered upon successful completion of all pretreatment baseline procedures. As stated above, all eligible 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	**Section 3.1.1 Core Safety Follow-up Component** The core safety follow-up component of the trial is a 6-month period in which pediatric subjects (children and adolescents) who previously participated in a trial of titrated IMP (tolvaptan in Trial 156-08-276; tolvaptan or placebo in Trial 156-13-207 or 156-12-205) will be followed once a month (alternating clinical trial site visits and telephone calls), regardless of the need for treatment for hyponatremia, to assess long term-safety of tolvaptan. This trial should directly follow completion or discontinuation of the previous trial. The final laboratory assessments performed in the previous trial of titrated oral IMP may serve as the baseline laboratory assessments in this trial, if possible.

Location	Old Text	Updated Text
	status as appropriate for each subject using diagnostic tests or evaluations (eg, fractional excretion of sodium [FENa], fractional excretion of urate [FE urate], urine osmolality, serum osmolality) employed in the usual clinical course of care. Eligible subjects will receive daily doses of oral tolvaptan based on individual titration results and clinical need. Subjects will be required to be in a hospital setting during initiation or up-titration of administration of tolvaptan. If a subject is not expected to receive a higher dose of tolvaptan, continued administration can be done outside of the hospital setting. Regardless of whether a subject is in the hospital setting or not, the subject should return to the clinical site for assessment of serum sodium concentrations on an ongoing basis (see Section 3.1.1.1) to monitor the stability of his/her hyponatremia or his/her achievement of normal or clinician-directed target range serum sodium. Some subjects are expected to need to remain on a stable dose of tolvaptan to maintain clinician-directed target range serum sodium concentrations. Treatment can continue per clinical need as determined by the investigator in consultation with the sponsor's medical monitor. Follow-up visits for safety and assessment of serum sodium concentrations can be adjusted per the guidelines in Section 3.1.1.1. Upon achieving normal or clinician-directed target range serum sodium, subjects should be assessed for the need for ongoing treatment and then return to the clinic site for serum sodium assessments at 48 (± 4) hours and 7 (+ 1) days after the last dose of tolvaptan. Up-titration of tolvaptan doses can occur once daily and will be based on serum sodium levels at > 20 hours following initiation of therapy and each subsequent dose; up-titration may not occur within 20 hours of the previous dose. Treatment can be discontinued and reinitiated as needed per individual subject's need (eg, during chemotherapy treatments). If subjects are off of tolvaptan treatment for ≥ 48 hours, reinitiation of treatment will require reassessment of eligibility criteria and should	

Location	Old Text	Updated Text
	begin in a hospital setting. Tolvaptan should be titrated with regular serum sodium assessments (see Section 3.1.1.1 and Section 3.2.1). After discontinuation of tolvaptan, serum sodium should be assessed at 48 (± 4) hours and 7 (+ 1) days post-last dose. Once a subject becomes legal adult age, the subject will be reconsented as appropriate and will be allowed to continue in the trial until tolvaptan becomes otherwise available to the subject. All pediatric subjects will be allowed to continue in the trial until tolvaptan becomes approved for the pediatric population.	
Section 3.1.1.1 Core Safety Follow-up Component Phases	**Section 3.1.1.1 Treatment Follow-up** • Subjects should have serum sodium assessments at a minimum of daily during the Titration Period. • During the Maintenance Period, for Months 1 to 3, serum sodium concentrations should be assessed at a minimum of every 2 weeks (± 2 days). • During the Maintenance Period, from Month 4 onward for consecutive treatment, subjects should return to the site minimally once per month (± 2 days) for assessment of serum sodium concentrations. • Alanine transaminase and AST should be assessed once a month while subjects are on tolvaptan. • A PK blood sample should be collected after 8 consecutive weeks of treatment. • If the principal investigator (PI) notes any other significant clinical change during the treatment cycle, additional serum sodium testing should be performed to ensure appropriate treatment of each subject.	**Section 3.1.1.1 Core Safety Follow-up Component Phases** Subjects enrolled in this trial are required to complete 7 visits regardless of their treatment status with tolvaptan. The Baseline Visit as well as Month 2, 4 and 6 Visits are performed in clinic while Month 1, 3 and 5 Visits can be conducted via telephone. During the in clinic visits subjects are evaluated for relevant information. Since all pediatric subjects (children and adolescents) who previously participated in a trial of titrated IMP (tolvaptan in Trial 156-08-276; tolvaptan or placebo in Trial 156-13-207 or 156-12-205) are eligible to participate in this trial there is no screening phase. Similarly, since the goal of the trial is to collect follow-up information for prior treatment there is no separate follow-up phase.
Section 3.1.2 Optional Tolvaptan Treatment Component	New section in this amendment	Subjects enrolled in the 6-month core safety follow-up component may meet the criteria for treatment with tolvaptan. This subset of the study population may receive cycles of tolvaptan per clinical need to treat their hyponatremia. If a subject has a clinical need for treatment with tolvaptan, the subject may be screened for eligibility to be dosed within this trial. The subject must have been off

Location	Old Text	Updated Text
		treatment with the IMP for 7 days following the end of treatment in the previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) to assess the subject's clinical need for dosing. Eligibility for tolvaptan treatment must be determined between Day -4 and Day -1 of each dosing cycle. Subjects can be treated with tolvaptan during and/or after the 6-month core safety follow-up component after evaluating the subject using the criteria outlined in Appendix 5. Thirty days after the start of tolvaptan treatment, all subjects receiving tolvaptan will discontinue treatment for up to 72 hours, during which the need for continuing treatment with tolvaptan will be reassessed. Subjects who resume dosing can do so at the same dose or a lower dose without having to go through the full titration cycle again. Subjects who have a dosing discontinuation of > 72 hours must repeat the full titration cycle in a hospital setting. The optional tolvaptan treatment component of the trial does not have a fixed stopping point. Subjects who have an ongoing need for treatment can continue to receive tolvaptan per the investigator's clinical judgment until they no longer have a need for treatment or all subjects have completed the 6 month Core Follow-up Component of the trial. Subjects who terminate tolvaptan treatment will have follow-up visits at 24 hours (± 4 hours), and at 7 (± 1) days post-last dose, and a telephone call at 14 days (+ 2 days) post-last dose. Additional follow-up contacts will be performed on a regular basis until the end of the trial.
Section 3.1.2.1 Optional Tolvaptan Treatment Cycles	New section in this amendment	This section describes the expectations for subjects participating in a treatment cycle of the Optional Tolvaptan Treatment Component. The minimum frequency of recurring laboratory assessments during the optional tolvaptan treatment component is shown in Appendix 6.

Location	Old Text	Updated Text
Section 3.1.2.1.1 Screening (Pretreatment Baseline)	New section in this amendment	A subject who requires tolvaptan treatment can be treated for as many cycles as deemed necessary by the investigator, and the duration of treatment cycles may vary per the investigator's assessment of clinical need. Regardless of the number of treatment cycles and the duration of tolvaptan treatment in each cycle, optional tolvaptan treatment cycles will consist of a Titration Phase, a Maintenance Phase, and a Follow-up Phase. Subjects participating in the 6-month core safety follow-up component may become eligible for tolvaptan treatment at any time if they have dilutional (euvolemic or hypervolemic) hyponatremia (serum sodium < 130 mEq/L [mmol/L]). The investigator is required to call the medical monitor to discuss the appropriateness of tolvaptan treatment for subjects who discontinued from the previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) early or demonstrated a lack of response to tolvaptan, but have a demonstrated clinical need for tolvaptan. 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 exclude such cases from the optional tolvaptan treatment component of the trial. To be eligible for the optional tolvaptan treatment component of this protocol, subjects must have persistent dilutional (euvolemic or hypervolemic) hyponatremia, defined as serum sodium assessments < 130 mEq/L (mmol/L) that are documented for at least 48 hours after the final dose of IMP in the previous trial and prior to the planned initiation of tolvaptan titration in this trial. These values can be documented using historical values previously obtained per standard of care. A third (immediate [STAT]) serum sodium assessment < 130 mEq/L (mmol/L), which will serve as the final treatment qualification, management strategy, and baseline value for efficacy endpoints, is to be obtained within 2 to 4 hours of the first dose of tolvaptan. Additional qualification assessments will be performed per etiology of hyponatremia.

Location	Old Text	Updated Text
Section 3.1.2.1.2 Treatment Initiation and Maintenance	New section in this amendment	A subject who requires tolvaptan treatment can be treated for as many cycles as deemed necessary by the investigator, and the duration of treatment cycles may vary per the investigator's assessment of clinical need. Regardless of the number of treatment cycles and the duration of tolvaptan treatment in each cycle, optional tolvaptan treatment cycles will consist of a Titration Phase, a Maintenance Phase, and a Follow-up Phase. The schedule of assessments for the optional tolvaptan treatment component is shown in Section 3.7.3. The first dose of tolvaptan will be administered upon successful completion of all pretreatment baseline procedures. Subjects will enter a titration phase and follow the titration schedule outlined in Section 3.2.1.2. Eligible subjects will receive daily doses of oral tolvaptan based on individual titration results and clinical need. Subjects will be required to be in a hospital setting during initiation or titration of tolvaptan. If a subject is not expected to receive a higher dose of tolvaptan, continued administration can be done outside of the hospital setting. Titration of tolvaptan doses can occur once daily and will be based on serum sodium levels at 24 hours following initiation of therapy and each subsequent dose. Titration of tolvaptan doses is limited to twice the previous dose, cannot exceed the maximum dose per body weight (mg/kg), and may not occur within 20 hours of the previous dose. Regardless of whether a subject is in the hospital setting or not, the subject should return to the clinical trial site for assessment of serum sodium concentrations on an ongoing basis to monitor the stability of his/her hyponatremia or his/her achievement of normal or clinician-directed target range serum sodium. Some subjects are expected to need to remain on a stable dose of tolvaptan to maintain target-range serum sodium concentrations as directed by the clinician. Treatment can continue per clinical need as determined by the investigator in consultation with the medical monitor. Follow-up visits for safety and assessment of serum sodium concentrations can be adjusted.

Location	Old Text	Updated Text
		During the first 30 days of treatment subjects should have serum sodium assessments at a minimum of once daily during the Titration Phase on Day 1 up to Day 4 of treatment, and at a minimum of once weekly thereafter once on a stable dose (ie, on Days 7, 14, 21, and 28). After the first 30 consecutive days of treatment, all subjects who receive tolvaptan will be assessed for the need to continue treatment (Section 3.7.3.2.4). However, subjects may be assessed, per investigator's discretion, for the need for ongoing treatment with tolvaptan at any time point during treatment. Subjects who demonstrate a need for tolvaptan treatment may continue treatment to maintain the normal or clinician-directed target range serum sodium. Procedures for reinitiation of tolvaptan treatment for subjects with a clinical need per the investigator's assessment are described in Section 1.1.1. Tolvaptan treatment can be discontinued and reinitiated as needed per individual subject's need (eg, during chemotherapy treatments). If subjects are off tolvaptan treatment for> 72 hours, reinitiation of treatment will require reassessment of eligibility criteria and will begin in a hospital setting. Tolvaptan should be titrated with regular serum sodium assessments (Section 3.2.1.2 and Section 3.7.4.1). During the second consecutive month of treatment, serum sodium concentrations should be assessed at a minimum of every 2 weeks (± 2 days). Once a subject has been treated for 2 months, if no new titration occurs, then at the beginning of third month, subjects can be considered to have entered the maintenance phase. They should return to the clinical trial site at a minimum of once per month (± 2 days) for a trial visit and an assessment of serum sodium concentrations. ALT, AST, and BT should be assessed, and a pregnancy test performed (on female subjects ≥ 12 years of age and

Location	Old Text	Updated Text
		female subjects < 12 years of age if menstruation has started), once a month while subjects are on tolvaptan. A PK blood sample should be collected after 8 consecutive weeks of treatment, which may include a discontinuation of ≤ 72 hours to assess the subject's need for continued treatment. If the principal investigator (PI) notes any other significant clinical change during the treatment cycle, additional serum sodium testing should be performed to ensure appropriate treatment of each subject.
Section 3.1.2.1.3 Follow-up Phase (End of Tolvaptan Treatment Cycle)	New section in this amendment	Subjects who discontinue tolvaptan treatment in the optional tolvaptan treatment component per the investigator's decision will return to the clinical trial site for serum sodium assessments at 24 (± 4) hours and at 7 (±1) days post-last dose, and will receive follow-up telephone calls at 14 (+2) days and every 3 months (± 2 weeks) post-last dose. In the Follow-up Phase (ie, at the end of Month 6 or at the end of the tolvaptan treatment), subjects should have serum sodium assessments at 24 (± 4) hours and 7 (+ 1) days, and 14 (+2) days post-last dose. ALT, AST, and BT should be assessed at 24 (± 4 hours) post-last dose, if more than 1 month has elapsed since LFTs were performed. An IRE form will be completed if the subject is a potential Hy's Law case (see Section 5.4). Potential Hy's Law cases will be followed up until the ALT, AST, and BT values are within normal limits.
Section 3.2 Treatments	Subjects enrolled in this trial will not receive IMP unless they demonstrate a clinical need as determined by the investigator and meet the eligibility criteria for treatment. If a subject has a clinical need for tolvaptan, the subject may be screened for eligibility to be dosed with tolvaptan. The subject must have been off of treatment with IMP for a minimum of 7 days following the end of treatment in the previous trial to assess the subject's clinical need for treatment with tolvaptan. Tolvaptan will initially be supplied as 3.75-, 7.5-, 15-, and 30-mg	The Core Safety Follow-up Component of the trial does not contain any trial specific treatments. However, subjects have the opportunity to receive treatment in the Optional Tolvaptan Treatment Component in which case the information outlined in the remainder of Section 3.2.1applies. For all subjects enrolled in the core safety follow-up component of the trial, the need for initiation of tolvaptan treatment will be assessed per protocol serum sodium guidelines and the duration of tolvaptan administration will determined by the PI per the subject's

Location	Old Text	Updated Text
	tablets. Upon the availability of a liquid formulation, the protocol will be amended to reflect additional dosing options. 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 tolvaptan will be given with 60 mL of water. Tolvaptan will be initially administered in a hospital setting for each cycle. Once the subject is maintaining a stable dose of tolvaptan, administration of the IMP can be done away from the clinic and regular assessments for safety will be performed. The duration of administration of tolvaptan will be per medical need as determined by the PI. Subjects may have short-term treatment (ie, a few days of treatment needed per episode of hyponatremia) or long-term treatment (ie, treatment for weeks to months with concomitant medication). Subjects will be administered tolvaptan on an age- and weight-based scale. Up-titration of tolvaptan doses can occur once daily and will be based on serum sodium levels at > 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 ≤ 4 mmol/L from baseline should warrant up-titration, which is limited to no more than twice the previous dose. • Subjects < 2 years of age or weighing < 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. • Subjects ≥ 2 years of age and weighing ≥ 10 to < 20 kg will be given a 3.75-mg tablet on Day 1 with possible	medical need.

Location	Old Text	Updated Text
	up-titration to 7.5- and 15-mg tablet doses. • 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. • Subjects weighing > 50 kg will be given a 15-mg tablet on Day 1 with possible up-titration to 30- and 60-mg tablet doses. For subjects weighing ≥ 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 until such time that an alternate dosing formulation is available. Subjects will have the opportunity to titrate as per medical need via the guidelines listed in 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 ≥ 12 mmol/L/24 hours. Subjects will receive daily doses of oral tolvaptan based on individual titration results and clinical need. Treatment can continue per clinical need as determined by the investigator in consultation with the sponsor medical monitor and follow-up visits for safety and serum sodium assessments can be adjusted per the guidelines in Section 3.1.1. If the subject's serum sodium has reached the normal or clinician-directed target range, dosing may stop. Initiation of tolvaptan treatment can be repeated as needed per individual subject's need. If subjects are off of tolvaptan treatment for ≥ 48 hours, reinitiation of treatment will require reassessment of the eligibility criteria.	

Location	Old Text	Updated Text
Section 3.2.1 Optional Tolvaptan Treatment	**Section 3.2.1. Titration Guidelines** The titration scheme is presented in Figure 3.2.1-1. If serum sodium increases > 4 to < 8 mmol/L/24 hours, then the dose of tolvaptan should remain the same. If serum sodium increases ≥ 8 mmol/L/24 hours or reaches a concentration ≥ 140 mmol/L, the dose of tolvaptan should be held and the medical monitor should be called. If serum sodium changes by ≤ 4 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, but should continue 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. Subjects requiring ongoing treatment with tolvaptan may continue as needed per clinician's discretion. A dosing schedule for subjects is presented in Table 3.2.1-1.	**Section 3.2.1 Optional Tolvaptan Treatment** No text in this section
Section 3.2.1.1 Tablet Formulation	New section in this amendment	Tolvaptan tablets will be administered orally QD, preferably in the morning hours, with a dose- proportional amount of water. Doses of ≥ 15 mg of tolvaptan will be given with 240 mL of water, 7.5 mg of tolvaptan will be given with 120 mL of water, and 3.75 mg of tolvaptan will be given with 60 mL of water. Any initiation or titration of tolvaptan must occur in a hospital setting. The maximum starting doses, by weight, for subjects are shown in Section 3.2.1.2 and are within the range previously used in trials involving adult hyponatremic subjects.

Location	Old Text	Updated Text
Section 3.2.1.2 Titration Guidelines for the Optional Tolvaptan Treatment Component	**Section 3.2.2 Rescue Therapy** Subjects with worsening hyponatremia symptoms during the trial may receive rescue therapy. Rescue therapy is defined as any hypertonic saline, isotonic saline (with or without diuretic for purpose of increasing the serum sodium level), plasmapheresis/dialysis, demeclocycline, urea, lithium, commercial vaptans, or any treatment intended to raise the level of serum sodium. A subject requiring rescue therapy at any time after enrollment will be discontinued from the trial treatment prior to receiving rescue therapy and should continue to be followed as per protocol. Treatment may be reinitiated only per consultation with the sponsor's medical monitor; however, subjects who have received rescue therapy secondary to inadequate response to tolvaptan will not be allowed to reinitiate tolvaptan treatment. Sodium values drawn up to, but not after, the initiation of rescue therapy will be included in the calculation of the efficacy endpoint.	**Section 3.2.1.2 Titration Guidelines for the Optional Tolvaptan Treatment Component** Subjects will be administered tolvaptan on an age- and weight-based scale. Tolvaptan doses can be titrated QD 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 20 hours of the previous dose. Titration is limited to no more than twice the previous dose and will be limited to the maximum dose per body weight. A change in serum sodium ≤ 4 mEq/L (mmol/L) from baseline should warrant titration. • Subjects < 2 years of age or weighing < 10 kg are excluded until an oral liquid formulation is available. • Subjects ≥ 2 years of age and weighing ≥ 10 to < 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. • 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. • Subjects weighing > 50 kg will be given a 15-mg tablet on Day 1 with possible up-titration to 30- and 60-mg tablet doses. • Subjects weighing ≥ 20 kg and taking moderate inhibitors of CYP3A4 will be given a half-dose (3.75 or 7.5 mg, by weight). • Subjects weighing > 50 kg and taking potent inhibitors of CYP3A4 will be given a one-quarter dose. • Subjects weighing < 20 kg and who are taking any CYP3A4 inhibitors will be excluded until such time that an oral liquid formulation is available. Subjects will have the opportunity to titrate per medical need according to the guidelines listed above, targeting a final serum sodium concentration between 135 and 140 mEq/L (mmol/L). The

Location	Old Text	Updated Text
		clinician-directed target range is also acceptable. Titration guidelines are designed to ideally achieve a change in serum sodium concentration of at least 4 to 8 mEq/L (mmol/L) /24 hours but not ≥ 12 mEq/L (mmol/L)/24 hours.
Section 3.2.2 Duration of Optional Tolvaptan Treatment	**Section 3.2.3 Fluid Restriction** The option of initiating fluid restriction (all fluids) to 1 liter/day for subjects with serum sodium < 130 mmol/L is available at the investigator's discretion. Fluid restriction should be withheld for at least the first 24 hours after tolvaptan administration in order to determine the rate and magnitude of serum sodium change. A supplemental serum sodium assessment is scheduled 8 hours following the first dose to provide additional information which may be used to guide the decision to initiate fluid restriction.	**Section 3.2.2 Duration of Optional Tolvaptan Treatment** Subjects will receive daily doses of oral tolvaptan based on individual titration results and clinical need. Treatment can continue per clinical need as determined by the investigator in consultation with the medical monitor and follow-up visits for safety and serum sodium assessments can be adjusted per the guidelines in Section 3.2.1.2**.** Initiation of tolvaptan treatment can be repeated per the individual subject's need. If subjects are off tolvaptan treatment for > 72 hours, reinitiation of treatment will require reassessment of the eligibility criteria and must occur in a hospital setting. For subjects who require long-term treatment, each subject will be required to temporarily discontinue treatment at 30 days after the start of tolvaptan and be evaluated for continued need for tolvaptan treatment. For subjects who discontinue treatment, if the subject's serum sodium values decrease to unacceptably low levels (per the investigator's judgement) during treatment discontinuation, the subject can reinitiate treatment with tolvaptan. If treatment is reinitiated within 72 hours after administration of the last dose of tolvaptan, subjects will not be required to reinitiate titration a hospital setting if they resume treatment at the same dose or a lower dose. If treatment is reinitiated > 72 hours after administration of the last dose of tolvaptan, subjects will be required to reinitiate titration in a hospital setting. A dosing schedule for subjects is presented in **Error! Reference source not found.**. .... Any subject enrolled in the core safety follow-up component who has a medical need for tolvaptan per the investigator's assessment,

Location	Old Text	Updated Text
		may have short-term treatment (ie, a few days of treatment needed per episode of hyponatremia) or long-term treatment (ie, treatment for weeks to months with concomitant medication). The need for treatment beyond 30 days will be determined by a scheduled treatment discontinuation after 30 days. 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 ≤ 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 ≤ 8 mEq/L (mmol/L)/24 hours in response to tolvaptan treatment and the serum sodium is ≤ 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 discontinuation, concomitant medication adjustment, fluid supplementation and/or withdrawal). • If serum sodium level increases by ≥ 12 mEq/L (mmol/L) in the 24 hour 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.

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr><td>Table 3.2.2-1 Optional Tolvaptan Treatment Component: Dosing Schedule (Tablets)</td><td>

Table 3.2.1-1 Dosing Schedule

Trial Day	Time	Dose
Dose 1 (Hour 0)	Immediately after baseline (within 3 ± 1 hours)	3.75, 7.5, or 15 mg (as applicable)
Dose 2	24 (± 4) hours postdose	3.75, 7.5, 15, or 30 mg (as applicable)
Doses ≥ 3	24 (± 4) hours postdose	3.75, 7.5, 15, 30, or 60 mg (as applicable)

</td><td>

Table 3.2.2-1 Optional Tolvaptan Treatment Component: Dosing Schedule (Tablets)

Dosing Time Point	Time	Dose
Dose 1 (Hour 0)	Immediately after baseline (within 2-4 hours)	3.75, 7.5, or 15 mg (as applicable)
Dose 2	24 (± 4) hours post previous dose	3.75, 7.5, 15, or 30 mg (as applicable)
Doses ≥ 3	24 (± 4) hours post previous dose	3.75, 7.5, 15, 30, or 60 mg (as applicable)

</td></tr>
</table>

Old Text: Figure 3.2.1-1

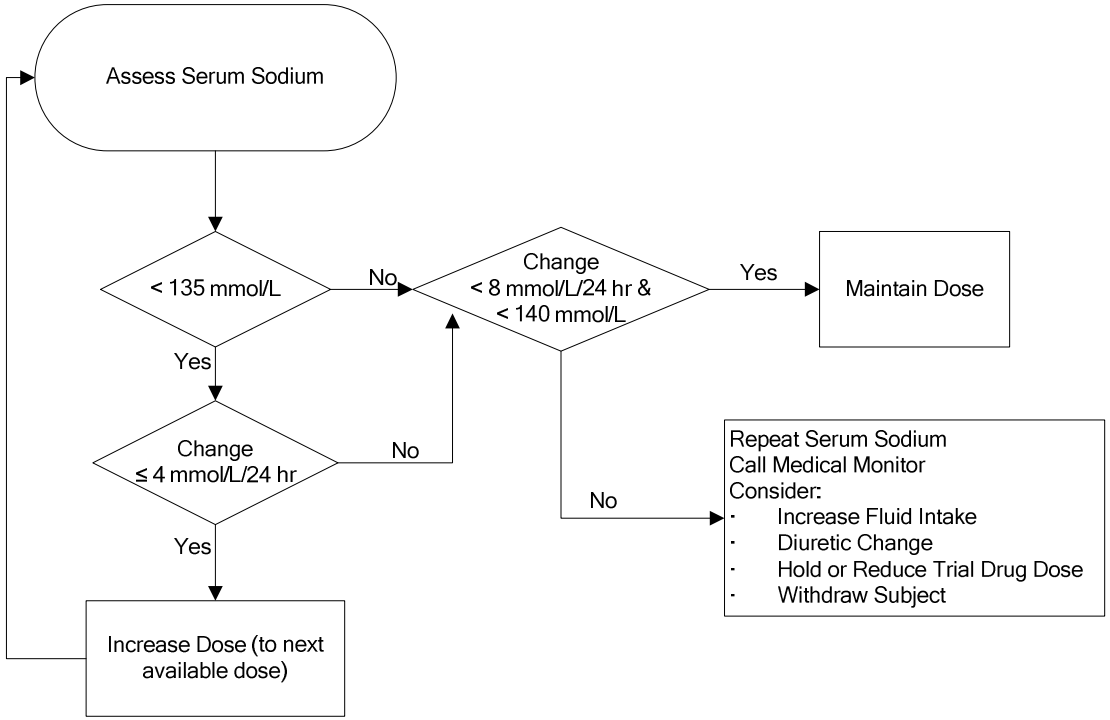


Figure 3.2.1-1 Titration Scheme

New Text: Figure 3.2.2-1

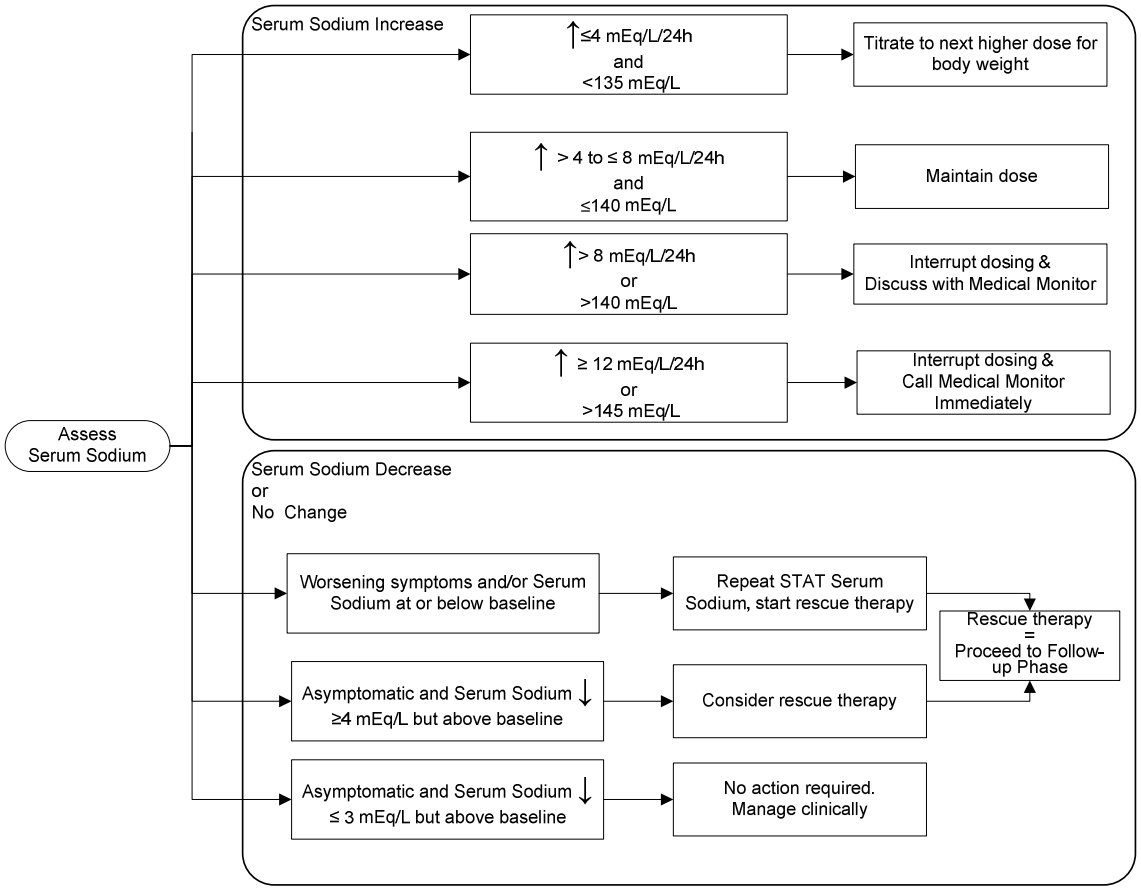


Figure 3.2.2-1 Titration Scheme

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr>
<td>Section 3.2.3
Rescue Therapy</td>
<td>
Section 3.2.4 Eligibility Criteria for Tolvaptan Treatment

Subjects must meet the eligibility criteria for tolvaptan treatment before being administered tolvaptan in each cycle. It is required to have documentation of chronic hyponatremia, defined by serum sodium < 130 mmol/L persisting for ≥ 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 ineligible for tolvaptan administration and may rescreen if eligible at a later date.

Table 3.2.4-1 Eligibility Criteria for Tolvaptan Treatment
<table>
<tr><td>1.</td><td>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</td></tr>
<tr><td>2.</td><td>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 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 mmol/L, which will serve as the baseline value for efficacy endpoints, is to be obtained within 3 (± 1) hours of the first dose of trial medication</td></tr>
<tr><td>3.</td><td>Ability to take oral medication as tablets</td></tr>
</table>
</td>
<td>
Section 3.2.3 Rescue Therapy

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

A subject requiring rescue therapy at any time during the optional tolvaptan treatment component will be discontinued from tolvaptan prior to receiving rescue therapy and should continue to be followed per the schedule of assessments in the core safety follow-up component of the trial. Treatment may be reinitiated only per consultation with the medical monitor. Subjects who have received rescue therapy because of inadequate response to tolvaptan will not be allowed to reinitiate tolvaptan treatment.

For subjects in the optional tolvaptan component only, serum sodium values drawn up to, but not after, the initiation of rescue therapy will be included in the calculation of the efficacy endpoint. Additional guidelines for rescue therapy concerning hyponatremia symptoms and decreasing serum sodium level are as follows:

• 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 ≥ 4 mEq/L (mmol/L), but is still above the baseline value, consider need for rescue therapy.
• If a subject is asymptomatic and serum sodium has decreased by ≤ 3 mEq/L (mmol/L), but is still above the baseline value, no action is required.
</td>
</tr>
</table>

Location	Old Text	Updated Text

4.	Ability to commit to remain abstinent or practice double-barrier birth control during tolvaptan treatment and for 14 days following the last dose of IMP for sexually active females of childbearing potential
5.	Ability to maintain adequate fluid intake whether orally or via IV support with adequate monitoring

Subjects will be ineligible for tolvaptan treatment if they meet any of the following criteria:

Table 3.2.4-2 Ineligibility Criteria for Tolvaptan Treatment

1.	Has evidence of hypovolemia or intravascular volume depletion (eg, hypotension, clinical evidence of volume depletion, response to saline challenge); if the subject has a systolic blood pressure < 90 mmHg or pulse > 120 bpm, then volume status should be specifically clinically assessed to rule out volume depletion
2.	Has serum sodium < 120 mmol/L, with or without associated neurologic impairment (ie, symptoms such as apathy, confusion, or seizures)
3.	Use of potent CYP3A4 inhibitors in subjects ≤ 50 kg or moderate CYP3A4 inhibitors in subjects < 20 kg (see Section 3.2)
4.	Lacks free access to water 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

Location	Old Text		Updated Text
	8.	Has eGFR < 30 mL/min/1.73 m2 calculated by the following equation: eGFR (mL/min/1.73 m2) = 0.413 × height (cm)/serum creatinine (mg/dL)	
	9.	Has AKI defined as: Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours; or Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume < 0.5 mL/kg/h for 6 hours	
	10.	Has severe or acute neurological symptoms requiring other intervention (eg, hyperemesis, obtundation, seizures)	
	11.	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	
	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 Pretreatment Baseline 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 mmol/L)	
	17.	Has screening liver function values > 3 × ULN	

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr><td></td><td>
<table>
<tr><td>18.</td><td>Has deficient coagulation (eg, cirrhotic at risk of 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 < 50,000/μL, or use of concomitant medications known to increase bleeding risk</td></tr>
<tr><td>19.</td><td>Has hyponatremia due to the result of any medication that can safely be withdrawn (eg, thiazide diuretics)</td></tr>
<tr><td>20.</td><td>Has hyponatremia (eg, hyponatremia in the setting of adrenal insufficiency, untreated hypothyroidism, or hypotonic fluid administration) that is most appropriately corrected by alternative therapies</td></tr>
<tr><td>21.</td><td>Is currently pregnant or breastfeeding</td></tr>
<tr><td>22.</td><td>Has any medical condition that, in the opinion of the investigator, could interfere with evaluation of the trial objectives or safety of the subjects (eg, Child-Pugh class C or NYHA class IV)</td></tr>
<tr><td>23.</td><td>Is deemed unsuitable for trial participation in the opinion of the investigator</td></tr>
</table>
AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; NYHA = New York Heart Association.
</td><td></td></tr>
<tr><td>Section 3.2.4
Fluid Restriction</td><td>New section in this amendment</td><td>Fluid restriction can be a standard of care in both the core safety follow-up component and the optional tolvaptan treatment component of the trial.

The option of initiating fluid restriction (all fluids) to ≤ 1 liter/day for tolvaptan-treated subjects with serum sodium < 130 mEq/L (mmol/L) is available at the investigator's discretion. Fluid restriction must not be initiated for at least the first 24 hours after tolvaptan administration in order to determine the rate and magnitude of serum sodium change. A supplemental serum sodium assessment is scheduled 8 hours following the first dose of tolvaptan to provide additional information which may be used to guide the</td></tr>
</table>

Location	Old Text	Updated Text
		decision to initiate fluid restriction in the future.
Section 3.3 Trial Population	Up to 140 male and female subjects may be eligible for this trial. All subjects will have enrolled in at least one of the previous tolvaptan pediatric hyponatremia trials (ie, 156-08-276, 156-12-205, or 156-13-207). The trial will be conducted at up to 65 centers globally.	No text in this section.
Section 3.3.1 Core Safety Follow-up Component	**Section 3.3.1 Trial Population for Tolvaptan Treatment** Subjects with euvolemic or hypervolemic hyponatremia (< 130 mmol/L) that persists despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist) may be eligible to be screened for treatment with tolvaptan. These subjects include, but are not limited to, those diagnosed and admitted to a hospital for treatment of heart failure, hepatocellular disease (including cirrhosis), or SIADH. Subjects with acute hyponatremia or hyponatremia expected to resolve spontaneously will be ineligible for tolvaptan treatment. 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 ineligible for tolvaptan treatment 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 ineligible for tolvaptan treatment. Children with Factor V Leiden or Factor VII abnormalities may be eligible for treatment only if the benefit is judged to outweigh any risk. Children with hepatocellular disease (including cirrhosis) who have platelet counts between 50,000 and 100,000/μL may be administered IMP 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 due to the large brain volumes in relatively small skulls. The most serious consequence of hyponatremia is hyponatremic encephalopathy,	**Section 3.3.1 Core Safety Follow-up Component** Up to 140 male or female subjects may be eligible for this trial. All subjects will have participated in one of the previous tolvaptan pediatric hyponatremia trials (156-08-276, 156-13-207, or 156-12-205). All subjects will be observed for post-treatment safety for at least 6 months. Subjects enrolled in the core safety follow-up component may enter the optional tolvaptan treatment component of the trial at any time during the conduct of the trial based on clinical need and the investigator's discretion.

Location	Old Text	Updated Text
	which occurs in over 50% of children with serum sodium < 125 mmol/L.[17] 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 ineligible for tolvaptan treatment (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).[18] 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 ≤ 120 mmol/L, hypernatremia, hypoxemia, severe liver disease, alcoholism, severe burns, severe malnutrition, hypokalemia, diabetes, or renal failure.[17,18,19,20] Subjects eligible for treatment with tolvaptan will be initially identified based on serum sodium concentrations that persist at levels < 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 Pretreatment Baseline period for tolvaptan treatment is ≥ 130 mmol/L, the subject will be ineligible for tolvaptan administration at that time. Subjects may be rescreened	

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr><td></td><td>for treatment, as appropriate.</td><td></td></tr>
<tr><td>Section 3.3.1.1 Tolvaptan Administration by Hyponatremia Etiology</td><td>Investigators should assess subjects' appropriateness to receive tolvaptan. Each investigator should ultimately use his/her medical judgment to make the final determination. The guidelines listed in Table 3.3.1.1-1 are to help guide the medical judgment of each investigator.
<table>
<tr><th colspan="3">Table 3.3.1.1-1 Screening Algorithms by Hyponatremia Etiology</th></tr>
<tr><th>SIADH/Other</th><th>CHF</th><th>Hepatocellular Disease</th></tr>
<tr><td>Two serum sodium assessments of < 130 mmol/L at least 12 hours apart</td><td>Two serum sodium assessments of < 130 mmol/L at least 12 hours apart</td><td>Two serum sodium assessments of < 130 mmol/L at least 12 hours apart</td></tr>
<tr><td>One serum sodium assessment 3 (± 1) hours before tolvaptan administration of < 130 mmol/L</td><td>One serum sodium assessment 3 (± 1) hours before tolvaptan administration of < 130 mmol/L</td><td>One serum sodium assessment 3 (± 1) hours before tolvaptan administration of < 130 mmol/L</td></tr>
<tr><td>Screen subjects per AKI criteria per treatment eligibility criteria</td><td>Screen subjects per AKI criteria per treatment eligibility criteria</td><td>Screen subjects per AKI criteria per treatment eligibility criteria</td></tr>
<tr><td>Collect labs[a]</td><td>Collect labs[a]</td><td>Collect labs[a]</td></tr>
<tr><td rowspan="2">Calculate serum osmolality, FENa, and FE urate as appropriate</td><td>Calculate serum osmolality, FENa, and FE urate as appropriate</td><td rowspan="2">Calculate serum osmolality, FENa, and FE urate as appropriate</td></tr>
<tr><td>Cardiologist documented diagnosis of CHF</td></tr>
</table></td><td>This section was removed in this amendment.</td></tr>
</table>

Location	Old Text	Updated Text
	<table><tr><td></td><td>Discontinue or stabilize diuretic use prior to tolvaptan administration</td><td></td></tr></table> AKI = acute kidney injury. [a]Refer to Table 3.7-2 and Table 3.7.3.2.1-1 for a complete list of laboratory assessments.	
Section 3.3.1.2 Hyponatremia due to Syndrome of Inappropriate Secretion of Antidiuretic Hormone	Evidence of low serum sodium should be demonstrated for at least 48 hours prior to scheduled tolvaptan administration. Two serum sodium assessments of < 130 mmol/L should be collected at least 12 hours apart. One serum sodium assessment of < 130 mmol/L should be collected 3 (± 1) hours before the initial tolvaptan administration. If any result, during the Pretreatment Baseline period is ≥ 130 mmol/L, the subject will be ineligible for treatment with tolvaptan. Subjects may be rescreened, as appropriate. Urine chemistry should be assessed and the serum osmolality, FENa, and FE urate should be calculated as appropriate for all subjects prior to the first dose of tolvaptan. Please see Table 3.7-2 for a full schedule of assessments and timing. Subjects must be screened per the acute kidney injury (AKI) criteria detailed in the treatment eligibility criteria (Section 3.2.4).	This section was removed in this amendment.
Section 3.3.1.3 Hyponatremia due to Congestive Heart Failure	Evidence of low serum sodium should be demonstrated for at least 48 hours prior to scheduled tolvaptan administration. Two serum sodium assessments of < 130 mmol/L should be collected at least 12 hours apart. One serum sodium assessment of < 130 mmol/L should be collected 3 (± 1) hours before the initial tolvaptan administration. If any result, during the Pretreatment Baseline period is ≥ 130 mmol/L, the subject will be ineligible for treatment with tolvaptan. Subjects may be rescreened, as appropriate. Urine chemistry should be assessed and the serum osmolality, FENa, and FE urate should be calculated as appropriate for all subjects prior to the first dose of tolvaptan. Please see Table 3.7-2 for a full schedule of assessments and timing.	This section was removed in this amendment.

Location	Old Text	Updated Text
	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 be contacted if there are questions. A definitive diagnosis of CHF by a cardiologist must be documented. Subjects must be screened per the AKI criteria detailed in the treatment eligibility criteria (Section 3.2.4).	
Section 3.3.1.4 Hyponatremia due to Hepatocellular Disease	Evidence of low serum sodium should be demonstrated for at least 48 hours prior to scheduled tolvaptan administration. Two serum sodium assessments of < 130 mmol/L should be collected at least 12 hours apart. One serum sodium assessment of < 130 mmol/L should be collected 3 (± 1) hours before the initial tolvaptan administration. If any result, during the Pretreatment Baseline period is ≥ 130 mmol/L, the subject will be ineligible for treatment with tolvaptan. Subjects may be rescreened, as appropriate. Urine chemistry should be assessed and the serum osmolality, FENa, and FE urate should be calculated as appropriate for all subjects prior to the first dose of tolvaptan. Please see Table 3.7-2 for a full schedule of assessments and timing. Subjects must be screened per the AKI criteria detailed in the treatment eligibility criteria (Section 3.2.4). The underlying etiology of hepatocellular disease must be documented.	This section was removed in this amendment.
Section 3.3.2 Optional Tolvaptan Treatment Component	New section in this amendment	Subjects enrolled in the Core Safety Follow-up Component of the trial may be eligible for treatment with tolvaptan. These subjects include, but are not limited to, those diagnosed and admitted to a hospital for treatment of heart failure, hepatocellular disease (including cirrhosis), or SIADH/other. Subjects with acute

Location	Old Text	Updated Text
		hyponatremia or hyponatremia expected to resolve spontaneously will be ineligible for tolvaptan treatment. 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 ineligible for tolvaptan treatment 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 ineligible for tolvaptan treatment.
Section 3.3.2.1 Hyponatremia Etiology in Children and Adolescents	New section in this amendment	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/μL 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.[17] Hyponatremic encephalopathy is seen in hospitalized children and adolescents 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 ineligible for tolvaptan treatment (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).[18] 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

Location	Old Text	Updated Text
		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 ≤ 120 mEq/L (mmol/L), hypernatremia, hypoxemia, severe liver disease, alcoholism, severe burns, severe malnutrition, hypokalemia, diabetes, or renal failure.[17,18,19,20] 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 ≥ 130 mEq/L (mmol/L), the subject will be ineligible for tolvaptan administration at that time. Subjects may be rescreened for treatment, as appropriate.
Section 3.4.1 Informed Consent	Written informed consent or patient information sheet (PIS) 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 Baseline 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 become legal adults prior to the end of the trial will be required to provide written informed consent at that time. ...	Written informed consent or patient information sheet (PIS) 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 baseline (which may be the final visit in the previous titrated oral IMP trial) 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 previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) or who become legal adults during this trial will be required to provide written informed consent as soon as they reach

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr><td></td><td></td><td>legal age.
...</td></tr>
<tr><td>Section 3.4.2 Inclusion Criteria</td><td>Eligible subjects must satisfy all informed consent requirements, as well as meet all the following inclusion criteria:</td><td>Subjects invited to participate in the core safety follow-up component of the trial must satisfy all informed consent requirements, as well as meet all the following inclusion criteria:
...
For initiation or reinitiation of tolvaptan treatment in the Optional Tolvaptan Treatment Component of the trial additional criteria apply as outlined in Appendix 5.</td></tr>
<tr><td>Table 3.4.2-1 Inclusion Criteria for Core Safety Follow-up Component</td><td>Table 3.4.2-1 Inclusion Criteria for All Subjects
1. Enrollment in at least one of the previous tolvaptan pediatric trials for hyponatremia (ie, Trial 156-08-276, 156-12-205, or 156-13-207)
2. Trial-specific written informed consent/assent obtained from a parent/guardian or legally acceptable representative, as applicable for local laws, prior to the initiation of any protocol-required procedures. In addition, the subject must provide informed assent at Baseline 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.
3. Ability to comply with all requirements of the trial
4. Willing to be clinically followed for 6 months</td><td>Table 3.4.2-1 Inclusion Criteria for Core Safety Follow-up Component
1. Enrollment in one of the previous tolvaptan pediatric trials for hyponatremia (ie, Trial 156-08-276, 156-13-207, or 156-12-205)
2. Trial-specific written informed consent/assent obtained from a parent/guardian or legally acceptable representative, as applicable for local laws, prior to the initiation of any protocol-required procedures. In addition, the subject must provide informed assent at baseline 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.
3. Ability to comply with all requirements of the trial
4. Willingness to be clinically followed for 6 months</td></tr>
<tr><td>Section 3.4.3 Exclusion Criteria</td><td>There are no exclusion criteria for entry into this trial.</td><td>There are no exclusion criteria for entry into the safety follow-up component of this trial.

For initiation or reinitiation of tolvaptan treatment in the Optional Tolvaptan Treatment Component of the trial additional criteria apply as outlined in Appendix 5.</td></tr>
<tr><td>Section 3.5.1 Primary</td><td>Section 3.5.1.1 Safety Variables</td><td>Section 3.5.1 Primary Outcome Variables</td></tr>
</table>

Location	Old Text	Updated Text
Outcome Variables	The primary safety variables include the following: • AEs, including cases of dehydration • Vital signs • Body weight, height, and growth percentiles • Tanner Stages	Data for the primary efficacy variable will be collected for all subjects receiving tolvaptan in the Optional Tolvaptan Treatment Component of the trial and will be summarized as follows: • Change from baseline in serum sodium while tolvaptan is being administered
Section 3.5.1.1.1 Safety Variables for Tolvaptan Treatment	In addition to the safety variables reported for all subjects, the following variables will be assessed for subjects on tolvaptan: • Percentage of subjects with overly rapid improvement in serum sodium (≥ 12 mmol/L in 24 hours after the first dose at introduction or reintroduction of IMP) • Percentage of subjects who experience recurrence of hyponatremia while on IMP • Clinical laboratory abnormalities: – Serum sodium, overly rapid changes in serum sodium – Changes from baseline in ALT and AST	This section was removed in this amendment
Section 3.5.2.1 Efficacy Variables	**Section 3.5.2.1 Efficacy Variables for Tolvaptan Treatment** The secondary efficacy endpoint is the change in serum sodium from baseline at each visit while the IMP is being administered. Serum sodium will be assessed daily during titration. Then, it will be assessed at each visit, at a minimum monthly once a subject has reached the optimal dose.	**Section 3.5.2.1 Efficacy Variables** Data for the secondary efficacy variables will be collected for all subjects receiving tolvaptan in the Optional Tolvaptan Treatment Component of the trial and will be summarized as follows: • Percentage of subjects who require rescue therapy while on tolvaptan • Percentage of subjects requiring continuation of tolvaptan following 30 days of treatment Additionally, for all subjects enrolled in the Core Safety Follow-up Component of the trial the following variable will be assessed and summarized: • Change from baseline in QoL assessments

Location	Old Text	Updated Text
Section 3.5.2.2 Safety Variables	**Section 3.5.2.2 Pharmacokinetic Variables for Tolvaptan Treatment** The PK endpoints are the plasma concentrations of tolvaptan and metabolites in subjects who have continued tolvaptan therapy for 8 consecutive weeks.	**Section 3.5.2.2 Safety Variables** Data for the secondary safety variables will be collected for all subjects enrolled in the Core Safety Follow-up Component of the trial. Safety variables listed below and their differences from baseline will be summarized. The primary safety variables are the following: • AE reporting • Growth percentiles for body height and body weight • Tanner Staging • Change from baseline in serum sodium concentration In addition to the safety variables reported for all subjects, the following variables will be assessed for subjects who enter the Optional Tolvaptan Treatment Component of the trial: • Percentage of subjects with overly rapid correction in serum sodium (≥ 12 mEq/L ([mmol/L]) in 24 hours after the first dose at introduction or reintroduction of tolvaptan) • Changes from baseline in ALT, AST, and BT.
Section 3.5.2.3 Pharmacokinetic Variable: Optional Tolvaptan Treatment Component	No text in this section	**Section 3.5.2.3 Pharmacokinetic Variable: Optional Tolvaptan Treatment Component** The PK endpoints are the plasma concentrations of tolvaptan and metabolites in subjects who have continued tolvaptan therapy for 8 consecutive weeks, ignoring short interruptions to assess need for continued therapy.
Section 3.5.3 Exploratory Variables	No text in this section.	Exploratory endpoints will include changes from baseline for the neurocognition test battery assessments..
Section 3.5.3.1	Exploratory endpoints will include Quality of Life assessments.	This section was removed in this amendment

Location	Old Text	Updated Text
Safety Variables		
Section 3.6 Measures to Minimize/Avoid Bias	This is an observational trial with an option for open-label treatment. Subjects will only be dosed based on clinical need and the investigator's discretion. The dose of the IMP assigned to an eligible subject is determined by the subject's age, weight, and the use of CYP3A4 inhibitors.	No measures to minimize bias were implemented as this is an observational trial with an option for open-label treatment. Subjects will only be dosed based on clinical need and the investigator's discretion. The dose of the IMP assigned to an eligible subject is determined by the subject's age, weight, and the use of CYP3A4 inhibitors.
Section 3.7 Trial Procedures	Parents or legal guardians will consent and subjects will assent (as applicable) at Baseline. Enrollment in this trial should directly follow completion or discontinuation of the previous trial (ie, 156-08-276, 156-12-205, or 156-13-207). The end of trial visit in the previous trial will serve as the Baseline Visit in this trial. Subjects will be followed monthly for 6 months, alternating between telephone calls and in-clinic visits, to clinically evaluate children and adolescent subjects with hyponatremia, regardless of the need for treatment. If a subject has a clinical need for tolvaptan, the subject may be screened for eligibility to be dosed with tolvaptan. The subject must have been off of treatment with IMP for a minimum of 7 days following the end of treatment in the previous trial to assess the subject's clinical need for treatment with tolvaptan. After enrollment in the trial, if subjects are to initiate tolvaptan treatment, screening for eligibility must occur −4 to −1 days prior to each dosing cycle. Eligible subjects will receive oral tolvaptan once daily based on clinical need as determined by the investigator in consultation with the sponsor's medical monitor. Subjects who meet the eligibility criteria for tolvaptan treatment will initially be administered a 3.75-, 7.5-, or 15-mg dose based on age, weight, and the use of CYP3A4 inhibitors on Day 1 of the cycle. Trial treatment should begin and be titrated in a hospital setting. Dosing of tolvaptan should occur in the morning. After titration is completed and the dose has stabilized in-hospital, subjects should return to the clinical site for assessment of serum sodium concentrations on an ongoing basis to monitor the stability of their hyponatremia or their achievement of normal or clinician-directed target range serum	No text in this section

Location	Old Text	Updated Text
	sodium per the guidelines in Section 3.1.1.1. Treatment can be discontinued and cycles may be repeated as needed per individual subject's need (eg, during chemotherapy treatments). If subjects are off of tolvaptan treatment for ≥ 48 hours, reinitiation of treatment will require reassessment of eligibility criteria and should begin in a hospital setting. Tolvaptan should be titrated with regular serum sodium assessments. After discontinuation of tolvaptan, serum sodium concentrations will be assessed at 48 (± 4) hours and 7 (+ 1) days post-last dose. Trial assessment time points are summarized in Table 3.7.1. Assessment time points for tolvaptan treatment are summarized in Table 3.7-2.	
Section 3.7.1 Core Safety Follow-up Component	New section in this amendment	Parents or legal guardians will consent and subjects will assent (as applicable) at baseline. Participation in this trial should directly follow completion or discontinuation of the previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205). The final laboratory assessments from the previous trial of titrated oral IMP will serve as the baseline laboratory assessments for this trial. Subjects will be followed monthly for 6 months, alternating between telephone calls and clinical trial site visits, to clinically evaluate children and adolescent subjects with dilutional (euvolemic or hypervolemic) hyponatremia, regardless of the need for treatment. Trial assessments and time points for the Core Safety Follow-up Component are summarized in Table 3.7.1-1 and described in Section 3.7.3.1.

Old Text: Table 3.7-1 Schedule of Assessments for All Subjects

Table 3.7-1 Schedule of Assessments for All Subjects

Procedures	Baseline Visit[a] Day 1	Months 1, 3, and 5 (± 2 weeks) Telephone Contact[b]	Months 2, 4, and 6 (± 2 weeks)/ET In-clinic Assessments
Informed consent and assent	X		
Review inclusion criteria	X		
Demographic information	X		
Medical and hyponatremia history	X		
Serum chemistry[c]	X		ALT and AST only: Month 2
Vital signs[d]	X		X
Directed physical examination	X		X
Body height and weight	X		X
Tanner Staging[e]	X		Month 6
Quality of Life	X		X
Concomitant medications	<----------	----------	---------->
Adverse events	<----------	----------	---------->

ET = early termination.

[a]The last visit of the previous trial will serve as the Baseline Visit. All assessments can be carried over to this trial.

[b]Telephone contacts can be replaced with in-clinic visits.

[c]All ALT and AST tests should have a reflexive total bilirubin if the ALT, AST, or both values are >3 × ULN.

[d]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.

[e]The collection of Tanner Staging data is required at the Month 6 in-clinic visit and every attempt should be made to collect this information. 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 in the US). A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging. Sites should make attempts to have examiners of both gender types. Attempts should be made to have the examination performed by the same gender as the subject. Otherwise, trial-affiliated personnel of the same gender as the subject (ie, nurse) should be in the same examination room as the subject.

New Text: Table 3.7.1-1 Core Safety Follow-up Component: Schedule of Assessments for All Subjects

Table 3.7.1-1 Core Safety Follow-up Component: Schedule of Assessments for All Subjects

Procedures	Baseline[a]	Month 1 (+2 Weeks)	Month 2 (+2 Weeks)	Month 3 (+2 Weeks)	Month 4 (+2 Weeks)	Month 5 (+2 Weeks)	Month 6 or Early Termination (+2 Weeks)
Informed consent and assent	X						
Review inclusion criteria	X						
Demographic information	X						
Telephone assessment[b]		X		X		X	
In-clinic assessment	X		X		X		X
Medical and hyponatremia history	X		X		X		X
Vital signs[c]	X		X		X		X
Directed physical examination	X		X		X		X
Body height/weight/ growth percentiles	X		X		X		X
Tanner Staging	X		X		X		X
Serum sodium	X		X		X		X
Assess ALT, AST, and BT	X		X		X		X
Neurocognitive Assessment[d]	X		X		X		X
Quality of Life	X		X		X		X
Concomitant medications	←	—	—	—	—	—	→
Adverse events	←	—	—	—	—	—	→

[a]The final laboratory assessments from the previous trial (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) can serve as the baseline laboratory assessments for this trial. All assessments, with the exception of the neurocognitive assessment, can be carried over from previous trial of titrated oral IMP to this trial, if possible. Body height, body weight, Tanner Staging and baseline laboratory assessments can be carried forward from the last visit in the previous trial if done within one month, but all other assessments must be completed at the baseline visit and all including height, Tanner Staging and laboratory assessments must be re-done if more than one month passes between trials.

[b]Telephone calls can be replaced with clinical site visits.

[c]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.

[d]Neurocognitive assessment will be performed at baseline and at Months 2, 4, and 6, and should be done within 1 hour of blood draws for serum sodium assessment.

Old Text: Table 3.7-1 Schedule of Assessments for Tolvaptan Treatment

Table 3.7-2 Schedule of Assessments for Tolvaptan Treatment

Procedures	Pretreatment Baseline Visit[a,b] Days −4 to −1	Treatment Cycle		Follow-up Period	
		Titration Period	Maintenance Period[c]	Initial Follow-up (48 ± 4 hours post-last dose)	7-day Follow-up (7 + 1 days post-last dose)
Review eligibility criteria for treatment	X				
Medical and hyponatremia history	X				
Urine pregnancy test[d]	X		Each visit	X	
ALT and AST[e]	X		Every month (± 2 days)		X
Serum sodium[f]	Within 48 hours prior to tolvaptan administration: 2 assessments at least 12 hours apart	**Day 1:** Baseline (predose, within 3 [± 1] hours of dosing), 8 hours post-first dose **Day 2 and during Titration Period:** 24 (± 4) hours post-previous dose	Each visit (**Months 1 to 3:** every 2 weeks [± 2 days] **Months ≥ 4:** every month [± 2 days])	X	X
Directed physical examination	X				
Tanner Staging[g]			Every 6 months		
Tolvaptan dosing[h]		←Once daily→			
Dispense IMP		End of the Titration Period	X		
IMP collection/reconciliation			X	X	
PK sample collection			1 sample after 8 consecutive weeks of dosing to be repeated upon reinitiation of therapy for 8 consecutive weeks		
Concomitant medications	<----------				---------->

Table 3.7-2 Schedule of Assessments for Tolvaptan Treatment

Procedures	Pretreatment Baseline Visit[a,b] Days −4 to −1	Treatment Cycle		Follow-up Period	
		Titration Period	Maintenance Period[c]	Initial Follow-up (48 ± 4 hours post-last dose)	7-day Follow-up (7 + 1 days post-last dose)
Adverse events	<----------	----------	----------	----------	---------->

[a] Assessments for the Pretreatment Baseline Visit of the first cycle can be carried over from the previous trial.

[b] Cycles can be repeated per clinical need. If a subject is off of tolvaptan treatment for ≥ 48 hours, reinitiation of treatment will require reassessment of eligibility criteria and should begin in a hospital setting.

[c] Visits for each cycle will occur minimally every 2 weeks (± 2 days) during Months 1 to 3, and monthly (± 2 days) from Month 4 onward.

[d] If applicable. Urine pregnancy tests will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started.

[e] All ALT and AST tests should have a reflexive total bilirubin if the ALT, AST, or both values are >3 × ULN.

[f] Within 48 hours prior to tolvaptan administration, 2 serum sodium assessments must be collected at least 12 hours apart. Baseline serum sodium testing can be waived if baseline is within 48 hours of the last dose administered or as past standard of care within 48 hours prior to tolvaptan administration.

[g] The collection of Tanner Staging data is required every 6 months and every attempt should be made to collect this information. 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 in the US). A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging. Sites should make attempts to have examiners of both gender types. Attempts should be made to have the examination performed by the same gender as the subject. Otherwise, trial-affiliated personnel of the same gender as the subject (ie, nurse) should be in the same examination room as the subject.

[h] The dose will be titrated at a minimum of 24-hour intervals (± 4 hours) from 3.75 to 7.5 to 15 mg for subjects ≥ 2 years of age and weighing ≥ 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.

New Text: Table Removed in this amendment

Location	Old Text	Updated Text
Section 3.7.2 Optional Tolvaptan Treatment Component	New section in this amendment	If a subject has a clinical need for tolvaptan, the subject may be screened for eligibility to be dosed with tolvaptan. To assess the subject's clinical need for tolvaptan, the subject must have been off treatment with IMP for 7 days following the end of treatment in the previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205). Eligible subjects will receive oral tolvaptan QD based on clinical need as determined by the investigator. Subjects who meet the eligibility criteria for tolvaptan treatment will initially be administered a 3.75-, 7.5-, or 15-mg dose based on age, weight, and the use of CYP3A4 inhibitors on Day 1 of the cycle. Trial treatment will begin and be titrated in a hospital setting. Dosing of tolvaptan should occur in the morning. After titration is completed and the dose has stabilized, subjects should return to the clinical trial site for assessment of serum sodium concentrations on an ongoing basis to monitor the stability of their hyponatremia or their achievement of normal or clinician-directed target range serum sodium per the guidelines in Section 3.2.1.2. Treatment can be discontinued and cycles may be repeated as needed per individual subject's need (eg, during chemotherapy treatments). If subjects are off tolvaptan treatment for > 72 hours, reinitiation of treatment, starting with titration, will require reassessment of the eligibility criteria, and titration will begin in a hospital setting. Tolvaptan should be titrated with regular serum sodium assessments. After discontinuation of tolvaptan, serum sodium concentrations will be assessed at the clinical trial site at 24 (± 4) hours and at 7 (± 1) days post-last dose. After the last follow-up visit, all subjects off tolvaptan treatment will be contacted for follow-up (AEs and concomitant medications) every 3 months. Trial assessments and time points for the Optional Tolvaptan Treatment Component are summarized in Table 3.7.2-1 and described in Section 3.7.3.2

Old Text: New table in this amendment

New Text: Table 3.7.2-1 Schedule of Assessments for Each Treatment Cycle

Table 3.7.2-3 Schedule of Assessments for Each Treatment Cycle

Procedures[a]	Pre-treatment Baseline[b]	Titration Phase[b]			Post-titration			Treatment Cycle Month 2	Treatment Cycle Month 3+ (Maintenance)	Follow- up Phase			
	Days -4 to -1	Day 1	Day 2 and 3	Day 4	Day 7, 14 and 21	Day 30 (±1)	Day 33 (-1)	every 2 weeks (±2 days)	Once monthly (±2 days)	24 (±4) hours post-last dose	7 (±1) days post-last dose	14 (±2) days post-last dose	every 3 months (±2 weeks)
Review eligibility criteria for treatment	X												
Vital signs	X	X	X	X	X	X	X	X	X	X	X		
Directed physical exam	X								X				
Body height and weight/ growth percentiles	X								X				
Pregnancy test[c]	X						X	X	X	X			
Clinical status assessment	X						X	X	X				
Assess ALT, AST, and BT[d]	X					X		X	X	X			
Assess serum sodium[e]	X	X	X	X	X	X	X	X	X	X	X		

Table 3.7.2-3 Schedule of Assessments for Each Treatment Cycle

Procedures[a]	**Pre-treatment Baseline**[b]	**Titration Phase**[b]			**Post-titration**			**Treatment Cycle Month 2**	**Treatment Cycle Month 3+ (Maintenance)**	**Follow- up Phase**			
	Days -4 to -1	**Day 1**	**Day 2 and 3**	**Day 4**	**Day 7, 14 and 21**	**Day 30 (±1)**	**Day 33 (-1)**	**every 2 weeks (±2 days)**	**Once monthly (±2 days)**	**24 (±4) hours post-last dose**	**7 (±1) days post-last dose**	**14 (±2) days post-last dose**	**every 3 months (±2 weeks)**
Tolvaptan dosing[f]		X	X	X	X	X	X	X	X				
Confirm stable dose				X									
Dispense tolvaptan drug kit				X			X	X	X				
Assess need for continued treatment							X						
Tolvaptan collection/ reconciliation					X	X		X	X	X			
PK sample collection[g]								X	X				
Telephone call												X	X
Concomitant medications	←												→
Adverse events	←												→

[a] Assessments that are part of a Core Safety Follow-up Component Trial Visit which happens to overlap with a visit in the Optional Tolvaptan Treatment Component only need to be performed once.

[b] Cycles can be repeated per clinical need. If a subject is off tolvaptan treatment for > 72 hours, titration/reinitiation of tolvaptan will require reassessment of eligibility criteria and will begin in a hospital setting.

[c] Serum or urine pregnancy tests will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. In Treatment Cycle Month 2 a pregnancy test should be performed a month after the previous assessment.

[d] In Treatment Cycle Month 2 liver function should be assessed a month after the previous assessment.

[e] Serum sodium will be assessed at the pretreatment baseline 48 hours prior to tolvaptan administration where 2 serum sodium assessments (<130 mEq/L [mmol/L) must be collected at least 12 hours apart. On Day 1 a STAT serum sodium sample will be assessed at 2 to 4 hours prior to first dose and another sample at 8 hours post-dose. On Day 2, 3 and 4 a sample will be assessed at 24 (± 4) hours post previous dose. On Days 7, 14, 21, and 30 at 24 (4) hours post-previous dose. At Day 33 serum sodium will be assessed between 48 and 72 hours post previous dose. In Treatment Cycle Month 2 a sample will be assessed every 14 (± 2) days. In Treatment Cycle Month ≥ 3 a sample will be assessed every month (± 2 days).

Location	Old Text	Updated Text
Section 3.7.3.1 Core Safety Follow-up Component	New section in this amendment	No text in this section
Section 3.7.3.1.1 Baseline for Core Safety Follow-up Component	**Section 3.7.3.1 Baseline** The last visit of the previous trial will serve as the Baseline Visit. All assessments can be carried over to this trial. The following procedures will be performed during the Baseline Visit (Day 1) to ensure 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. Informed consent/assent needs to be obtained only before entering the trial for the first time. d) ICF, assent, and/or PIS will be obtained from each subject's parent or legal guardian prior to any trial procedures being conducted. e) Each subject will indicate willingness to participate in the trial by signing or marking an assent form (as applicable) supplied for this purpose. 2) Inclusion criteria will be reviewed. 3) Demographic information will be collected only before enrolling in the trial; data can be carried over from the previous trial. 4) Medical and hyponatremia history will be recorded separately; data can be carried over from the previous trial. Medical history should include the subject's current list of medical problems. 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. 5) Any observable symptoms of hyponatremia will be assessed and recorded separately. 6) Serum chemistry laboratory samples (see **Table 3.7.3.2.1-**	**Section 3.7.3.1.1 Baseline for Core Safety Follow-up Component** For all subjects who enroll in this trial, the final laboratory assessments in the previous trial can serve as the baseline laboratory assessments. The following procedures will be performed during the baseline visit: 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. Informed consent/assent needs to be obtained only before entering the trial for the first time. f) ICF, assent, and/or PIS will be obtained from each subject's parent or legal guardian prior to any trial procedures being conducted. g) Each subject will indicate willingness to participate in the trial by signing or marking an assent form (as applicable) supplied for this purpose. 2) Inclusion criteria will be reviewed. 3) Demographic information will be collected. 4) Medical and hyponatremia history will be recorded separately. Medical history should include the subject's current list of medical problems in addition to the history recorded for the prior trial. The hyponatremia medical history should include the etiology of subject's hyponatremia (including the tests specified in Section **Error! Reference source not found.**) and what treatment was administered before trial enrollment. A detailed history specific to etiology of hyponatremia will also be recorded. 5) Any observable symptoms of hyponatremia will be assessed and recorded separately. 6) Vital signs (blood pressure, heart rate, respiratory rate, and

Location	Old Text	Updated Text
	1) will be transferred from the last assessments from the previous trial or collected, as appropriate. 7) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be transferred from the last assessments from the previous trial or assessed after the subject has been supine for ≥ 3 minutes, as appropriate. Vital signs should be performed prior to the blood draws. 8) A directed physical examination will be transferred from the last assessments from the previous trial or performed, as appropriate. 9) Body height and weight will be transferred from the last assessments from the previous trial or measured, as appropriate, and body mass index will be calculated. 10) Tanner Staging will be transferred from the last assessments from the previous trial or completed as part of the physical examination, as appropriate. 11) Quality of Life assessments will be transferred from the last assessments from the previous trial or performed as part of the physical examination, as appropriate. 12) Concomitant medications will be recorded. 13) Adverse events will be assessed.	temperature) will be transferred from the last assessments from the previous trial or assessed after the subject has been supine for ≥ 3 minutes, as appropriate. Vital signs should be performed prior to the blood draws. 7) A directed physical examination will be transferred from the last assessments from the previous trial or performed, as appropriate. 8) Body height and body weight will be transferred from the last assessments from the previous trial or measured, as appropriate. 9) Growth percentile will be calculated. Prior growth development information should also be collected, if available. 10) Tanner Staging will be transferred from the last assessments from the previous trial or completed as part of the physical examination, as appropriate. Historical staging information should also be collected, if available. 11) The final laboratory assessments from the previous trial can serve as baseline laboratory assessments in this trial (see Appendix 6), as appropriate. 12) Serum sodium will be assessed. 13) Neurocognitive assessments will be performed, as appropriate by age and where available, within 1 hour of the blood draw for serum sodium assessment. 14) Quality of Life assessment will be performed, as appropriate by age and where available. 15) Concomitant medications will be recorded. 16) Adverse events will be assessed.
Section 3.7.3.1.2 Months 1, 3, and 5	**Section 3.7.1.2 Months 1, 3, and 5** Subjects and/or their parents or legal guardians will be contacted by telephone or via a visit at the end of Months 1, 3, and 5 (± 2 weeks) to assess any new or ongoing AEs and to collect information on any medications administered since the last visit.	**Section 3.7.3.1.2 Months 1, 3, and 5** Subjects and/or their parents or legal guardians will be contacted by telephone or will be asked to attend a clinical trial site visit at the end of Months 1, 3, and 5 (+ 2 weeks) to assess any new or ongoing AEs and to collect information on any medications administered since the last visit.
Section 3.7.3.1.3	**Section 3.7.1.3 Months 2, 4, and 6/Early Termination**	**Section 3.7.3.1.3 Months 2, 4, and 6/Early Termination**

Location	Old Text	Updated Text
Months 2, 4, and 6/Early Termination	Subjects will return to the clinic at the end of Months 2, 4, and 6 (± 2 weeks) or at early termination (ET) and the following assessments will be performed: 1) A blood sample for ALT and AST testing (with reflexive total bilirubin assessed if the ALT, AST, or both values are > 3 × ULN) will be collected at Month 2 or at ET, if ET occurs before Month 2. 2) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed at each visit after the subject has been supine for ≥ 3 minutes. Vital signs should be performed prior to the blood draws. 3) A directed physical examination will be performed at each visit. 4) Body height and weight will be measured at each visit. 5) Tanner Staging will be completed at Month 6 or at ET. 6) Quality of Life assessments will be performed at each visit as part of the physical examination. 7) Concomitant medications will be recorded. 8) Adverse events will be assessed.	Subjects will return to the clinical trial site at the end of Months 2, 4, and 6 (+ 2 weeks) or at early termination (ET) and the following assessments will be performed: 1) Medical and hyponatremia history will be recorded separately. Medical history should include the subject's current list of medical problems in addition to the history recorded for the prior trial. The hyponatremia medical history should include the etiology of subject's hyponatremia (including the tests specified in Section 3.2.2) and what treatment was administered before trial enrollment. A detailed history specific to etiology of hyponatremia will also be recorded. 2) Any observable symptoms of hyponatremia will be assessed and recorded separately. 3) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed at each visit after the subject has been supine for ≥ 3 minutes. Vital signs should be performed prior to the blood draws. 4) A directed physical examination will be performed at each visit. 5) Body height will be measured at each visit. 6) Body weight will be measured at each visit. 7) Growth percentile will be calculated. 8) Tanner Staging will be completed at the Month 6 clinical trial site visit or at ET according to the instructions specified in Section 3.7.5.6 and Appendix 4. 9) A blood sample for serum sodium, ALT, AST, and BT will be collected at 24 hours (± 4 hours) post-last dose. 10) Neurocognitive assessments will be performed, as appropriate by age and where available, within 1 hour of the blood draw for serum sodium assessment. 11) Quality of Life assessment will be performed, as appropriate by age and where available. 12) Concomitant medications will be recorded. 13) Adverse events will be assessed.

Location	Old Text	Updated Text
Section 3.7.3.2 Optional Tolvaptan Treatment Component	**Section 3.7.1.4 Schedule of Assessments for Tolvaptan Treatment** All assessments to be conducted while subjects are treated with tolvaptan should be synchronized with those collected as part of the overall trial as possible (ie, assessments should not be performed twice at the same time point). Cycles can be repeated per clinical need during the initial 6 months of the trial and/or after the subject has completed the initial 6 months of follow-up. If a subject is off of tolvaptan treatment for ≥ 48 hours, reinitiation of treatment will require reassessment of the eligibility criteria and should begin in a hospital setting.	**Section 3.7.3.2 Optional Tolvaptan Treatment Component** The procedures to be performed at the required visits for subjects in need of tolvaptan treatment and for each tolvaptan treatment cycle are summarized in this section. If possible, all assessments while subjects are treated with tolvaptan should be synchronized with those performed as part of the core safety follow-up component of the trial (ie, assessments should not be performed twice at the same time point). Cycles can be repeated per clinical need during the initial 6 months of the trial and/or after the subject has completed the initial 6 months of follow-up. If a subject is off tolvaptan treatment for > 72 hours, titration and reinitiation of treatment will require reassessment of the eligibility criteria and will begin in a hospital setting.
Section 3.7.3.2.1 Pretreatment Baseline Visit	**Section 3.7.1.4.1 Pretreatment Baseline Visit** The following procedures will be performed during the Pretreatment Baseline Visit (Days −4 to −1) to ensure the subject qualifies for treatment with tolvaptan: 1) Eligibility criteria for tolvaptan treatment will be reviewed. 2) 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. 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 the etiology of hyponatremia will also be recorded. 3) Any observable symptoms of hyponatremia will be assessed and recorded separately. 4) A urine pregnancy test will be performed for female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. 5) A blood sample for ALT and AST testing (with reflexive	**Section 3.7.3.2.1 Pretreatment Baseline Visit** For subjects with a clinical need for tolvaptan treatment, the baseline visit for the core safety follow-up component of the trial may serve as the pretreatment baseline visit for the optional tolvaptan treatment component. The following procedures will be performed during the pretreatment baseline visit (Days −4 to −1) to ensure the subject qualifies for each tolvaptan treatment cycle: 1) Eligibility criteria (see Appendix 5) will be reviewed. 2) A clinical status assessment will be performed. 3) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed at each visit after the subject has been supine for ≥ 3 minutes. Vital signs should be performed prior to the blood draws. 4) A directed physical examination will be performed. 5) Body height will be measured. 6) Body weight will be measured. 7) Growth percentile will be calculated. 8) A blood sample for ALT, AST, and BT will be collected. 9) A serum or urine pregnancy test will be performed on female subjects ≥ 12 years of age and female subjects

Location	Old Text	Updated Text
	total bilirubin assessed if the ALT, AST, or both values are > 3 × ULN) will be collected. 6) Within 48 hours prior to tolvaptan administration, 2 samples for serum sodium testing will be collected at least 12 hours apart. These sample collections may be waived if they occur within 48 hours of the last dose of tolvaptan or as past standard of care within 48 hours prior to tolvaptan administration. 7) A directed physical examination will be performed. 8) Concomitant medications will be recorded. 9) Adverse events will be assessed.	< 12 years of age if menstruation has started. 10) Within 48 hours prior to tolvaptan administration, 2 samples for serum sodium testing will be collected at least 12 hours apart. 11) Concomitant medications will be recorded. 12) Adverse events will be assessed.
Section 3.7.3.2.2 Titration Phase	**Section 3.7.1.4.2 Titration Period**	**Section 3.7.3.2.2 Titration Phase**
Section 3.7.3.2.2.1 Day 1	**Section 3.7.1.4.2.1 Day 1** Subjects will be administered the first dose of tolvaptan (initially and for reinitiation of treatment) in a hospital setting. The following procedures will be performed on Day 1: 1) Blood samples for serum sodium testing should be collected STAT at baseline (within 3 [± 1] hours prior to dosing) and minimally 8 hours post-first dose per protocol; serum sodium may be further assessed as per clinician preference during the first 24 hours post-first dose. 2) Any observable symptoms of hyponatremia will be assessed at baseline (prior to dosing) to confirm eligibility. 3) Tolvaptan will be administered as a 3.75-, 7.5-, or 15-mg dose based on age, weight, and the use of CYP3A4 inhibitors. 4) Concomitant medications will be recorded. 5) Adverse events will be assessed.	**Section 3.7.3.2.2.1 Day 1** Subjects will be administered the first dose of tolvaptan (initially and for reinitiation of treatment, if the latter occurs > 72 hours after a discontinuation) in a hospital setting. The following procedures will be performed on Day 1: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for STAT serum sodium testing will be collected within 2 to 4hours prior to dosing. Results need to be reviewed prior to dosing to confirm continued treatment eligibility of the subject. 3) Tolvaptan will be administered. 4) A blood sample for serum sodium testing will be collected 8 hours post-first dose in the current treatment cycle. 5) Concomitant medications will be recorded. 6) Adverse events will be assessed.
Section 3.7.3.2.2.2 Day 2 up to Day 4	**Section 3.7.1.4.2.2 Day 2 Through the End of the Titration Period**	**Section 3.7.3.2.2.2 Day 2 up to Day 4** ...

Location	Old Text	Updated Text
	... 1) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 2) Tolvaptan will be titrated per the titration guidelines (Section 3.2.1 for the assigned weight group. 3) At the end of the titration period, sufficient IMP will be dispensed for subjects that are outpatients for once daily dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to return any remaining IMP at the next visit for dose reconciliation. ...	1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 3) Administer tolvaptan. Tolvaptan will be titrated per the titration guidelines (see Section 3.2.1.2) for the assigned weight group. 4) On Day 4, if a stable dose of tolvaptan has been confirmed, the initial titration phase will conclude, and sufficient tolvaptan will be dispensed for subjects that are outpatients for QD dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation. ...
Section 3.7.3.2.3 Days 7, 14, and 21	New section in this amendment	Serum sodium will be assessed a minimum of once weekly during the first month of the treatment cycle, on the morning of Days 7, 14, and 21before the next dose of tolvaptan. The following assessments will be performed during each in-clinic visit during the first month of the treatment cycle: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 3) Tolvaptan will be administered. 4) Concomitant medications will be recorded. 5) Adverse events will be assessed.

Location	Old Text	Updated Text
Section 3.7.3.2.4 30 (± 1) Days Post-first Dose	New section in this amendment	After 30 days of tolvaptan treatment, all subjects should discontinue treatment for assessment of continued need for tolvaptan treatment. 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 3) A blood sample for ALT, AST, and BT will be collected. 4) Tolvaptan will be administered. 5) Advise subject to skip the next 2 doses. 6) Concomitant medications will be recorded. 7) Adverse events will be assessed.
Section 3.7.3.2.5 Day 33 (- 1)	New section in this amendment	The following assessments will be performed: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 1) A clinical status assessment will be performed. 2) A serum or urine pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. 3) A blood sample for serum sodium testing must be assessed to confirm the need for continuation of treatment. Refer to Figure 3.1-1 and Section 3.2.2 for the trial schematic and a description of the treatment continuation decision. 4) Tolvaptan will be administered if need for continued treatment is confirmed. Subjects who reinitiate treatment at the same dose or a lower dose of tolvaptan after discontinuation for up to 72 hours will not be required to reinitiate treatment in a

Location	Old Text	Updated Text
		hospital setting. If subjects are off tolvaptan treatment for > 72 hours, reinitiation of treatment, starting with titration (Section 3.2.1.2), will require reassessment of the eligibility criteria, and titration will begin in a hospital setting. Tolvaptan should be titrated with regular serum sodium assessments. 5) Concomitant medications will be recorded. 6) Adverse events will be assessed.
Section 3.7.3.2.6 Treatment Cycle Month 2: Every 2 Weeks (±2 days)	New section in this amendment	The next clinic visit should occur 2 weeks after the decision to continue treatment is made and then 2 weeks thereafter if treatment is continued. The following assessments will be performed during each in-clinic visit during the second month of each treatment cycle: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 3) A blood sample for ALT, AST, and BT will be collected (at the end of Treatment Cycle Month 2). 4) For each treatment cycle, a single PK blood sample will be collected after 8 consecutive weeks of tolvaptan dosing for the determination of tolvaptan and metabolites plasma concentrations. 5) A clinical status assessment will be performed. 6) A serum or urine pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started (at the end of Treatment Cycle Month 2 only). 7) Tolvaptan will be administered. 8) Sufficient tolvaptan will be dispensed for subjects that are

Location	Old Text	Updated Text
		outpatients for QD dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation. 9) Concomitant medications will be recorded. 10) Adverse events will be assessed.
Section 3.7.3.2.7 Maintenance Phase	New Section in this amendment	No Text in this section
Section 3.7.3.2.7.1 Treatment Cycle Month 3 (and every month thereafter) (±2 days)	**Section 3.7.1.4.3 Maintenance Period** Subjects will return to the site for safety and assessment of serum sodium concentrations at intervals discussed in Section 3.1.1.1. The following procedures will be performed: 1) A urine pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. 2) A blood sample for ALT and AST testing (with reflexive total bilirubin assessed if the ALT, AST, or both values are > 3 × ULN) will be collected every month (± 2 days). 3) A blood sample for serum sodium testing should be taken at each visit. 4) Tanner Staging will be completed every 6 months. 5) Tolvaptan will be administered once daily. 6) Sufficient IMP will be dispensed for subjects that are outpatients for once daily dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to return any remaining IMP at the next visit for dose reconciliation. 7) For each initiation or reinitiation of tolvaptan treatment, a single blood sample will be collected after 8 consecutive weeks of tolvaptan dosing for the determination of tolvaptan and metabolites plasma concentrations. 8) Concomitant medications will be recorded. 9) Adverse events will be assessed.	**Section 3.7.3.2.7.1 Treatment Cycle Month 3 (and every month thereafter) (±2 days)** Subjects will return to the clinical trial site for assessment of safety and of serum sodium concentrations at the intervals discussed in Section 3.1.2. The following procedures will be performed: 1) A serum or urine pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. 2) A directed physical examination will be performed. 3) A clinical status assessment will be performed. 4) A blood sample for ALT, AST, and BT will be collected every month. 5) A blood sample for serum sodium testing should be taken at each visit. 6) Tolvaptan will be administered. 7) Sufficient tolvaptan will be dispensed for subjects that are outpatients for QD dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation. 8) If a PK sample has not been taken at the end of the Treatment Cycle Month 2 visits, a single PK blood sample will be collected after 8 consecutive weeks of tolvaptan dosing for the determination of tolvaptan and metabolites plasma concentrations. 9) Concomitant medications will be recorded.

Location	Old Text	Updated Text
		10) Adverse events will be assessed. Tolvaptan treatment cycles may be repeated per a subject's clinical need and the discretion of the investigator. Subjects may be evaluated for continued need for tolvaptan treatment at additional clinical trial site visits per the investigator's discretion. After discontinuation of tolvaptan, serum sodium concentrations will be assessed at 24 (± 4) hours and at 7 (+ 1) days post-last dose.
Section 3.7.3.2.8 Follow-up Phase	New section in this amendment	No text in this section.
Section 3.7.3.2.8.1 First Follow-up: 24 (± 4) hours post-last dose	**Section 3.7.1.4.4 Initial Follow-up Visit** After discontinuation from treatment, the subject must return to the site at approximately 48 (± 4) hours post-last dose. The following procedures will be performed: 1) A urine pregnancy test will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. 2) A blood sample for serum sodium testing should be obtained at 48 (± 4) hours post-last dose. 3) Any remaining IMP will be collected from the subjects. 4) Concomitant medications will be recorded. 5) Adverse events will be assessed.	**Section 3.7.3.2.8.1 First Follow-up: 24 (± 4) hours post-last dose** After discontinuation from treatment, the subject must return to the site at approximately 24 (± 4) hours post-last dose. The following procedures will be performed: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for ALT, AST, and BT testing will be collected. 3) A serum or urine pregnancy test will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started (if not done within the last 30 days). 4) A blood sample for serum sodium testing will be collected at 24 (± 4) hours post-last dose. 5) Any remaining tolvaptan will be collected from the subjects. 6) Concomitant medications will be recorded. 7) Adverse events will be assessed.
Section 3.7.3.2.8.2 Second Follow-	**Section 3.7.1.4.5 7-day Follow-up Visit** A follow-up visit will occur 7 (+ 1) days after the last dose of trial	**Section 3.7.3.2.8.2 Second Follow-up: 7 (± 1) days post-last dose** An additional follow-up visit will occur 7 (± 1) days post-last dose.

Location	Old Text	Updated Text
up: 7 (± 1) days post-last dose	medication. 1) A blood sample for serum sodium testing will be collected. 2) A blood sample for ALT and AST testing (with reflexive total bilirubin assessed if the ALT, AST, or both values are > 3 × ULN) will be collected. 3) Concomitant medications will be recorded. 4) Adverse events will be assessed. Cycles may be repeated per a subject's clinical need and the discretion of the investigator.	The following assessments will be performed: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing will be collected. 3) Concomitant medications will be recorded. 4) Adverse events will be assessed.
Section 3.7.3.2.8.3 Third Follow-up: 14 (± 2) days post-last dose	New section in this amendment	A follow-up telephone contact will occur at 14 (± 2) days post-last dose for assessment of adverse events and concomitant medications. 3) Concomitant medications will be recorded. 4) Adverse events will be assessed.
Section 3.7.3.2.8.4 Additional Follow-up Contacts	New section in this amendment	Follow-up telephone contacts will occur every 3 months (± 2 weeks) for all subjects who are not receiving tolvaptan treatment. 1) Concomitant medications will be recorded. 2) Adverse events will be assessed.
Section 3.7.4 Efficacy Assessments	**Section 3.7.2 Efficacy Assessments** See Section 3.7.5.	**Section 3.7.4 Efficacy Assessments** No text in this section
Section 3.7.4.1 Serum Sodium Concentrations	New section in this amendment	No text in this section
Section 3.7.4.1.1 Pretreatment Baseline Visit	New section in this amendment	All subjects should have blood samples collected for serum sodium assessment at the baseline visit or transferred from the last visit of the previous trial. Within 48 hours prior to tolvaptan administration, 2 blood samples will be collected at least 12 hours apart for assessment of baseline serum sodium to determine subject eligibility for tolvaptan treatment. A third serum sodium sample should be drawn within 2 to 4 hours prior to dosing; the results must be verified to be < 130 mEq/L (mmol/L) prior to the first dose in each treatment cycle.

Location	Old Text	Updated Text
Section 3.7.4.1.2 Initial Titration Phase and Month 1	New section in this amendment	During the Titration Phase (the first 30 days of treatment) subjects should have serum sodium assessments at a minimum of QD on Day 1 up to Day 4 of treatment, and at a minimum of once weekly thereafter (ie, on Days 7, 14, 21, and 28 of Month 1). On Day 1, a serum sodium sample should be collected STAT and recorded in the CRF at a minimum of 8 hours post-first dose and 24 (± 4) hours post-previous dose.
Section 3.7.4.1.3 Assessment of Continued Need for Tolvaptan Treatment	New section in this amendment	Tolvaptan administration will be discontinued after 30 days of treatment to assess the subjects' need for continued treatment. Procedures for reinitiation of tolvaptan treatment for subjects with a clinical need per the investigator's assessment are described in Section **Error! Reference source not found.**. During the second consecutive month of treatment, serum sodium concentrations should be assessed at a minimum of every 2 weeks (± 2 days).
Section 3.7.4.1.4 Maintenance Phase	New section in this amendment	Once subjects have been treated for 2 months, and are on a stable dose with no additional titration required, they can be considered to enter a Maintenance Phase from the third month onward. At this point, the subjects should return to the clinical trial site at a minimum of once per month (± 2 days) for assessment of serum sodium concentrations. When a subject is discontinued from tolvaptan, serum sodium must be assessed at 24 (± 4) hours, and at 7 (± 1) days post-last dose.
Section 3.7.4.1.5 Unscheduled Assessments	New section in this amendment	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.
Section 3.7.4.2 Quality of Life Assessments	New section in this amendment	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 ≥ 2 years of age, however availability may be limited for certain ages and languages. The age groups covered by these assessments are Toddler

Location	Old Text	Updated Text
		(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. The PedsQL Generic Core Scale consists of 23 items encompassing physical, emotional, social, and school domains. The PedsQL Multidimentional 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 Baseline, Month 2, Month 4, and at Month 6 or Early Termination during the Core Safety Follow-up Component.
Section 3.7.5 Safety Assessments	**Section 3.7.3 Safety Assessments** No text in this section	**Section 3.7.5 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. Body height, body weight, Tanner Staging and baseline laboratory assessments can be carried over from the previous trial of titrated oral IMP to this trial, if no more than one month passes between trials. 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 3.7.5.2.
Section 3.7.5.1 Adverse Events	**Section 3.7.3.1 Adverse Events** Refer to Section 5, Reporting of Adverse Events. In particular, the following AEs must be actively monitored: absolute serum sodium level ≥ 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, ≥ 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	**Section 3.7.5.1 Adverse Events** Refer to Section 5, Reporting of Adverse Events. In addition, for subjects on tolvaptan treatment active monitoring is required for: • Absolute serum sodium level ≥ 145 mEq/L (mmol/L) or an overly rapid correction of the serum sodium level (an increase in serum sodium of > 8 mEq/L [mEq/L (mmol/L)] over a 10-hour period, ≥ 12 mEq/L [mEq/L (mmol/L)] over a 24-hour period, or a rate of correction in serum sodium

Location	Old Text	Updated Text
	detail).	concentration that the investigator deems too rapid), neurologic symptoms, or other signs or symptoms suggestive of osmotic demyelination (see Section 5.3.1for more details). • Elevations in AST or ALT that are ≥ 2 × ULN or levels that increase ≥ 2 times their previously observed level. If this occurs, a BT level should also be evaluated. See Section 3.7.3.5.1 for more information and Section 5.4 for detailed instructions on how this type of event should be captured. • Worsening symptoms of hyponatremia • Hypovolemia or hypotension requiring intervention.
Section 3.7.5.2 Clinical Laboratory Tests: Core Safety Follow-up Component	**Section 3.7.3.2 Clinical Laboratory Tests** Table 3.7.3.2-1 presents the protocol-required clinical laboratory results (serum chemistry, including liver function tests) that are reported as part of the trial results. Serum chemistry will either be measured at Baseline or transferred from the last visit of the previous trial. At Month 2 or at ET, if ET occurs before the Month 2 Visit, only ALT and AST (with reflexive total bilirubin assessment if the ALT, AST, or both values are > 3 × ULN) will be measured. No further laboratory assessments are required per protocol except as needed for the follow-up of AEs. **Table 3.7.3.2-1 Safety Clinical Laboratory Tests for All Subjects**	**Section 3.7.5.2 Clinical Laboratory Tests: Core Safety Follow-up Component** For all subjects enrolled in the core safety follow-up component, serum sodium assessments and LFTs will either be performed at baseline or transferred from the last visit of the previous trial. At Months 2, 4, and 6, serum sodium will be assessed. At Month 2 or at ET, if ET occurs before the Month 2 Visit, ALT, AST, and BT will be measured. No further laboratory assessments are required per protocol except as needed for the follow-up of AEs.

Location	Old Text	Updated Text
	Serum Chemistry: ALT Alkaline phosphatase AST Bicarbonate (or carbon dioxide) Bilirubin, total Blood urea nitrogen Calcium Chloride Cholesterol, total Creatinine Gamma glutamyl transferase Glucose Lactic dehydrogenase Potassium Protein, total Sodium Triglycerides Uric acid	
Section 3.7.5.3 Clinical Laboratory Tests: Optional Tolvaptan Treatment Component	**Section 3.7.3.2.1 Clinical Laboratory Tests for Tolvaptan Treatment** Table 3.7.3.2.1-1 presents the protocol-required clinical laboratory results (serum sodium, ALT, and AST with reflexive total bilirubin assessment if the ALT, AST, or both values are > 3 × ULN) that are reported as part of the trial results for subjects on tolvaptan. If these results are to be obtained as part of the standard of care for the subject, the timing should be coordinated per the schedule of assessments (Table 3.7-2), whenever possible, to minimize the number of blood draws for the subject.	**Section 3.7.5.3 Clinical Laboratory Tests: Optional Tolvaptan Treatment Component** Table 3.7.5.3-1 presents the protocol-required clinical laboratory results (serum sodium, ALT, AST, and BT) that are reported as part of the trial results for subjects in the optional tolvaptan treatment component. If these results are to be obtained as part of the standard of care for the subject, the timing should be coordinated per the schedule of assessments (Section 3.7.3), whenever possible, to minimize the number of blood draws for the subject **while at the same time ensuring that liver function tests are monitored on a monthly basis while continuing treatment with tolvaptan.**
Table 3.7.5.3-1 Safety Clinical Laboratory Tests During Tolvaptan Treatments	**Table 3.7.3.2.1-1 Safety Clinical Laboratory Tests During Tolvaptan Treatment**	**Table 3.7.5.3-1 Safety Clinical Laboratory Tests During Tolvaptan Treatment**

Location	Old Text	Updated Text
	ALT AST Reflexive total bilirubin <u>Efficacy:</u> Serum sodium <u>Additional Tests:</u> Urine pregnancy test (if applicable)	ALT AST BT Efficacy: Serum sodium <u>Additional Tests:</u> Serum or urine pregnancy test (if applicable)
Section 3.7.5.3.1 Monitoring of Liver Transaminases	**Section 3.7.3.2.2 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 is between 3 and 14 months of chronic treatment with tolvaptan. For a subject that experiences an elevation in AST or ALT that is ≥ 3 ×ULN or whose levels increase ≥ 3 times their previous observed value, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 × ULN or ≥ 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 case report forms (CRFs). See Section 5.4 for detailed instructions on how to capture this type of event.	**Section 3.7.5.3.1 Monitoring of Liver Transaminases** Long-term use of tolvaptan has demonstrated the potential to cause a clinically significant elevation in liver function test values. 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 ≥ 2 × ULN or whose levels increase ≥ 2 times their previous observed value, a BT level should also be evaluated. These elevated values should be confirmed by retesting. If BT is ≥ 2 × ULN or ≥ 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 CRFs. See Section 5.4.1 for detailed instructions on how this type of event should be captured.
Section 3.7.5.4 Physical Examination and Vital Sign Assessments	**Section 3.7.3.3 Physical Examination and Vital Sign Assessments** ... Body weight will be measured at the Month 2, 4, and 6 Visits. Every effort should be made to ensure that body weight measurements will be 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. ...	**Section 3.7.5.4 Physical Examination and Vital Sign Assessments** ... Body weight will be measured at the Month 2, 4, and 6 Visits. Every effort should be made to ensure that body weight measurements will be performed in a reproducible and consistent manner. Body weight measurements should be performed at the clinical trial 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. ...

Location	Old Text	Updated Text
Section 3.7.5.5 Tanner Staging	**Section 3.7.3.4 Tanner Staging** The collection of Tanner Staging data is required at the Month 6 Visit or at ET and every 6 months during tolvaptan treatment; every attempt should be made to collect this information. 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 in the US). A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging. Sites should make attempts to have examiners of both gender types. Attempts should be made to have the examination performed by the same gender as the subject. Otherwise, trial-affiliated personnel of the same gender as the subject (ie, nurse) should be in the same examination room as the subject. ...	**Section 3.7.5.5 Tanner Staging** The collection of Tanner Staging data is required for all subjects in the core safety follow-up component at the Month 6 Visit. Every attempt should be made to collect this information. 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 in the US). A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging. Sites should make attempts to have examiners of both sexes. Attempts should be made to have the examination performed by the same sex 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. ...
Section 3.7.3.5 Electrocardiogram Assessments	Electrocardiograms (ECGs) will be recorded only as warranted; there are no trial mandated ECGs.	This section was removed in this amendment
Section 3.7.5.6 Hyponaterima History	**Section 3.7.3.6 Hyponaterima History** Each subject's hyponatremia medical history will be recorded at Baseline. The hyponatremia history should include the etiology of subject's hyponatremia (including tests per protocol) and what treatment was administered before trial enrollment. Symptoms potentially attributable to hyponatremia should be specifically assessed for prior history. The hyponatremia assessment at Baseline will consist of documentation of hyponatremia etiology (eg, SIADH, hepatocellular disease [including cirrhosis], CHF, or 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.	**Section 3.7.5.6 Hyponaterima History** Each subject's hyponatremia medical history will be recorded at baseline. The hyponatremia history should include the etiology of subject's hyponatremia (including tests per protocol) and what treatment was administered before trial enrollment. Symptoms potentially attributable to hyponatremia should be specifically assessed for prior history. The hyponatremia assessment at baseline will consist of documentation of hyponatremia etiology (eg, SIADH, hepatocellular disease [including cirrhosis], heart failure, or 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.

Location	Old Text	Updated Text
Section 3.7.5.7 Clinical Status Assessment	New section in this amendment	Clinical status assessments will be performed per inpatient standard of care and should include review of patient 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.
Section 3.7.6 Pharmacokinetic Assessments	**Section 3.7.4 Pharmacokinetic Assessments**	**Section 3.7.6 Pharmacokinetic Assessments**
Section 3.7.6.1 Blood Collection Times	**Section 3.7.4.1 Blood Collection Times** For those subjects undergoing treatment with tolvaptan for at least 8 consecutive weeks for each initiation or reinitiation of therapy, a single blood sample to measure tolvaptan and metabolite concentrations at steady state will be obtained for each cycle. The date and time of the PK sample and the date and time of the dose given immediately prior to the PK sample will be recorded on the CRFs.	**Section 3.7.6.1 Blood Collection Times** For subjects undergoing treatment with tolvaptan for at least 8 consecutive weeks for each initiation or reinitiation of therapy, a single blood sample to measure tolvaptan and metabolite concentrations at steady state will be obtained for each cycle. The date and time of the PK sample and the date and time of the dose given immediately prior to the PK sample will be recorded on the CRFs. For each subject all samples will be collected according to local guidelines and best practices for pediatric care. If a sample is missing because of limitations in allowable blood volumes based on local regulations or local practice this will not count as a protocol deviation.
Section 3.7.7 Exploratory Assessments	**Section 3.7.5 Exploratory Assessments** Exploratory assessments include overall serum sodium concentrations and daily clinical status assessments.	**Section 3.7.7 Exploratory Assessments** Exploratory assessments include a neurocognition test battery. These assessments will be performed for all subjects in the core safety follow-up component of the trial.
Section 3.7.7.1 Neurocognitive	**Section 3.7.5.1 Serum Sodium Concentrations**	**Section 3.7.7.1 Neurocognitive Assessments**

Location	Old Text	Updated Text
Assessments	Monitoring frequency of serum sodium is at the discretion of the clinical investigator; however, it is required to be performed minimally once per day during titration. Please see the minimum required sample collection guidelines for all subjects noted in Section 3.1.1.1 and Section 3.7.2. All subjects should have blood samples collected for serum sodium assessment at the Baseline Visit or transferred from the last visit of the previous trial. Within 48 hours prior to tolvaptan administration, 2 blood samples will be collected at least 12 hours apart for assessment of baseline serum sodium to determine subject eligibility for tolvaptan treatment. These sample collections may be waived if they occur within 48 hours of the last dose of tolvaptan or as past standard of care within 48 hours prior to tolvaptan administration. A third serum sodium sample should be drawn within 3 [± 1] hours prior to dosing; the results must be verified to be < 130 mmol/L prior to the first dose. A serum sodium sample should be collected STAT and recorded in the CRF minimally at 8 hours post-first dose and 24 (± 4) hours post-previous dose during the Titration Period and then minimally during the Maintenance Period every 2 weeks (± 2 days) during Months 1 to 3. From Month 4 onward for consecutive treatment, serum sodium should be assessed minimally once per month (± 2 days). When a subject is discontinued from tolvaptan, serum sodium must be assessed at 48 (± 4) hours and 7 (+ 1) days post-last dose. 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.	Neurocognitive assessments will be performed at baseline and at Months 2, 4, and 6 during the Core Safety Follow-up Component. Age appropriate (4-18 years of age) neurocognitive assessments 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, and One Back Test. The tests will focus on the domains of processing speed, attention/vigilance, visual memory and working memory. 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. The assessment time points correlate with serum sodium assessments and should occur within an hour of serum sodium blood draws.
3.7.8 End of Trial	**3.7.6 End of Trial**	**3.7.8 End of Trial**

Location	Old Text	Updated Text
	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 CRF page for the last subject completing or withdrawing from the trial.	The End of Trial Date is defined as the last Date of Contact or the Date of Final Contact Attempt from the Follow-up CRF page for the last subject completing or withdrawing from the trial.
Section 3.8.1 Entire Trial or Treatment Component(s)	**Section 3.8.1 Entire Trial or Treatment Arm(s)**	**Section 3.8.1 Entire Trial or Treatment Component(s)**
Section 3.8.3 Indivdual Subject	... 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: • The subject's serum sodium increases by > 8 mmol/L in any 10-hour period following dosing on Day 1 of a cycle • The subject's serum sodium increases by ≥ 12 mmol/L in the 24-hour period following dosing • At any time after dosing, the subject's serum sodium is ≥ 145 mmol/L. ...	... In addition, subjects on tolvaptan treatment who meet the following criteria should have results confirmed with a repeat test. • The subject's serum sodium increases by > 8 mEq/L (mmol/L) in any 10-hour period following dosing on Day 1 of a cycle • The subject's serum sodium increases by ≥ 12 mEq/L (mmol/L) in the 24-hour period following dosing • At any time after dosing, the subject's serum sodium is ≥ 145 mEq/L (mmol/L). • Evidence of dehydration • Abnormal liver function tests (see Section 5.4) If the result is confirmed, the medical monitor should be contacted to consider options of down-titration, dose discontinuation, concomitant medication adjustment, fluid supplementation, and/or withdrawal. ...
Section 3.9 Screen Failure	A screen failure subject is one from whom informed consent/assent (if applicable) is obtained and is documented in writing (ie, the subject's parent or legal guardian signs an ICF or PIS), but who is not started on treatment, whether through randomization or open assignment.	Since the core component of this trial is a 6-month safety follow-up trial, no subject will be considered a screen failure.
Section 3.10 Definition of Completed Subjects	The observation 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 was on tolvaptan treatment. Subjects who are evaluated at the last scheduled visit during the observation period will be defined as trial completers.	The core safety follow-up component of the trial is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial regardless of whether or not the subject was on tolvaptan treatment. Subjects who are evaluated at the last scheduled visit during the core safety follow-up component

Location	Old Text	Updated Text
	For purposes of this trial, subjects who complete the Month 6 Visit will be defined as trial completers. Any visits beyond the Month 6 Visit will be considered "follow-up" visits for the purpose of evaluating safety and efficacy for those subjects who require continued treatment with tolvaptan. Prior to the end of the trial, the sites should document each subject's final visit, including the date of the last dose and the number of treatment cycles.	will be defined as trial completers. For purposes of this trial, subjects who complete the Month 6 visit will be defined as trial completers. Any visits beyond the Month 6 Visit will be considered "follow-up" visits for the purpose of evaluating safety and efficacy for those subjects who require treatment with tolvaptan. Prior to the end of the trial, each subject's final visit should be documented, including the date of the last dose and the number of treatment cycles.
Section 3.11 Definition of Lost to Follow-up	Subjects or subjects' parents/guardians who cannot be contacted on or before their final visit 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). It is expected that 3 documented attempts will be made to determine a subject's current health status before assigning a "lost to follow-up" status.	Subjects or subjects' parents/guardians who cannot be contacted on or before their final visit 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 call with the subject, statement by a family member or primary care physician, or public records). It is expected that 3 documented attempts will be made to determine a subject's current health status before assigning a "lost to follow-up" status.
Section 3.12 Subject Compliance	Compliance will be ensured by watching the subject take his/her trial medication while the subject is hospitalized or during clinic visits. For nonclinic 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 CRF and on the Drug Accounting Form.	For the Core Safety Follow-up Component compliance is defined as completion of all visits. For the Optional Tolvaptan Treatment Component 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 CRF and on the Drug Accounting Form.
Section 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,	In the event of a significant deviation from the protocol because of an emergency, accident, or mistake (eg, violation of informed consent/assent process, tolvaptan dispensing or subject dosing error,

Location	Old Text	Updated Text
	treatment assignment error, or subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the site monitor.	treatment assignment error, or subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the site monitor.
Section 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 with tolvaptan until 24 hours post-last dose of IMP. In addition, the use of alcohol within 72 hours prior to dosing and during tolvaptan treatment is prohibited. The use of saline in this population should be closely monitored. The use of hypertonic saline (3% or greater) within 8 hours of the initial screening laboratory collection prior to tolvaptan treatment is prohibited. The use of hypertonic saline (3% or greater) is *highly discouraged* during tolvaptan treatment. Please see Section 3.2.4 for the list of prohibited medications during tolvaptan treatment. The use of normal saline (0.9%) is allowed during the Pretreatment Baseline Period until the beginning of treatment; normal saline use can resume during the follow-up period. 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.	The ingestion of pomelo, grapefruit, grapefruit juice, products containing Seville oranges, and St. John's Wort is prohibited from 72 hours prior to dosing with tolvaptan until 24 hours post-last dose of tolvaptan. In addition, the use of alcohol within 72 hours prior to dosing and during tolvaptan treatment is prohibited. The use of saline in this population should be closely monitored. The use of hypertonic saline (3% or greater) within 8 hours of the initial screening laboratory collection prior to tolvaptan treatment is prohibited. The use of hypertonic saline (3% or greater) is *highly discouraged* during tolvaptan treatment. Please see Section 4.1 for the list of prohibited medications during tolvaptan treatment. The use of normal saline (0.9%) is allowed during the Pretreatment baseline Period until the beginning of treatment; normal saline use can resume during the follow-up period. 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.
Section 5.1 Definitions	An AE is defined as any new untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. ... • 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 OPDC. Pregnancy will only be documented on the AE CRF if there is an abnormality or complication.	An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. ... 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 OPDC. Pregnancy will only be documented on the AE CRF if there is an abnormality or complication.

Location	Old Text	Updated Text
	... IMP Causality: Assessment of causal relationship of an AE to the use of the IMP: **Related**: There is a reasonable possibility of a causal relationship. **Possibly related**: There is a reasonable causal relationship between the IMP and the AE. Dechallenge is lacking or unclear. **Unlikely related**: There is a temporal relationship to IMP administration, but there is not a reasonable causal relationship between the IMP and the AE. **Not Related**: There is no temporal or reasonable relationship to the IMP administration.	... IMP Causality: Assessment of causal relationship of an AE to the use of the IMP: **Related**: There is a reasonable probability or possibility of a temporal and causal relationship between the study drug and the AE. **Not Related**: There is no temporal or causal relationship to the study drug administration.
Section 5.2 Eliciting and Reporting Adverse Events	The investigator will periodically assess subjects for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following nonleading question: "How have you felt since your last visit?" All AEs (serious and non-serious) reported by the subject must be recorded on the source documents and CRFs provided by the sponsor. ...	The investigator will periodically assess subjects for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following non-leading question: "How have you felt since yesterday/last time we spoke?" All AEs (serious and non-serious) reported by the subject must be recorded on the source documents and CRFs provided by the sponsor. ...
Section 5.3 Immediately Reportable Events	... Non-serious events that require discontinuation of IMP (including laboratory abnormalities) should be reported to INC Research within 3 working days. The IRE form must be completed and sent by fax or overnight courier to the sponsor. ...	... Non-serious events that require discontinuation of tolvaptan (including laboratory abnormalities) should be reported to INC Research within 3 working days. The IRE form must be completed and sent by fax or overnight courier to the sponsor. ...
Section 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 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	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 overly rapid correction does not occur in

Location	Old Text	Updated Text
	population. Rapid correction of hyponatremia is defined as any increase in serum sodium ***≥ 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.	this pediatric population. Rapid correction of hyponatremia is defined as any increase in serum sodium ≥ 12 mEq/L (mmol/L)/24 hours. If this change is observed during the trial, it should be reported as an Immediately Reported Event (IRE) following the instructions detailed in Section 5.3.
Section 5.3.1.2 Other Hyponatremia-related Adverse Event	Other events related to hyponatremia should be monitored closely and reported as appropriate depending on their severity: • Absolute serum sodium level ≥ 145 mmol/L • Any increase in serum sodium > 8 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 ...	Other events related to hyponatremia should be monitored closely and reported as appropriate depending on their severity: • Absolute serum sodium level ≥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 ...
Section 5.4 Potential Hy's Law Cases	For a subject who experiences an elevation in AST or ALT that is ≥ 3 × ULN or whose levels increase ≥ 3 times their initial baseline value, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 × ULN or ≥ 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 CRFs. ...	The definition of Hy's Law laboratory criteria is provided in Section 1.3. 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 ≥ 2 × ULN or whose levels increase ≥ 2 times their initial baseline value, a BT level should also be evaluated. Elevated values should be confirmed via retest. If the BT is ≥ 2 × ULN or ≥ 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 CRFs. ...
Section 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 3 × ULN is generally accepted as a medically significant occurrence across various medical cultures. For a subject that experiences an elevation in AST or ALT that is ≥ 3 ×ULN or whose levels increase ≥ 3 times their initial baseline value in subjects with an elevated baseline value, a total bilirubin	Management of abnormal liver function test results should be based on the investigator's clinical judgment. A liver function test result that is 2 × 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 ≥ 2 × ULN or whose levels increase ≥ 2 times their initial baseline value in subjects with an elevated baseline value, a BT level should

Location	Old Text	Updated Text
	level should also be evaluated. If the total bilirubin is ≥ 2 × ULN or ≥ 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 CRFs. The following guideline for repeat testing may be used by investigators as a reference for any subject with an ALT or AST ≥ 3 × 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). ... 2) The 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.	also be evaluated. If the BT is ≥ 2 × ULN or ≥ 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 CRFs. The following guideline for repeat testing may be used by investigators as a reference for any subject with an ALT or AST ≥ 2 × ULN: 1) ALT, AST, alkaline phosphatase, and BT 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. ... 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.
Section 5.4.1.1 Criteria for Discontinuation From the Optional Tolvaptan Treatment Component of the Trial due to Liver Transaminase Elevations	**Section 5.4.1.1 Criteria for Discontinuation From the Trial 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 ≥ 8 × ULN 2) ALT or AST ≥ 5 × ULN for more than 2 weeks 3) ALT or AST ≥ 3 × ULN AND (total bilirubin ≥ 2 × ULN or INR > 1.5) 4) ALT or AST ≥ 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) If there is any question about how to proceed with a particular subject's case, do not hesitate to contact your regional medical	**Section 5.4.1.1 Criteria for Discontinuation From the Optional Tolvaptan Treatment Component of the Trial due to Liver Transaminase Elevations** A subject must be discontinued from tolvaptan treatment on confirmation of any of the following criteria: 1) ALT or AST ≥ 8 × ULN 2) ALT or AST ≥ 5 × ULN for more than 2 weeks 3) ALT or AST ≥ 3 × ULN AND (BT ≥ 2 × ULN or INR > 1.5) 4) ALT or AST ≥ 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) and signs of jaundice

Location	Old Text	Updated Text
	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. For a link to this guidance along with up-to-date information from the FDA regarding drug-induced liver injury please use the following internet addresses: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm071471.htm	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 it. 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.[22,23]
Section 5.5 Pregnancy	Female subjects of childbearing potential who are sexually active must use an effective method of birth control during tolvaptan treatment 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 a bilateral oophorectomy and/or hysterectomy; or male partners who have had a bilateral orchiectomy) or remains 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 vasectomy and tubal ligation, may fail, leading to pregnancy. 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: • 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 Prior to trial enrollment, female subjects of childbearing potential	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 vasectomy and tubal ligation, may fail, leading to pregnancy. 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: • 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

Location	Old Text	Updated Text
	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 her parent/guardian. 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). If a subject or investigator suspects that a female subject may be 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 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 withdrawn from the trial. (Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the trial medical monitor.) The investigator must immediately notify INC Research of any pregnancy associated with IMP exposure during the trial and for at least 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 the Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy. Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator 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	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. 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). If a subject or investigator suspects that the subject may be 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. (Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the trial medical monitor.) 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. 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

Location	Old Text	Updated Text
	will be followed for a minimum of 6 months.	will be followed for a minimum of 6 months.
Section 5.7 Follow-up of Adverse Events	For this trial, information on AEs will be followed until the Month 6 Visit or for up to 7 days after the last dose of IMP, whichever is later.	For subjects in the core safety follow-up component of this trial, information on AEs will be followed until the Month 6 Visit. For subjects who receive tolvaptan in the optional tolvaptan treatment component of this trial, information on AEs will be followed for 14 days after administration of the last dose of tolvaptan, with an in-person visit at 7 post-last dose and 14 days post-last dose by telephone call.
Section 5.7.1 Follow-up of Non-serious Adverse Events	Non-serious AEs that are identified on the last scheduled contact must be recorded on the AE CRF with the current status noted. All non-serious events that are ongoing at this time will be recorded as ongoing on the CRF.	Non-serious AEs that are identified on the last scheduled contact must be recorded on the AE CRF with the current status noted. If a subject has not recovered from and AE, follow-up visits must be scheduled until the AE is resolved or has stabilized without expectation of further improvement. Visits can be scheduled at a reasonable frequency for the AEs being followed, eg, every 7-28 days. In order to characterize or exclude possible drug-related safety issues, additional laboratory or other procedures may be requested. These data should be shared with the sponsor in the same confidential manner as the on-study data. All non-serious events that are ongoing at this time will be recorded as ongoing on the CRF. During data 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).
Section 5.7.2 Follow-up of Post Trial Serious Adverse Events	... This trial requires that subjects be actively monitored for SAEs until the Month 6 Visit or up to 7 days after the last dose of IMP, whichever is later.	... This trial requires that subjects be actively monitored for SAEs until the Month 6 Visit or up to 14 days after the last dose of tolvaptan, whichever is later.

Location	Old Text	Updated Text
Section 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.	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 tolvaptan, should be reported to INC Research. This may include SAEs that are captured on follow-up telephone call 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.
Section 6.1 Pharmacokinetic Analysis	For those subjects undergoing chronic treatment with tolvaptan for at least 8 consecutive weeks for each initiation or reinitiation of therapy, the concentration of tolvaptan and metabolites will be obtained and summarized using descriptive statistics.	For those subjects undergoing chronic treatment with tolvaptan for at least 8 consecutive weeks for each initiation or reinitiation of therapy, the concentration of tolvaptan and metabolites will be obtained and summarized using descriptive statistics.
Section 7.1 Sample Size	Sample size was not determined by a formal computation to achieve a target power. It is expected that approximately 140 subjects may enroll from previous tolvaptan pediatric trials for hyponatremia (ie, Trials 156-08-276, 156-12-205, and 156-13-207).	Sample size was not determined by a formal computation to achieve a target power. It is expected that approximately 140 subjects may enroll from previous tolvaptan pediatric trials for hyponatremia (ie, Trials 156-08-276, 156-13-207, and 156-12-205).
Section 7.2 Datasets for Analysis	The following datasets are defined for this trial: Intent to Treat Dataset: comprises all subjects for whom an ICF is signed for the trial. Safety Dataset: comprises those subjects who receive at least one dose of IMP. Efficacy Dataset: comprises those subjects in the Safety Dataset who have at least one post-baseline efficacy evaluation for serum sodium concentration.	The following datasets are defined for this trial: • Core Safety Follow-up Component – Core Dataset: comprises all subjects for whom an ICF is signed for the trial. • Optional Tolvaptan Treatment Component – Safety Dataset: comprises those subjects who receive at least one dose of tolvaptan. – Efficacy Dataset: comprises those subjects in the Safety Dataset who have at least one post-baseline efficacy evaluation for serum sodium concentration.

Location	Old Text	Updated Text
Section 7.4.1 Primary Outcome Analysis	The following primary endpoints include: • AEs, including cases of dehydration • Vital signs • Body weight, height, and growth percentiles • Tanner Stages • Clinical laboratory abnormalities for subjects on tolvaptan: – Serum sodium, overly rapid changes in serum sodium – Changes from baseline in ALT and AST • Percentage of subjects with overly rapid improvement in serum sodium (≥ 12 mmol/L in 24 hours after the first dose at introduction or reintroduction of IMP) • Percentage of subjects who experience recurrence of hyponatremia while on IMP A paired Student's t-test will be used to evaluate growth data, eg, height, body weight, and growth percentiles. Tanner Stages will be analyzed using the Cochran-Mantel-Haenszel row mean scores differ test controlling for subjects. All other primary endpoints will be summarized using descriptive statistics.	The primary endpoint for all subjects participating in the Optional Tolvaptan Treatment Component of the trial is: • Change from baseline in serum sodium while tolvaptan is being administered by visit
Section 7.4.2 Secondary Outcome Analyses	The secondary endpoint of this trial is the change in serum sodium from baseline at each visit while the IMP is being administered and will be analyzed by descriptive statistics.	The secondary endpoints for all subjects receiving tolvaptan in the Optional Tolvaptan Treatment Component of the trial include the following: • Percentage of subjects who require rescue therapy while on tolvaptan • Percentage of subjects requiring continuation of tolvaptan following 30 days of treatment • Percentage of subjects with overly rapid correction in serum sodium (≥ 12 mmol/L in 24 hours after the first dose at introduction or reintroduction of tolvaptan) • Changes from baseline in ALT, AST and BT

Location	Old Text	Updated Text
		In addition, the secondary endpoints for subjects participating in the Core Safety Follow-up Component of the trial include: • Frequency of AE reports • Change from baseline in QoL assessments (by visit) • Change from baseline in growth percentiles (by visit) for – body weight – body height • Tanner Staging progression score (at 6 months) • Change from baseline in serum sodium by visit A paired Student's t-test will be used to evaluate growth data, eg, body height and body weight percentiles. Tanner staging will be analyzed using the Cochran-Mantel-Haenszel row mean scores differ test controlling for subjects. All other endpoints will be summarized using descriptive statistics.
Section 7.4.3 Exploratory Outcome Analyses	The exploratory outcome variable is Quality of Life assessments. This endpoint will be analyzed by descriptive statistics.	The exploratory outcome variables are changes from baseline for the neurocognitive battery assessments and will be summarized using descriptive statistics.
Section 7.5 Analysis of Demographic and Baseline Charateristics	In general, baseline measurements of safety and efficacy variables are defined as their last measurements prior to the first dose of IMP. Demographic characteristics and medical history at Baseline will be summarized by descriptive statistics, eg, proportion, mean, median, standard deviation, minimum, and maximum values.	Demographic characteristics and medical history at baseline will be summarized by descriptive statistics, eg, proportion, mean, median, standard deviation, minimum, and maximum values.
Section 7.6 Safety Analyses	Safety variables 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.	No text in this section

Location	Old Text	Updated Text
Section 7.6.1 Physical Examination and Vitals Signs Data	**Section 7.6.1 Adverse Events** All AEs will be coded by Medical Dictionary for Regulatory Activities system organ class and preferred term. The incidence of the following events will be summarized: a) TEAEs by severity b) Potentially drug-related TEAEs c) TEAEs with an outcome of death d) Serious TEAEs e) Discontinuations due to TEAEs	**Section 7.6.1 Physical Examination and Vitals 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.
Section 7.6.2 Clinical Laboratory 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. Where predose baseline values are unavailable, summary statistics of available data at each visit will be presented.	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. Where baseline values are unavailable, summary statistics of available data at each visit will be presented.
Section 7.6.3 Adverse Events	**Section 7.6.3 Physical Examination and Vitals 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. Tanner Staging will be analyzed as described in Section 7.4.1.	**Section 7.6.3 Adverse Events** All AEs will be coded by Medical Dictionary for Regulatory Activities system organ class and preferred term. The incidence of the following events will be summarized for all subjects (AEs) and all subjects receiving tolvaptan (TEAEs): 1) AEs and TEAEs by severity 2) Potentially drug-related TEAEs 3) AEs and TEAEs with an outcome of death 4) Serious AEs and TEAEs 5) Discontinuations due to AEs and TEAEs
Section 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. Each package used in the dosing period will be labeled to clearly disclose the subject ID, compound ID, trial number, the sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements, and other	Tolvaptan will be provided to the investigator(s) by the sponsor (or designated agent). Tolvaptan will be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets. Each package used in the dosing period will be labeled to clearly disclose the subject ID, compound ID, trial number, the sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements,

Location	Old Text	Updated Text
	information required by local regulatory authorities. 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 ≥ 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 kg and who are taking any CYP3A4 inhibitors. Once available, the protocol will be amended to include the details of this formulation.	and other information required by local regulatory authorities. 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 ≥ 10 kg. A liquid 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 kg and who are taking any CYP3A4 inhibitors. Once available, the protocol will be amended to include the details of this formulation.
Section 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 will be stored at 25°C (77°F) or below, with excursions allowed from 15°C to 30°C (59°F 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.	Tolvaptan 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. Tolvaptan will be stored at 25°C (77°F) or below, with excursions allowed from 15°C to 30°C (59°F to 86°F). The clinical trial site staff or designated personnel will maintain a temperature log in the drug storage area recording the temperature at least once each working day.
Section 8.3 Accountability	The investigator, or designee, must maintain an inventory record of IMP received, dispensed, administered, and returned.	The investigator, or designee, must maintain an inventory record of tolvaptan received, dispensed, administered, and returned.
Section 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.	Upon completion or termination of the trial, all unused and/or partially used tolvaptan must be returned to OPDC (or a designated contractor). All tolvaptan 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 tolvaptan.
Section 8.5.1 Eliciting and Reporting Product Quality	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 investigator or designee must record all PQCs identified through any means from the receipt of tolvaptan from the sponsor through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify

Location	Old Text	Updated Text
Complaints	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. ...	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. ...
Section 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; • 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, and duration of any AEs and the investigator's assessment of relationship to the 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 all clinicians who made an entry in the progress notes. ...	During each subject's visit to the clinical trial site, 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; • 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, and duration of any AEs and the investigator's assessment of relationship to tolvaptan 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 all clinicians who made an entry in the progress notes. ...
Section 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 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	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 tolvaptan development is discontinued, the date 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

Location	Old Text	Updated Text
	investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial. 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.	investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, because of 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.
Section 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) 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. ...	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) will be allowed full access to inspect and copy the records. All supplies of tolvaptan, 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. ...
Section 13 Amendment Policy	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.	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 the tolvaptan tablets 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.

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr><td></td><td>...</td><td>...</td></tr>
<tr><td>Section 14
References</td><td>...
13 OPC-41061 Investigator's Brochure. Rockville (MD): Otsuka Pharmaceutical Development & Commercialization, Inc.; Edition 19. Otsuka Report, issued 11 Jul 2013.
...
17 Moritz ML, Ayus JC. Preventing neurological complications from dysnatremias in children. Pediatr Nephrol. 2005;20:1687-1700.</td><td>...
13 OPC-41061 Investigator's Brochure. Rockville (MD): Otsuka Pharmaceutical Development & Commercialization, Inc.; Edition 20. Otsuka Report, issued 11 Jul 2014.
...
17 Moritz ML, Ayus JC. Preventing neurological complications from dysnatremias in children. Pedatr Nephrol. 2005;20:1687-1700.
...
22 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: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.
23 U.S. Food and Drug Administration. [available on the internet, last updated 22Jan2014; cited 14Feb2014]. Available from: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm071471.htm</td></tr>
<tr><td>Appendix 1
Names of Sponsor Personnel</td><td>Report Immediately Reportable Events (serious adverse events, potential Hy's Law cases, pregnancies, and adverse events requiring discontinuation of trial drug) to INC Research as follows:
<table><tr><th>Country</th><th>Safety Fax Numbers</th></tr><tr><td>United States</td><td>PPD (primary) or PPD PPD (alternative)</td></tr><tr><td>Argentina</td><td>PPD</td></tr><tr><td>Australia</td><td>PPD</td></tr><tr><td>Belgium</td><td>PPD</td></tr><tr><td>Canada</td><td>PPD (primary) or PPD PPD (alternative)</td></tr><tr><td>Columbia</td><td>PPD</td></tr><tr><td>Czech Republic</td><td>PPD</td></tr></table></td><td>Report Immediately Reportable Events (serious adverse events, potential Hy's Law cases, pregnancies, and adverse events requiring discontinuation of IMP) as follows:
<table><tr><th>Country</th><th>Safety Fax Numbers</th></tr><tr><td>Australia</td><td>PPD</td></tr><tr><td>Belgium</td><td>PPD</td></tr><tr><td>Canada</td><td>PPD (primary) or PP PPD (alternative)</td></tr><tr><td>Czech Republic</td><td>PPD</td></tr><tr><td>Germany</td><td>PPD</td></tr><tr><td>Italy</td><td>PPD</td></tr></table></td></tr>
</table>

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr>
<td></td>
<td>
<table>
<tr><td>Finland</td><td>PPD</td></tr>
<tr><td>France</td><td>PPD</td></tr>
<tr><td>Georgia</td><td>No toll free number available; please dial PPD (primary) or PPD (alternative)</td></tr>
<tr><td>Germany</td><td>PPD</td></tr>
<tr><td>Hong Kong</td><td>PPD</td></tr>
<tr><td>Israel</td><td>PPD</td></tr>
<tr><td>Italy</td><td>PPD</td></tr>
<tr><td>Korea</td><td>PPD</td></tr>
<tr><td>Latvia</td><td>PPD</td></tr>
<tr><td>Malaysia</td><td>PPD</td></tr>
<tr><td>Mexico</td><td>PPD</td></tr>
<tr><td>Netherlands</td><td>PPD</td></tr>
<tr><td>Philippines</td><td>PPD</td></tr>
<tr><td>Peru</td><td>PPD</td></tr>
<tr><td>Poland</td><td>PPD</td></tr>
<tr><td>Romania</td><td>PPD</td></tr>
<tr><td>Russia</td><td>PPD</td></tr>
<tr><td>Serbia</td><td>PPD</td></tr>
<tr><td>Singapore</td><td>PPD</td></tr>
<tr><td>South Africa</td><td>PPD</td></tr>
<tr><td>Spain</td><td>PPD</td></tr>
<tr><td>Taiwan</td><td>PPD</td></tr>
<tr><td>Thailand</td><td>PPD</td></tr>
<tr><td>Turkey</td><td>No toll free number available; please dial PPD (primary) or PPD (alternative)</td></tr>
<tr><td>Ukraine</td><td>PPD</td></tr>
<tr><td>United Kingdom</td><td>PPD</td></tr>
</table>
Medical Monitors:
Primary:
PPD
</td>
<td>
<table>
<tr><td>Netherlands</td><td>PPD</td></tr>
<tr><td>Peru</td><td>PPD</td></tr>
<tr><td>Poland</td><td>PPD</td></tr>
<tr><td>Romania</td><td>PPD</td></tr>
<tr><td>Spain</td><td>PPD</td></tr>
<tr><td>Turkey</td><td>No toll free number available; please dial PPD (primary) or PPD (alternative)</td></tr>
<tr><td>United Kingdom</td><td>PPD</td></tr>
<tr><td>United States</td><td>PPD (primary) or PP (alternative)</td></tr>
</table>
Project Leader/Medical Director:
PPD
PPD
Phone PPD Fax PPD

Clinical Management:
PPD
PPD
Phone PPD Fax PPD

PPD
PPD
Phone PPD Fax PPD
</td>
</tr>
</table>

Location	Old Text	Updated Text
	PPD INC Research 3201 Beechleaf Court, Suite 600 Raleigh, North Carolina 27604 US Phone PPD Mobile PPD E-Mail PPD Back-up: PPD PPD INC Research 580 Union Square Drive New Hope, Pennsylvania 18938 US Phone PPD Mobile PPD E-Mail PPD <u>Europe/Rest of World:</u> PPD PPD INC Research Ul.Emaus 5 30-201 Krakow, Poland Phone PPD E-Mail PPD **Medical Director:** PPD PPD Phone PPD Fax PPD **Clinical Management:** PPD PPD Phone PPD Fax PPD PPD Phone PPD Fax PPD	

Location	Old Text	Updated Text
Appendix 2 Institutions Concerned With the Trial	**Sponsor** Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, US Phone: PPD **Medical Monitoring** INC Research 3201 Beechleaf Court, Suite 600 Raleigh, North Carolina 27604-1547, US Phone: PPD Fax: PPD **Trial Management & Clinical Monitoring** INC Research 3201 Beechleaf Court, Suite 600 Raleigh, North Carolina 27604-1547, US Phone: PPD **Electronic Data Capture** MediData Solutions 79 Fifth Avenue, 8th Floor New York, New York 10003, US Phone: PPD Fax: PPD **Investigational Materials** Fisher Clinical Services 7554 Schantz Road Allentown, Pennsylvania 18106, US **Study Communications & Patient/Site Support** BBK Worldwide 117 Kendrick Street,	Institutions concerned with this trial are: **Sponsor** Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, USA Phone: PPD **Medical Monitoring** INC Research 3201 Beechleaf Court, Suite 600 Raleigh, North Carolina 27604-1547, USA Phone: PPD Fax: PPD **Medical Monitor:** PPD PPD PPD INC Research 580 Union Square Drive New Hope, Pennsylvania 18938 US Phone PPD PPD Mobile PPD E-Mail PPD PPD **Trial Management & Clinical Monitoring** INC Research 3201 Beechleaf Court, **Electronic Data Capture** MediData Solutions 79 Fifth Avenue, 8th

Location	Old Text	Updated Text
	Phone: PPD Fax: PPD **Central Laboratory (PK)** ICON Development Solutions, Inc. 8282 Halsey Road Whitesboro, New York 13492, US Phone: PPD	Suite 600 Raleigh, North Carolina 27604-1547, USA Phone: PPD **Investigational Materials** Almac Clinical Services Limited Seagoe Industrial Estate 9 Charlestown Road Craigavon County Armagh BT63 5PW United Kingdom **IRT Systems (treatment assignment)** S-CLINICA 1500 Market Street 12th Floor East Tower Philadelphia, Pennsylvania 19102, USA Phone: PPD **Clinical Laboratory Supplies**
	Suite 600 Needham, Massachusetts 02494, US Phone: PPD	Floor New York, New York 10003, USA Phone: PPD Fax: PPD **Study Communications & Patient/Site Support** Mathews Media Group 700 King Farm Boulevard, Suite 500 Rockville, MD 20850, USA Phone: PPD **Central Laboratory (PK)** ICON Development Solutions, Inc. 8282 Halsey Road Whitesboro, New York 13492, USA Phone: PPD **Neurocognitive Battery**

Location	Old Text	Updated Text
		Covance Central Laboratory Services 8211 SciCor Drive Indianapolis, Indiana 46214, USA Phone: PPD Cogstate, Ltd. 195 Church Street 8th Floor New Haven, CT 06510 USA Phone: PPD

Location	Old Text	Updated Text
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 CRF, not the scheduled time for the drawing. The exact time of dosing should also be noted. **Plasma Samples for Tolvaptan** Blood (1 mL) will be collected into plastic Vacutainer tubes containing sodium 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 at −20°C or on dry ice. Samples should be shipped monthly. **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.	All tubes must be labeled using the central laboratory's bar code labels provided with the sample collection kits. The central laboratory's requisition form must be completely filled out in regards to all the sample information. In addition, the subject ID number and date of collection must be hand-written on the sample tube. It is important to note the exact time of the blood collection on the eCRF. Each specimen must be labeled using a waterproof pen. A label suitable for the storage conditions must contain the subject ID number and date of collection, must correspond to the requisition form, and must be firmly attached. The requisition form must contain the name, address, and telephone number of the contact person from the trial site. **Plasma Samples for Tolvaptan** Blood (1 mL) will be collected into plastic Vacutainer 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 at −20°C or on dry ice. Samples should be shipped monthly. **Shipment of Plasma** Plasma samples must be neatly packed in the kits provided by the central laboratory and restrained in a Styrofoam container that is completely filled with dry ice to avoid air spaces that allow evaporation of the dry ice. The Styrofoam container should be sealed with tape and placed in a cardboard box. The central laboratory must be alerted of sample shipment. Packages must not be shipped on Thursday, Fridays, Saturdays, or any day prior to a holiday without the expressed consent of OPDC or the central laboratory. Shipments from clinical trial sites will be via an overnight carrier to the central laboratory (Clinical Laboratory Supplies, Covance Central).

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr><td>Appendix 5 Optional Tolvaptan Treatment Component: Eligibility Criteria</td><td>New section in this amendment</td><td>Subjects will be eligible for tolvaptan treatment if they meet the criteria outlined in the table below.

Eligibility Criteria for Optional Tolvaptan Treatment

1. Male or female subjects ≥ 4 weeks (or ≥ 44 weeks adjusted gestational age) to < 18 years old
2. The subject must have been off treatment with the investigational medicinal product (IMP) for 7 days following the end of treatment in the previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) to assess the subject’s clinical need for dosing
3. Persistent dilutional (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 to 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 the pretreatment baseline for this trial and must be able to understand that</td></tr>
</table>

Location	Old Text	Updated Text

	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 tolvaptan for sexually active females of childbearing potential

Subjects will be ineligible for tolvaptan treatment if they meet any of the following criteria:

Ineligibility Criteria for Tolvaptan Treatment	
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.	Use of potent CYP3A4 inhibitors in subjects ≤ 50 kg or moderate CYP3A4 inhibitors in subjects < 20 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
8.	Has eGFR < 30 mL/min/1.73 m^2 calculated by the following equation: eGFR (mL/min/1.73 m^2) = 0.413 × height (cm)/serum

Location	Old Text	Updated Text
		creatinine (mg/dL)
		9. Has AKI defined as: • Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours; or • Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or • Urine volume < 0.5 mL/kg/h for 6 hours
		10. Has severe or acute neurological symptoms requiring other intervention (eg, hyperemesis, obtundation, seizures)
		11. 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
		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 the pretreatment visit 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])

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>17.</td><td>Has screening liver function values > 3 × ULN. An IRE form will be completed if the subject is a potential Hy's Law case (any increase of AST or ALT ≥ 2 × ULN or baseline value with an increase in BT ≥ 2 × ULN or baseline value).</td></tr>
<tr><td>18.</td><td>Has deficient coagulation (eg, cirrhotic at risk of 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 < 50,000/μL, or use of concomitant medications known to increase bleeding risk</td></tr>
<tr><td>19.</td><td>Has hyponatremia due to the result of any medication that can safely be withdrawn (eg, thiazide diuretics)</td></tr>
<tr><td>20.</td><td>Has hyponatremia (eg, hyponatremia in the setting of adrenal insufficiency, untreated hypothyroidism, or hypotonic fluid administration) that is most appropriately corrected by alternative therapies</td></tr>
<tr><td>21.</td><td>Is currently pregnant or breastfeeding</td></tr>
<tr><td>22.</td><td>Has any medical condition that, in the opinion of the investigator, could interfere with evaluation of the trial objectives or safety of the subjects.</td></tr>
<tr><td>23.</td><td>Is deemed unsuitable for trial participation in the opinion of the investigator</td></tr>
<tr><td>24.</td><td>Participation in an investigational drug trial (other than Trials 156-08-276, or 156-13-207 or 156-12-205) within the past 30 days, without prior approval from the medical monitor</td></tr>
<tr><td>25.</td><td>Subjects <2 years of age, weight <10 kg, or who cannot swallow an oral tablet are excluded until an oral liquid formulation becomes available</td></tr>
</table>
AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; ICU = intensive care unit; IRE = Immediately Reportable Event; ULN = upper limit of normal
</td></tr>
</table>

<table>
<tr><th>Location</th><th>Old Text</th><th>Updated Text</th></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Appendix 6 Optional Tolvaptan Treatment Component: Laboratory Assessment Schedule</td><td>New section in this amendment</td><td>
<table>
<tr><th colspan="4">Frequency of Recurring Laboratory Assessments</th></tr>
<tr><th>Treatment Phase</th><th>Serum Sodium</th><th>LFTs (ALT, AST, BT)</th><th>PK[a]</th></tr>
<tr><td>Pretreatment Baseline doses</td><td>Day -1 to Day -4: assessments ≤ 130 mEqL (mmol/L) ≥ 12 hours apart</td><td></td><td></td></tr>
<tr><td>Month 1: Titration[b]</td><td>Once daily</td><td></td><td></td></tr>
<tr><td>Month 1: Post-titration[c]</td><td>Once weekly</td><td>Once monthly</td><td></td></tr>
<tr><td>Month 2: Post-titration (steady dose)</td><td>Every 2 weeks</td><td>Once monthly</td><td>Once post 8 weeks of continous treatment</td></tr>
<tr><td>Month 3+ post-titration (steady dose): Maintenance</td><td>Once monthly</td><td>Once monthly[d,e]</td><td></td></tr>
<tr><td>Month 6, End of Treatment or Early Termination</td><td>24 (±4) hours and 7 (±1) days</td><td></td><td></td></tr>
</table>
[a]Once post 8 weeks for every new cycle of treatment
[b]Day 1 up to Day 4
[c]Days 7, 14, 21, and 28
[d]AST, ALT, and BT will be assessed if more than 1 month has elapsed since LFTs were performed
</td></tr>
</table>

Location	Old Text	Updated Text
		[c]See Section 3.7.5.3.1 for more information and Section 5.4 for detailed instructions on follow-up of subjects with elevations in AST, ALT, or BT that are ≥ 2 × ULN or levels that increase ≥ 2 x from baseline.

Amendment Number: 2
Issue Date: 26 February 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.
- Additional background data from non-clinical juvenile toxicity studies.
- Updates to clarify prohibition of hypertonic saline.
- Clarify roll-over into extension study 156-11-294.
- Clarification of scheduled treatment interruption after 30 days of treatment and close clinical monitoring with the addition of visits.

BACKGROUND:

This protocol is the safety follow-up study to all trials in the tolvaptan pediatric hyponatremia program and is required by the EU Paediatric Investigation Plan.

The study provides a mandatory 6 month safety follow-up for all subjects regardless of treatment status. Those subjects who have a continued medical need for treatment have the opportunity to receive tolvaptan.

For all subjects the main focus is to provide information on the developmental impact and quality of life associated with tolvaptan therapy. For those subjects who continue to receive treatment safety and efficacy of long-term treatment will be evaluated.

Updates have been made to address 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
Title Page:	Issue Date: 31 October 2013 Date of Amendment 1: 5 September 2014	Issue Date: 31 October 2013 Date of Amendment 1: 5 September 2014 Date of Amendment 2: 26 February 2015
Protocol Synopsis Objectives:	This trial will consist of a core safety follow-up component (duration: 6 months) and an optional tolvaptan treatment component (duration: variable, depending on the subjects' continuing need for tolvaptan treatment). The objectives of this trial are:	The objective of this trial is to provide 6 months of safety follow-up for children who have participated in prior tolvaptan hyponatremia trials. In addition, there is an option to receive continuing treatment of variable duration based on medical need.
Protocol Synopsis Subject Population:	Up to 140 male or female subjects may be eligible for this trial; subjects will need to have participated in one of the previous tolvaptan pediatric trials for dilutional (euvolemic or hypervolemic) hyponatremia (ie, Trials 156-08-276, 156-13-207, or 156-12-205).	Approximately 140 male or female subjects may be eligible for this trial; subjects will need to have participated in one of the previous tolvaptan pediatric trials for dilutional (euvolemic or hypervolemic) hyponatremia (ie, Trials 156-08-276, 156-13-207, or 156-12-205).
Protocol Synopsis Inclusion/Exclusion Criteria:	• Participation in one of the previous tolvaptan pediatric trials for hyponatremia (ie, Trials 156-08-276, 156-13-207, or 156-12-205).	• Enrollment in one of the previous tolvaptan pediatric trials for hyponatremia (ie, Trials 156-08-276, 156-13-207, or 156-12-205).
Protocol Synopsis Trial Sites:	Subjects may be enrolled at up to 65 clinical trial sites globally.	Subjects may be enrolled at approximately 75 clinical trial sites globally.
Investigational Medicinal Product, Dose, Formulation, Mode of Administration:	Subjects enrolled in this trial will not receive tolvaptan unless they demonstrate a clinical need as determined by the investigator and meet the eligibility criteria for treatment. Tolvaptan will initially be supplied as 3.75-, 7.5-, 15-, and	Subjects enrolled in this trial will not receive tolvaptan unless they demonstrate a clinical need as determined by the investigator and meet the eligibility criteria for optional tolvaptan treatment. Tolvaptan will initially be supplied as 3.75-, 7.5-, 15-, and 30-mg spray-dried tablets. Upon the availability of an alternate formulation, the

Location	Old Text	Updated Text
	30-mg spray-dried tablets. Upon the availability of an oral liquid formulation, the protocol will be amended to reflect additional dosing options.	protocol will be amended to reflect additional dosing options.
Protocol Synopsis Trial Assessments:	Safety: • Vital signs • Physical examinations • Body height and weight/Growth percentiles • Tanner Staging • Clinical laboratory tests: Serum sodium assessments and liver function tests (alanine transaminase [ALT], aspartate aminotransferase [AST], and total bilirubin [BT]) • Adverse event reporting Efficacy: • Serum sodium concentration • Continued need for tolvaptan treatment after the first 30 days of treatment • Quality of Life	• Vital signs • Physical examinations • Body height and weight/Growth percentiles • Tanner Staging • Clinical laboratory tests: Serum sodium assessments and liver function tests (alanine transaminase [ALT], aspartate aminotransferase [AST], and total bilirubin [BT]) • Adverse event reporting • Continued need for tolvaptan treatment after the first 30 days of treatment • Quality of Life
Protocol Synopsis Criteria for Evaluation:	Safety: • Percentage of subjects with overly rapid correction in serum sodium (≥ 12 mEq/L [mmol/L]) in 24 hours after the first dose at introduction or reintroduction of tolvaptan) • Changes from baseline in ALT, AST, and BT for subjects on tolvaptan • Frequency of AE reports for all subjects • Changes from baseline in growth percentiles (weight and height) for all subjects	Safety: • Percentage of subjects with overly rapid correction in serum sodium (≥ 12 mEq/L [mmol/L]) in 24 hours after the first dose at introduction or reintroduction of tolvaptan • Changes from baseline in ALT, AST, and BT for subjects on tolvaptan • Frequency of AE reports for all subjects • Changes from baseline in growth percentiles (weight and height) for all subjects • Tanner Staging progression for all subjects

Location	Old Text	Updated Text
	• Tanner Staging progression for all subjects	• Change from baseline in serum sodium concentration
Protocol Synopsis Trial Duration:	The core safety follow-up component of the trial is expected to continue until all enrolled subjects from Trials 156-08-276, 156-13-207, or 156-12-205 have been followed for a minimum of 6 months. For subjects in the optional tolvaptan treatment component, the length of participation for each individual subject will vary depending on duration of treatment required and the need for repeated treatments. The opportunity to participate in the Optional Tolvaptan Treatment Component is planned to remain open until the last subject completes the Core Safety Follow-up Component.	The core safety follow-up component of the trial is expected to continue until all enrolled subjects from Trials 156-08-276, 156-13-207, or 156-12-205 have been followed for 6 months. For subjects in the optional tolvaptan treatment component, the length of participation for each individual subject will vary depending on duration of treatment required and the need for repeated treatments. The opportunity to participate in the Optional Tolvaptan Treatment Component is planned to remain open until the last subject completes the Core Safety Follow-up Component.
List of Abbreviations and Definitions of Terms:	Addition of 3 terms: IDMC, MHRA, and WOCBC Deletion of 1 term: PIS Patient Information Sheet	IDMC Independent Data Monitoring Committee MHRA Medicines and Healthcare Products Regulatory WOCBC Women of child-bearing potential
1 Introduction:	The United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have required that pediatric trials be conducted for tolvaptan for the indication of hyponatremia. This trial is an extension trial to follow children and adolescent subjects who participated in a previous tolvaptan pediatric trial for hyponatremia. In addition, this trial will allow continued access to tolvaptan to those subjects with a clinical need per the investigator's discretion.	The United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have required that pediatric trials be conducted for tolvaptan for the indication of hyponatremia. This trial is an extension trial to follow children and adolescent subjects who participated in a previous tolvaptan pediatric trial for hyponatremia for safety. In addition, this trial will allow continued access to tolvaptan to those subjects with a clinical need per the investigator's discretion.
1.1.1 Juvenile Toxicity Data:	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 1,000 mg/kg/day and tolerable at 100 mg/kg/day	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 1,000 mg/kg/day and tolerable at 100 mg/kg/day and lower.

Location	Old Text	Updated Text
	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.[27]
1.2.1 Pharmacokinetics/Pharmacodynamics:	Since inception of the program, a total of 46 phase 1 trials have been completed with tolvaptan (as of 31 Mar 2014) in healthy subjects or special populations in Japan, the United Kingdom, China, Korea, Argentina, and the US. One phase 1 trial is ongoing. 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	Since inception of the program, a total of 53 clinical pharmacology trials have been completed with tolvaptan (as of 11 Jul 2014) in healthy subjects or special populations in Japan, the United Kingdom, China, Korea, Argentina, and the US. One phase 1 trial is ongoing. 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 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

Location	Old Text	Updated Text
	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.[27] 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.[27] 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_{τ}) 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%). 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	absorption and elimination processes.[27] 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.[27] 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_{τ}) 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%). 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%.[27] 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

Location	Old Text	Updated Text
	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%. 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 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 AUC_{τ}). When administered with the potent CYP3A4 inhibitor	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_{τ}). 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_t) 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_t 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

Location	Old Text	Updated Text
	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_t) 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_t are decreased 83% and 87%, respectively. 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. 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,	were observed. 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. 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 plasma osmolality, and increased plasma AVP concentrations and renin activity, but no dose-related increases were observed for any other parameter. Details of the currently available pharmacokinetic (PK)/pharmacodynamic (PD) data for the compound are available in the IB.

Location	Old Text	Updated Text
	increased serum sodium and plasma osmolality, and increased plasma AVP concentrations and renin activity, but no dose-related increases were observed for any other parameter. 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. Details of the currently available pharmacokinetic (PK)/pharmacodynamic (PD) data for the compound are available in the IB.	
1.3 Known and Potential Risks and Benefits:	As of 31 Mar 2014, pooled exposure data are available from 88 trials, including 7201 subjects worldwide who were exposed to oral doses of tolvaptan. The extent of exposure to oral tolvaptan by dose in the pooled database (N = 7201) comprises 3115 subjects in trials for heart failure, 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, 391 subjects in trials for cardiac edema, 855 subjects in trials for hepatic edema, 37 subjects with renal impairment in a phase 1 trial, and 1061 healthy subjects in clinical pharmacology trials.	As of 31 Mar 2014, pooled exposure data are available from 88 trials, including 7201 subjects worldwide who were exposed to oral doses of tolvaptan spray-dried tablets. The extent of exposure to oral tolvaptan by dose in the pooled database (N = 7201) comprises 3115 subjects in trials for heart failure, 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, 391 subjects in trials for cardiac edema, 855 subjects in trials for hepatic edema, 37 subjects with renal impairment in a phase 1 trial, and 1061 healthy subjects in clinical pharmacology trials. The most commonly reported TEAEs (by > 10% incidence and greater

Location	Old Text	Updated Text
	The most commonly reported 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 TEAEs (> 5% incidence) in the placebo subjects were peripheral oedema, diarrhoea, headache, ascites, vomiting, dyspnoea, nausea, and hypotension. The IB provides a thorough review of the adverse events (AEs) experienced with this compound during clinical trials.	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 TEAEs (> 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 tolvaptan during clinical trials.
2.1.1 Core Safety Follow-up Component:	The primary purpose of this component of this trial is to follow children and adolescent subjects who have previously participated in a trial of titrated oral IMP (tolvaptan in Trial 156-08-276; tolvaptan or placebo in Trial 156-13-207 or Trial 156-12-205) for dilutional (euvolemic or hypervolemic) hyponatremia regardless of their	The primary purpose of this component of this trial is to follow children and adolescent subjects who have previously participated in a trial of titrated oral IMP (tolvaptan in Trial 156-08-276; tolvaptan or placebo in Trial 156-13-207 or Trial 156-12-205) for dilutional (euvolemic or hypervolemic) hyponatremia for safety, regardless of their treatment status

Location	Old Text	Updated Text
	treatment status with tolvaptan. The minimum duration of safety follow-up will be 6 months.	with tolvaptan. The duration of safety follow-up will be 6 months.
2.1.2 Optional Tolvaptan Treatment Component:	Children and adolescent subjects who have previously participated in a tolvaptan hyponatremia trial (Trials 156-08-276, 156-13-207, or 156-12-205) who meet the eligibility criteria for treatment with tolvaptan may be eligible for one or more additional cycles of tolvaptan treatment. Depending upon clinical need and the investigator's discretion, subjects in the core safety follow-up component may receive no treatment, be treated per the local standard of care for hyponatremia, or start treatment with tolvaptan. Based on the various underlying etiologies contributing to hyponatremia, the need for treatment may differ per individual subject. Therefore, some of the subjects may require a regimen with tolvaptan to supplement treatment following the completion of the earlier short-term efficacy, safety, PK, and PD trials (Trials 156-08-276, 156-13-207, or 156-12-205), and this protocol is designed to accommodate short-term, long-term, and repeated tolvaptan treatment cycles as necessary. Each tolvaptan treatment cycle will consist of a titration phase and a maintenance phase, with a planned discontinuation of treatment on Day 30 for assessment of the need for continued treatment. After demonstrating the need for continued tolvaptan treatment beyond the first 30 days, subjects taking concomitant medications, with underlying conditions, or receiving treatments that contraindicate the discontinuation	Any subject enrolled in the core safety follow-up component who has a medical need for tolvaptan and who meets the eligibility criteria for treatment with tolvaptan may be eligible for one or more additional cycles of tolvaptan treatment. Depending upon clinical need and the investigator's discretion, subjects in the core safety follow-up component may receive no treatment, be treated per the local standard of care for hyponatremia, or start treatment with tolvaptan. Based on the various underlying etiologies contributing to hyponatremia, the need for treatment may differ per individual subject. Therefore, some of the subjects may require a regimen with tolvaptan to supplement treatment following the completion of the earlier short-term efficacy, safety, PK, and PD trials (Trials 156-08-276, 156-13-207, or 156-12-205), and this protocol is designed to accommodate short-term, long-term, and repeated tolvaptan treatment cycles as necessary. Each tolvaptan treatment cycle will consist of a titration phase and a maintenance phase. Each treatment cycle will have a planned interruption of treatment on Day 30 for assessment of the need for continued treatment. Subjects who are expected to receive tolvaptan for greater than 30 days consecutive duration should demonstrate the need for continued treatment by discontinuing tolvaptan for up to 2 consecutive doses while undergoing close monitoring of serum sodium levels. However, there is a subgroup ofsubjects who have an identifiable cause for hyponatremia that has not (or cannot be) changed that will be excused from this brief interruption of tolvaptan. Examples of such causes include concomitant treatment for refractory seizures with a hyponatremia-inducing medication such as

Location	Old Text	Updated Text
	of tolvaptan treatment may be exempted from treatment discontinuation.	oxcarbazepine (which can increase vasopressin production by the pituitary) that cannot be changed or discontinued, or subjects with a known underlying hyponatremia inducing condition such as volume overload from a failing Fontan repair. 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. 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. 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..
2.2 Dosing Rationale:	In the optional tolvaptan treatment component of the trial, eligible subjects with a demonstrated clinical need will be dosed with tolvaptan based on age, weight, and the use of CYP3A4 inhibitors. Subjects < 2 years of age, or < 10 kg, or those who cannot swallow a tablet, will be excluded until	In the optional tolvaptan treatment component of the trial, eligible subjects with a demonstrated clinical need will be dosed with tolvaptan based on age, weight, and the use of CYP3A4 inhibitors. Subjects < 2 years of age, or < 10 kg, or those who cannot swallow a tablet, will be excluded from the treatment option of this protocol until an alternate formulation

Location	Old Text	Updated Text
	an oral liquid formulation becomes available. Subjects ≥ 2 years of age and weighing ≥ 10 to < 20 kg will receive an oral QD dose of tolvaptan starting as a 3.75-mg spray-dried tablet. Subjects weighing 20 to 50 kg, inclusive, will receive an oral QD dose of tolvaptan starting as a 7.5-mg spray-dried tablet. Subjects weighing > 50 kg will receive an oral QD dose of tolvaptan starting as a 15-mg spray-dried tablet. For subjects weighing ≥ 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 oral liquid formulation is available.	becomes available. The liquid suspension formulation available for short-term use in the 156-08-276 trial is not available in this trial. Subjects ≥ 2 years of age and weighing ≥ 10 to < 20 kg will receive an oral QD dose of tolvaptan starting as a 3.75-mg spray-dried tablet. Subjects weighing 20 to 50 kg, inclusive, will receive an oral QD dose of tolvaptan starting as a 7.5-mg spray-dried tablet. Subjects weighing > 50 kg will receive an oral QD dose of tolvaptan starting as a 15-mg spray-dried tablet. For subjects weighing ≥ 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 optional tolvaptan treatment until such time that an alternate formulation is available.
Figure 3.1-1 Trial Design Schematic:		Schematic revised to reflect updated text in this section.
3.1.1.1 Core Safety Follow-up Component Phases:	Subjects enrolled in this trial are required to complete 7 visits regardless of their treatment status with tolvaptan. The Baseline Visit as well as Month 2, 4 and 6 Visits are performed in clinic while Month 1, 3 and 5 Visits can be conducted via telephone. During the in clinic visits subjects are evaluated for relevant information. Since all pediatric subjects (children and adolescents) who previously participated in a trial of titrated IMP (tolvaptan in Trial 156-08-276; tolvaptan or placebo in Trial 156-13-207 or 156-12-205) are eligible to participate	Subjects enrolled in this trial are required to complete 7 visits regardless of their treatment status with tolvaptan as well as the follow-up telephone calls until the trial is closed. The Baseline Visit as well as Month 2, 4 and 6 Visits are performed in clinic while Month 1, 3 and 5 Visits can be conducted via telephone. During the in clinic visits subjects are evaluated for relevant trial information. After completion of the 6 month core follow-up visits, subjects will continue to be contacted at 3 month intervals to obtain basic safety updates. All pediatric subjects (children and adolescents) who previously participated in a trial of titrated IMP (tolvaptan in Trial 156-08-276;

Location	Old Text	Updated Text
	in this trial there is no screening phase. Similarly, since the goal of the trial is to collect follow-up information for prior treatment there is no separate follow-up phase.	tolvaptan or placebo in Trial 156-13-207 or 156-12-205) are eligible to participate in this trial. There is no screening phase.
3.1.2 Optional Tolvaptan Treatment Component:	Subjects enrolled in the 6-month core safety follow-up component may meet the criteria for treatment with tolvaptan. This subset of the study population may receive cycles of tolvaptan per clinical need to treat their hyponatremia. If a subject has a clinical need for treatment with tolvaptan, the subject may be screened for eligibility to be dosed within this trial. The subject must have been off treatment with the IMP for 7 days following the end of treatment in the previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) to assess the subject's clinical need for dosing. Eligibility for tolvaptan treatment must be determined between Day -4 and Day -1 of each dosing cycle. Subjects can be treated with tolvaptan during and/or after the 6-month core safety follow-up component after evaluating the subject using the criteria outlined in Appendix 5. Thirty days after the start of tolvaptan treatment, all subjects receiving tolvaptan will discontinue treatment for up to 72 hours, during which the need for continuing treatment with tolvaptan will be reassessed. Subjects who resume dosing can do so at the same dose or a lower dose without having to go through the full titration cycle again. Subjects who have a dosing discontinuation of > 72 hours must repeat the full titration cycle in a hospital setting.The	Subjects enrolled in the 6-month core safety follow-up component who have a clinical need for tolvaptan, per the investigator's assessment, and meet the criteria for treatment with tolvaptan, may receive cycles of tolvaptan to treat their hyponatremia. The subject must have completed the follow-up period of the previous trial prior to receiving the first dose of IMP. Eligibility for tolvaptan treatment must be determined between Day -4 and Day -1 of each dosing cycle. Subjects can be treated with tolvaptan during and/or after the 6-month core safety follow-up component after evaluating the subject using the criteria outlined in Appendix 5. Thirty days after the start of tolvaptan treatment in the first cycle, subjects receiving tolvaptan will interrupt treatment for 2 doses (Days 31-32). The need for continuing treatment will be assessed minimally once daily during this time. Subjects who resume dosing within 72 hours post last dose (either on Day 32 or by the morning of Day 33), based on medical need, can do so at the same dose or a lower dose without having to go through the full titration cycle again. Subjects who have a dosing discontinuation of > 2 doses must enter a new treatment cycle and repeat the full titration cycle in a hospital setting. Pediatric subjects in 156-11-294 who interrupt tolvaptan treatment (for 2 doses) for the purpose of re-evaluation to continue treatment beyond 30 days will have serum sodium levels and neurocognitive symptoms monitored closely. Subjects who demonstrate a decline in serum sodium level will be restarted at the prior dose of tolvaptan as per clinician

Location	Old Text	Updated Text
	optional tolvaptan treatment component of the trial does not have a fixed stopping point. Subjects who have an ongoing need for treatment can continue to receive tolvaptan per the investigator's clinical judgment until they no longer have a need for treatment or all subjects have completed the 6 month Core Follow-up Component of the trial. Subjects who terminate tolvaptan treatment will have follow-up visits at 24 hours (± 4 hours), and at 7 (± 1) days post-last dose, and a telephone call at 14 days (+ 2 days) post-last dose. Additional follow-up contacts will be performed on a regular basis until the end of the trial.	judgment. Subjects whose serum sodium declines ≥ 4 mEq/L (mmol/L) or who exhibit symptoms of hyponatremia will be immediately placed under direct observation (e.g., short stay unit) as per clinician judgment and will be restarted at either a lower dose or the previous dose of tolvaptan and closely monitored until stable. Investigators should consider the overall clinical status of the subject (including underlying etiology of hyponatremia and volume assessment), prior response to tolvaptan, concomitant medications, age, and weight when determining the appropriate dose at which to restart a subject after a brief discontinuation of tolvaptan to assess the need for further treatment. Investigators should discuss any concerns with the medical monitor. The optional tolvaptan treatment component of the trial does not have a fixed stopping point. Subjects who have an ongoing need for treatment can continue to receive tolvaptan per the investigator's clinical judgment until they no longer have a need for treatment or all subjects have completed the 6 month Core Follow-up Component of the trial. Subjects who terminate tolvaptan treatment will have follow-up visits at 24 hours (± 4 hours), and at 7 (± 1) days post-last dose, and a telephone call at 14 days (+ 2 days) post-last dose. Additional follow-up contacts will be performed on a regular basis until the end of the trial.
3.1.2.1.2 Treatment Initiation and Maintenance:	During the first 30 days of treatment subjects should have serum sodium assessments at a minimum of once daily during the Titration Phase on Day 1 up to Day 4 of treatment, and at a minimum of once weekly thereafter once on a stable dose (ie, on Days 7, 14, 21, and 28). After the first 30 consecutive days of treatment, all subjects who receive tolvaptan will be assessed for the need to	During the first 30 days of treatment subjects should have serum sodium assessments at a minimum of once daily during the Titration Phase on Day 1 up to Day 4 of treatment, and at a minimum of once weekly thereafter once on a stable dose (ie, on Days 7, 14, 21, and 28). 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

Location	Old Text	Updated Text
	continue treatment (Section 3.7.3.2.4). However, subjects may be assessed, per investigator's discretion, for the need for ongoing treatment with tolvaptan at any time point during treatment. Subjects who demonstrate a need for tolvaptan treatment may continue treatment to maintain the normal or clinician-directed target range serum sodium. Procedures for reinitiation of tolvaptan treatment for subjects with a clinical need per the investigator's assessment are described in Section **Error! Reference source not found.**. Tolvaptan treatment can be discontinued and reinitiated as needed per individual subject's need (eg, during chemotherapy treatments). If subjects are off tolvaptan treatment for > 72 hours, reinitiation of treatment will require reassessment of eligibility criteria and will begin in a hospital setting. Tolvaptan should be titrated with regular serum sodium assessments (Section 3.2.1.2 and Section 3.7.4.1).	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). After the first 30 consecutive days of treatment, all subjects who receive tolvaptan will have a scheduled interruption of tolvaptan to assess the need to continue treatment (Section 3.7.3.2.4). However, subjects may be assessed, per investigator's discretion, for the need for ongoing treatment with tolvaptan at any time point during treatment. Subjects who demonstrate a need for tolvaptan treatment may continue treatment to maintain the normal or clinician-directed target range serum sodium. Procedures for reinitiation of tolvaptan treatment for subjects with a clinical need per the investigator's assessment are described in Section **Error! Reference source not found.**. Tolvaptan treatment can be discontinued and reinitiated as needed per individual subject's need (eg, during chemotherapy treatments). If subjects are off tolvaptan treatment for > 72 hours, reinitiation of treatment will require reassessment of eligibility criteria and will begin in a hospital setting as part of a new treatment cycle. Tolvaptan should be titrated with regular serum sodium assessments (Section 3.2.1.2 and Section 3.7.4.1).
3.1.2.1.3 Follow-up Phase (End of Tolvaptan Treatment Cycle):	Subjects who discontinue tolvaptan treatment in the optional tolvaptan treatment component per the investigator's decision will return to the clinical trial site for serum sodium assessments at 24 (± 4) hours and at 7 (±1) days post-last dose, and will receive follow-up telephone	Subjects who discontinue tolvaptan treatment in the optional tolvaptan treatment component per the investigator's decision will return to the clinical trial site for serum sodium assessments at 24 (± 4) hours and at 7 (±1) days post-last dose, and will receive follow-up telephone calls at 14 (+2) days and every 3 months (± 2 weeks) post-last dose. In the Follow-

Location	Old Text	Updated Text
	calls at 14 (+2) days and every 3 months (± 2 weeks) post-last dose. In the Follow-up Phase (ie, at the end of Month 6 or at the end of the tolvaptan treatment), subjects should have serum sodium assessments at 24 (± 4) hours and 7 (+ 1) days, and 14 (+2) days post-last dose. ALT, AST, and BT should be assessed at 24 (± 4 hours) post-last dose, if more than 1 month has elapsed since LFTs were performed. An IRE form will be completed if the subject is a potential Hy's Law case (see Section 5.4). Potential Hy's Law cases will be followed up until the ALT, AST, and BT values are within normal limits.	up Phase (ie, at the end of Month 6 or at the end of the tolvaptan treatment), subjects should have serum sodium assessments at 24 (± 4) hours and 7 (+ 1) days post-last dose. ALT, AST, and BT should be assessed at 24 (± 4 hours) post-last dose, if more than 1 month has elapsed since LFTs were performed. An IRE form will be completed if the subject is a potential Hy's Law case (see Section 5.4). Potential Hy's Law cases will be followed up until the ALT, AST, and BT values are within normal limits.
3.2 Treatments:	For all subjects enrolled in the core safety follow-up component of the trial, the need for initiation of tolvaptan treatment will be assessed per protocol serum sodium guidelines and the duration of tolvaptan administration will determined by the PI per the subject's medical need.	For all subjects enrolled in the core safety follow-up component of the trial, the need for initiation of tolvaptan treatment will be assessed per the protocol's serum sodium guidelines and the duration of tolvaptan administration will be determined by the PI per the subject's medical need.
3.2.1.2 Titration Guidelines for the Optional Tolvaptan Treatment Component:	Subjects will be administered tolvaptan on an age- and weight-based scale. Tolvaptan doses can be titrated QD 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 20 hours of the previous dose. Titration is limited to no more than twice the previous dose and will be limited to the maximum dose per body weight. A change in serum sodium ≤ 4 mEq/L (mmol/L) from baseline should warrant titration. • Subjects < 2 years of age or weighing < 10 kg are	Subjects will be administered tolvaptan on an age- and weight-based scale. Tolvaptan doses can be titrated QD 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 20 hours of the previous dose. Titration is limited to no more than twice the previous dose and will be limited to the maximum dose per body weight. A change in serum sodium ≤ 4 mEq/L (mmol/L) from baseline should warrant titration. • Subjects < 2 years of age or weighing < 10 kg are not eligible for treatment until an alternate formulation is available. • Subjects ≥ 2 years of age and weighing ≥ 10 to < 20 kg will be

Location	Old Text	Updated Text
	excluded until an oral liquid formulation is available. • Subjects ≥ 2 years of age and weighing ≥ 10 to < 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. • 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. • Subjects weighing > 50 kg will be given a 15-mg tablet on Day 1 with possible up-titration to 30- and 60-mg tablet doses. • Subjects weighing ≥ 20 kg and taking moderate inhibitors of CYP3A4 will be given a half-dose (3.75 or 7.5 mg, by weight). • Subjects weighing > 50 kg and taking potent inhibitors of CYP3A4 will be given a one-quarter dose. • Subjects weighing < 20 kg and who are taking any CYP3A4 inhibitors will be excluded until such time that an oral liquid formulation is available.	given a 3.75-mg tablet on Day 1 with possible up-titration to 7.5- and 15-mg tablet doses. • 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. • Subjects weighing > 50 kg will be given a 15-mg tablet on Day 1 with possible up-titration to 30- and 60-mg tablet doses. • Subjects weighing ≥ 20 kg and taking moderate inhibitors of CYP3A4 will be given a half-dose (3.75 or 7.5 mg, by weight). • Subjects weighing > 50 kg and taking potent inhibitors of CYP3A4 will be given a one-quarter dose. • Subjects weighing < 20 kg and who are taking any CYP3A4 inhibitors will be excluded until such time that an alternate formulation is available.
3.2.2 Duration of Optional Tolvaptan Treatment:	For subjects who require long-term treatment, each subject will be required to temporarily discontinue treatment at 30 days after the start of tolvaptan and be evaluated for continued need for tolvaptan treatment.	For subjects who require long-term treatment, each subject (exceptions listed in Section 2.1.2) will be required to temporarily discontinue treatment at 30 days after the start of tolvaptan and be evaluated for continued need for tolvaptan treatment.
3.2.3 Rescue Therapy:	A subject requiring rescue therapy at any time during the optional tolvaptan treatment component will be discontinued from tolvaptan prior to receiving rescue therapy and should continue to be followed per the schedule of assessments in the core safety follow-up component of the trial. Treatment may be reinitiated only per consultation	A subject requiring rescue therapy at any time during the optional tolvaptan treatment component will be discontinued from tolvaptan prior to receiving rescue therapy and should continue to be followed per the schedule of assessments in the optional tolvaptan treatment component and the core safety follow-up component of the trial, as appropriate. Treatment may be reinitiated only per consultation with the medical

Location	Old Text	Updated Text
	with the medical monitor. Subjects who have received rescue therapy because of inadequate response to tolvaptan will not be allowed to reinitiate tolvaptan treatment.	monitor. Subjects who have received rescue therapy because of inadequate response to tolvaptan will not be allowed to reinitiate tolvaptan treatment.
3.3.1 Core Safety Follow-up Component:	Up to 140 male or female subjects may be eligible for this trial. All subjects will have participated in one of the previous tolvaptan pediatric hyponatremia trials (156-08-276, 156-13-207, or 156-12-205). All subjects will be observed for post-treatment safety for at least 6 months. Subjects enrolled in the core safety follow-up component may enter the optional tolvaptan treatment component of the trial at any time during the conduct of the trial based on clinical need and the investigator's discretion.	Approximately 140 male or female subjects may be eligible for this trial. All subjects will have participated in one of the previous tolvaptan pediatric hyponatremia trials (156-08-276, 156-13-207, or 156-12-205). All subjects will be observed for safety for 6 months regardless of treatment status and followed until the end of the trial. Subjects enrolled in the core safety follow-up component may enter the optional tolvaptan treatment component of the trial at any time during the conduct of the trial based on clinical need and the investigator's discretion.
3.3.2 Optional Tolvaptan Treatment Component:	Subjects enrolled in the Core Safety Follow-up Component of the trial may be eligible for treatment with tolvaptan. These subjects include, but are not limited to, those diagnosed and admitted to a hospital for treatment of heart failure, hepatocellular disease (including cirrhosis), or SIADH/other. Subjects with acute hyponatremia or hyponatremia expected to resolve spontaneously will be ineligible for tolvaptan treatment. 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 ineligible for tolvaptan treatment if this is not possible. Children with hypovolemic hyponatremia or those who are at risk of such, secondary to any underlying conditions that	Subjects enrolled in the Core Safety Follow-up Component of the trial may be eligible for treatment with tolvaptan. These subjects include, but are not limited to, those diagnosed and admitted to a hospital for treatment of heart failure, hepatocellular disease (including cirrhosis), or SIADH/other. Subjects with acute hyponatremia or hyponatremia expected to resolve spontaneously will be ineligible for tolvaptan treatment. Children with an impaired ability to sense or communicate their thirst will either be required to undergo closer observation, laboratory and urine output monitoring, or will be ineligible for tolvaptan treatment 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 ineligible for tolvaptan treatment. For initiation or reinitiation of tolvaptan treatment in the Optional

Location	Old Text	Updated Text
	cause volume depletion, are ineligible for tolvaptan treatment.	Tolvaptan Treatment Component of the trial additional criteria apply as outlined in Appendix 5.
3.4.1 Informed Consent/Assent:	Written informed consent or patient information sheet (PIS) 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 baseline (which may be the final visit in the previous titrated oral IMP trial) 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 previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) or who become legal adults during this 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)	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 baseline (which may be the final visit in the previous titrated oral IMP trial) 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 previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) or who become legal adults during this 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 and local regulatory requirements. The investigator agrees to obtain approval from the sponsor of any written ICF used in the trial, prior to submission to the IRB/IEC. Investigators may discuss trial availability and the possibility for entry

Location	Old Text	Updated Text
	Guideline and local regulatory requirements. The investigator agrees to obtain approval from the sponsor of any written ICF 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).	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). Investigators may obtain consent and assent for this trial while the subject is still enrolled in the previous trial (Trial 156-08-276, Trial 156-13-207 and Trial 156-12-205). ...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.
3.4.3 Exclusion Criteria:	There are no exclusion criteria for entry into the safety follow-up component of this trial. For initiation or reinitiation of tolvaptan treatment in the Optional Tolvaptan Treatment Component of the trial additional criteria apply as outlined in Appendix 5.	There are no exclusion criteria for entry into the trial.
3.5.2.2 Safety Variables:	The primary safety variables are the following: • AE reporting • Growth percentiles for body height and body weight • Tanner Staging • Change from baseline in serum sodium concentration	The safety variables are the following: • AE reporting • Growth percentiles for body height and body weight • Tanner Staging • Change from baseline in serum sodium concentration
3.5.2.3 Pharmacokineti	The PK endpoints are the plasma concentrations of tolvaptan and metabolites in subjects who have continued	The PK endpoints are the plasma concentrations of tolvaptan and metabolites in subjects who have continued tolvaptan therapy for

Location	Old Text	Updated Text
c Variable: Optional Tolvaptan Treatment Component	tolvaptan therapy for 8 consecutive weeks, ignoring short interruptions to assess need for continued therapy.	8 consecutive weeks, ignoring short interruptions (up to 2 missed doses) to assess need for continued therapy.

Old Text: Table 3.7.1-1 Schedule of Assessments

Table 3.7.1-1 Core Safety Follow-up Component: Schedule of Assessments for All Subjects

Procedures	Baseline[a]	Month 1 (+2 Weeks)	Month 2 (+2 Weeks)	Month 3 (+2 Weeks)	Month 4 (+2 Weeks)	Month 5 (+2 Weeks)	Month 6 or Early Termination (+2 Weeks)
Informed consent and assent	X						
Review inclusion criteria	X						
Demographic information	X						
Telephone assessment[b]		X		X		X	
In-clinic assessment	X		X		X		X
Medical and hyponatremia history	X		X		X		X
Vital signs[c]	X		X		X		X
Directed physical examination	X		X		X		X
Body height/weight/ growth percentiles	X		X		X		X
Tanner Staging	X		X		X		X
Serum sodium	X		X		X		X
Assess ALT, AST, and BT	X		X		X		X
Neurocognitive Assessment[d]	X		X		X		X
Quality of Life	X		X		X		X
Concomitant medications	←	———	———	———	———	———	→
Adverse events	←	———	———	———	———	———	→

[a] The final laboratory assessments from the previous trial (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) can serve as the baseline laboratory assessments for this trial. All assessments, with the exception of the neurocognitive assessment, can be carried over from previous trial of titrated oral IMP to this trial, if possible. Body height, body weight, Tanner Staging, and baseline laboratory assessments can be carried forward from the last visit in the previous trial if done within one month, but all other assessments must be completed at the baseline visit and all including height, Tanner Staging and laboratory assessments must be re-done if more than one month passes between trials.

[b] Telephone calls can be replaced with clinical site visits.

[c] 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.

[d] Neurocognitive assessment will be performed at baseline and at Months 2, 4, and 6, and should be done within 1 hour of blood draws for serum sodium assessment.

New Text: Table 3.7.1-1 Schedule of Assessments

Table 3.7.1-1 Core Safety Follow-up Component: Schedule of Assessments for All Subjects

Procedures	Baseline[a]	Month 1 (+2 Weeks)	Month 2 (+2 Weeks)	Month 3 (+2 Weeks)	Month 4 (+2 Weeks)	Month 5 (+2 Weeks)	Month 6 or Early Termination (+2 Weeks)	every 3 months (±2 weeks)
Informed consent and assent	X							
Review inclusion criteria	X							
Demographic information	X							
Telephone assessment[b]		X		X		X		X
In-clinic assessment	X		X		X		X	
Medical history	X							
Hyponatremia history	X		X		X		X	
Vital signs[c]	X		X		X		X	
Directed physical examination	X		X		X		X	
Body height/weight/ growth percentiles	X		X		X		X	
Tanner Staging[d]	X						X	
Serum sodium	X		X		X		X	
Assess ALT, AST, and BT	X		X		X		X	
Neurocognitive Assessment[e]	X		X		X		X	
Quality of Life	X		X		X		X	
Concomitant medications	←							→
Adverse events	←							→

[a] The final laboratory assessments for LFT from the previous trial (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) can serve as the baseline laboratory assessments for this trial. Assessments, with the exception of the serum sodium, QoL, and neurocognitive assessment, can be carried over from a previous trial of titrated oral IMP to this trial, if possible and if not more than 1 month has passed between the 2 trials.

[b] Telephone calls can be replaced with clinical site visits.

[c] 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.

[d] A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging.

[e]Neurocognitive assessment will be performed at baseline and at Months 2, 4, and 6, and should be done within 1 hour of blood draws for serum sodium assessment.

Location	Old Text	Updated Text
3.7.2 Optional Tolvaptan Treatment Component:	Trial treatment will begin and be titrated in a hospital setting.	Trial treatment will begin and titration must occur in a hospital setting. ... If subjects are off tolvaptan treatment for > 72 hours, reinitiation of treatment, starting with titration, will require reassessment of the eligibility criteria, and titration will begin in a hospital setting as part of a new treatment cycle.

Old Text: Table 3.7.2-1 Schedule of Assessments

Table 3.7.2-1 Schedule of Assessments for Each Treatment Cycle													
Procedures[a]	**Pretreatment Baseline[b]**	**Titration Phase[b]**			**Post-titration**			**Treatment Cycle Month 2**	**Treatment Cycle Month 3+ (Maintenance)**	**Follow- up Phase**			
	Days -4 to -1	**Day 1**	**Day 2 and 3**	**Day 4**	**Day 7, 14 and 21**	**Day 30 (±1)**	**Day 33 (-1)**	**every 2 weeks (±2 days)**	**Once monthly (±2 days)**	**24 (±4) hours post-last dose**	**7 (±1) days post-last dose**	**14 (±2) days post-last dose**	**every 3 months (±2 weeks)**
Review eligibility criteria for treatment	X												
Vital signs	X	X	X	X	X	X	X	X	X	X	X		
Directed physical exam	X								X				
Body height and weight/ growth percentiles	X								X				
Pregnancy test[c]	X						X	X	X	X			
Clinical status assessment	X						X	X	X				
Assess ALT, AST, and BT[d]	X					X		X	X	X			
Assess serum sodium[e]	X	X	X	X	X	X	X	X	X	X	X		
Tolvaptan dosing[f]		X	X	X	X	X	X	X	X				

Table 3.7.2-1 Schedule of Assessments for Each Treatment Cycle

Procedures[a]	**Pretreatment Baseline**[b]	**Titration Phase**[b]			**Post-titration**			**Treatment Cycle Month 2**	**Treatment Cycle Month 3+ (Maintenance)**	**Follow- up Phase**			
	Days -4 to -1	**Day 1**	**Day 2 and 3**	**Day 4**	**Day 7, 14 and 21**	**Day 30 (±1)**	**Day 33 (-1)**	**every 2 weeks (±2 days)**	**Once monthly (±2 days)**	**24 (±4) hours post-last dose**	**7 (±1) days post-last dose**	**14 (±2) days post-last dose**	**every 3 months (±2 weeks)**
Confirm stable dose				X									
Dispense tolvaptan drug kit				X			X	X	X				
Assess need for continued treatment							X						
Tolvaptan collection/ reconciliation					X	X		X	X	X			
PK sample collection[g]								X	X				
Telephone call												X	X
Concomitant medications	←												→
Adverse events	←												→

[a] Assessments that are part of a Core Safety Follow-up Component Trial Visit which happens to overlap with a visit in the Optional Tolvaptan Treatment Component only need to be performed once.

[b] Cycles can be repeated per clinical need. If a subject is off tolvaptan treatment for > 72 hours, titration/reinitiation of tolvaptan will require reassessment of eligibility criteria and will begin in a hospital setting.

[c]Serum or urine pregnancy tests will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. In Treatment Cycle Month 2 a pregnancy test should be performed a month after the previous assessment.

[d]In Treatment Cycle Month 2 liver function should be assessed a month after the previous assessment.

[e]Serum sodium will be assessed at the pretreatment baseline 48 hours prior to tolvaptan administration where 2 serum sodium assessments (<130 mEq/L [mmol/L) must be collected at least 12 hours apart. On Day 1 a STAT serum sodium sample will be assessed at 2 to 4 hours prior to first dose and another sample at 8 hours post-dose. On Day 2, 3 and 4 a sample will be assessed at 24 (± 4) hours post previous dose. On Days 7, 14, 21, and 30 at 24 (4) hours post-previous dose. At Day 33 serum sodium will be assessed between 48 and 72 hours post previous dose. In Treatment Cycle Month 2 a sample will be assessed every 14 (± 2) days. In Treatment Cycle Month ≥ 3 a sample will be assessed every month (± 2 days).

[f]The dose will be titrated based on serum sodium results assessed at a minimum of 24-hour intervals (± 4 hours) from 3.75 to 7.5 to 15 mg for subjects ≥ 2 years of age and weighing ≥ 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 may be sequentially titrated to the maximal dose allowed for their weight group. After the first 30 days of treatment, subjects will discontinue treatment with tolvaptan for up to 72 hours (2 skipped doses) to assess continued need for treatment.

[g]One PK sample should be taken after 8 weeks of continuous treatment per cycle.

New Text: Table 3.7.2-1 Schedule of Assessments

Table 3.7.2-1 Schedule of Assessments for Each Treatment Cycle

Procedures[a]	**Pretreatment Baseline**[b]	**Titration Phase**[b]			**Post-titration**						**Treatment Cycle Month 2**	**Treatment Cycle Month 3+ (Maintenance)**	**Follow- up Phase**[h]		
	Days -4 to -1	**Day 1**	**Day 2 and 3**	**Day 4**	**Day 7, 14 and 21**	**Day 30 (±1)**	**Day 31 (-1)**	**Day 32 (-1)**	**Day 33 (-1)**	**Day 34 (-1)**	**every 2 weeks (±2 days)**	**Once monthly (±2 days)**	**24 (±4) hours post-last dose**	**7 (±1) days post-last dose**	**14 (±2) days post-last dose**
Review eligibility criteria for treatment	X														
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Directed physical exam	X											X			
Body height and weight/ growth percentiles	X											X			
Pregnancy test[c]	X								X		X	X	X		
Clinical status assessment	X						X	X	X	X	X	X			
Assess ALT, AST, and BT[d]	X					X					X	X	X		
Assess serum sodium[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tolvaptan dosing[f]		X	X	X	X	X			X	X	X	X			

Table 3.7.2-1 Schedule of Assessments for Each Treatment Cycle

Procedures[a]	**Pretreatment Baseline**[b]	**Titration Phase**[b]			**Post-titration**						**Treatment Cycle Month 2**	**Treatment Cycle Month 3+ (Maintenance)**	**Follow- up Phase**[h]		
	Days -4 to -1	**Day 1**	**Day 2 and 3**	**Day 4**	**Day 7, 14 and 21**	**Day 30 (±1)**	**Day 31 (-1)**	**Day 32 (-1)**	**Day 33 (-1)**	**Day 34 (-1)**	**every 2 weeks (±2 days)**	**Once monthly (±2 days)**	**24 (±4) hours post-last dose**	**7 (±1) days post-last dose**	**14 (±2) days post-last dose**
Confirm stable dose				X											
Dispense tolvaptan drug kit				X	X				X	X	X	X			
Assess need for continued treatment									X						
Tolvaptan collection/ reconciliation					X	X					X	X	X		
PK sample collection[g]											X	X			
Telephone call															X
Concomitant medications	←														→
Adverse events	←														→

[a] Assessments that are part of a Core Safety Follow-up Component Trial Visit which happens to overlap with a visit in the Optional Tolvaptan Treatment Component only need to be performed once.

[b] Titration can be up to 4 days. Cycles can be repeated per clinical need. If a subject is off tolvaptan treatment for > 72 hours, titration/reinitiation of tolvaptan will require reassessment of eligibility criteria and will begin in a hospital setting as part of a new treatment cycle.

[c]Pregnancy tests will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. In Treatment Cycle Month 2 a pregnancy test should be performed a month after the previous assessment.

[d]In Treatment Cycle Month 2 liver function should be assessed a month after the previous assessment.

[e]Serum sodium will be assessed at the pretreatment baseline 48 hours prior to tolvaptan administration where 2 serum sodium assessments (<130 mEq/L [mmol/L) must be collected at least 12 hours apart. On Day 1 a STAT serum sodium sample will be assessed at 2 to 4 hours prior to first dose and another sample at 8 hours postdose. On Day 2, 3 and 4 a sample will be assessed at 24 (± 4) hours post previous dose. On Days 7, 14, 21, and 30 at 24 (4) hours post-previous dose. At Day 33 serum sodium will be assessed between 48 and 72 hours post previous dose. In Treatment Cycle Month 2 a sample will be assessed every 14 (± 2) days. In Treatment Cycle Month ≥ 3 a sample will be assessed every month (± 2 days). 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, as well as at 6 hours 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).

[f]The dose will be titrated based on serum sodium results assessed at a minimum of 24-hour intervals (± 4 hours) from 3.75 to 7.5 to 15 mg for subjects ≥ 2 years of age and weighing ≥ 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 may be sequentially titrated to the maximal dose allowed for their weight group. After the first 30 days of treatment, subjects will discontinue treatment with tolvaptan for up to 72 hours (2 skipped doses) to assess continued need for treatment.

[g]One PK sample should be taken after 8 weeks of continuous treatment per cycle. This may include a discontinuation of < 72 hours to assess the subject's need for continued treatment.

[h]Subjects who elect to opt out of treatment within a treatment cycle should immediately proceed to the Follow-up Phase.

Location	Old Text	Updated Text
3.7.3.1.1 Baseline for Core Safety Follow-up Component:	For all subjects who enroll in this trial, the final laboratory assessments in the previous trial can serve as the baseline laboratory assessments. The following procedures will be performed during the baseline visit: 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. Informed consent/assent needs to be obtained only before entering the trial for the first time. h) ICF, assent, and/or PIS will be obtained from each subject's parent or legal guardian prior to any trial procedures being conducted. i) Each subject will indicate willingness to participate in the trial by signing or marking an assent form (as applicable) supplied for this purpose. 2) Inclusion criteria will be reviewed. 8) Body height and body weight will be transferred from the last assessments from the previous trial or measured, as appropriate. 9) Growth percentile will be calculated. Prior growth development information should also be collected, if available. 10) Tanner Staging will be transferred from the last assessments from the previous trial or completed as part of the physical examination, as appropriate. Historical staging information should also be collected, if available. 11) The final laboratory assessments from the previous trial can serve as baseline laboratory assessments in this trial (see Appendix 6), as appropriate.	For all subjects who enroll in this trial, the final assessments in the previous trial can serve as the baseline assessments, as applicable. If more than one month passes between the 2 trials, all assessments need to be completed. The following procedures will be performed during the baseline visit: 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. Investigators may obtain consent and assent for this trial while the subject is still enrolled in the previous trial (Trial 156-08-276, Trial 156-13-207 and Trial 156-12-205). Informed consent/assent needs to be obtained each time a subject matriculates into the next age group. j) ICF and assent, will be obtained from each subject's parent or legal guardian prior to any trial procedures being conducted. k) Each subject will indicate willingness to participate in the trial by signing or marking an assent form (as applicable) supplied for this purpose. 2) Inclusion criteria for entry into the Core Safety Follow-up Component will be reviewed. 8) Body height and body weight will be transferred from the last assessments from the previous trial or measured, as appropriate. For children ≤ 2 years of age, the assessments cannot be transferred. 9) Growth percentile will be calculated. Prior growth development information should also be collected, if available. 10) Tanner Staging will be transferred from the last assessments from the previous trial or completed as part of the physical examination, as appropriate. Historical staging information should also be collected, if available. 11) The final LFT assessments from the previous trial can serve as baseline LFT assessments in this trial (see Section 3.7.5.2), as

Location	Old Text	Updated Text
	12) Serum sodium will be assessed. 13) Neurocognitive assessments will be performed, as appropriate by age and where available, within 1 hour of the blood draw for serum sodium assessment. 14) Quality of Life assessment will be performed, as appropriate by age and where available. 15) Concomitant medications will be recorded. 16) Adverse events will be assessed.	appropriate. 12) Serum sodium will be assessed. 13) Neurocognitive assessments will be performed, as appropriate by age and where available, within 1 hour of the blood draw for serum sodium assessment. 14) Quality of Life assessment will be performed, as appropriate by age and where available. 15) Concomitant medications will be recorded. 16) Adverse events will be assessed.
3.7.3.1.3 Months 2, 4, and 6/Early Termination:	Subjects will return to the clinical trial site at the end of Months 2, 4, and 6 (+ 2 weeks) or at early termination (ET) and the following assessments will be performed: 1) Medical and hyponatremia history will be recorded separately. Medical history should include the subject's current list of medical problems in addition to the history recorded for the prior trial. The hyponatremia medical history should include the etiology of subject's hyponatremia (including the tests specified in Section 3.2.2) and what treatment was administered before trial enrollment. A detailed history specific to etiology of hyponatremia will also be recorded.	Subjects will return to the clinical trial site at the end of Months 2, 4, and 6 (+ 2 weeks) or at early termination (ET) and the following assessments will be performed: 1) Hyponatremia history will be recorded separately. The hyponatremia history should include the etiology of subject's hyponatremia (including the tests specified in Section 3.2.2) and what treatment was administered before trial enrollment. A detailed history specific to etiology of hyponatremia will also be recorded.
3.7.3.1.3.1 Additional Follow-up Contacts:	Section moved from later in the protocol.	Follow-up contacts will occur every 3 months (± 2 weeks) for all subjects. 1) Concomitant medications will be recorded. 2) Adverse events will be assessed.
3.7.3.2 Optional Tolvaptan Treatment Component:	If possible, all assessments while subjects are treated with tolvaptan should be synchronized with those performed as part of the core safety follow-up component of the trial (ie, assessments should not be performed twice at the same time	If possible, all assessments while subjects are treated with tolvaptan should be synchronized with those performed as part of the core safety follow-up component of the trial (ie, assessments should not be performed twice at the same time point). Cycles can be repeated based on clinical

Location	Old Text	Updated Text
	point). Cycles can be repeated per clinical need during the initial 6 months of the trial and/or after the subject has completed the initial 6 months of follow-up. If a subject is off tolvaptan treatment for > 72 hours, titration and reinitiation of treatment will require reassessment of the eligibility criteria and will begin in a hospital setting.	need during the initial 6 months of the trial and/or after the subject has completed the initial 6 months of follow-up. If a subject is off tolvaptan treatment for > 72 hours, titration and reinitiation of treatment will require reassessment of the eligibility criteria and will begin in a hospital setting.
3.7.3.2.1 Pretreatment Baseline Visit:	For subjects with a clinical need for tolvaptan treatment, the baseline visit for the core safety follow-up component of the trial may serve as the pretreatment baseline visit for the optional tolvaptan treatment component. The following procedures will be performed during the pretreatment baseline visit (Days −4 to −1) to ensure the subject qualifies for each tolvaptan treatment cycle: 9) A serum or urine pregnancy test will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started.	For subjects with a clinical need for tolvaptan treatment, the following procedures will be performed during the pretreatment baseline visit (Days −4 to −1) to ensure the subject qualifies for each tolvaptan treatment cycle: 9) A pregnancy test will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started.
3.7.3.2.2.1 Day 1:	1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for STAT serum sodium testing will be collected within 2 to 4 hours prior to dosing. Results need to be reviewed prior to dosing to confirm continued treatment eligibility of the subject. 3) Tolvaptan will be administered. 4) A blood sample for serum sodium testing will be	1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for STAT serum sodium testing will be collected within 2 to 4 hours prior to dosing. Results need to be reviewed prior to dosing to confirm continued treatment eligibility of the subject. 3) 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

Location	Old Text	Updated Text
	collected 8 hours post-first dose in the current treatment cycle. 5) Concomitant medications will be recorded. 6) Adverse events will be assessed.	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). 4) Tolvaptan will be administered. 5) A blood sample for serum sodium testing will be collected 8 hours post-first dose in the current treatment cycle. 6) Concomitant medications will be recorded. 7) Adverse events will be assessed.
3.7.3.2.2.2 Day 2 Up to Day 4:	Because each individual's clinical circumstances differ, the investigator will individualize an evaluation scheme for the titration period. The primary evaluation will be that of serum sodium concentrations and relevant clinical laboratory assessments. The investigator should schedule evaluations daily while the subject remains in a hospital setting per the schedule of assessments. The following procedures will be performed during the titration period: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 3) Administer tolvaptan. Tolvaptan will be titrated per the titration guidelines (see Section 3.2.1.2) for the assigned weight group.	The primary evaluation will be that of serum sodium concentrations and relevant clinical laboratory assessments. The investigator should schedule evaluations daily while the subject remains in a hospital setting per the schedule of assessments. The following procedures will be performed during the titration period: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 3) 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 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

Location	Old Text	Updated Text
		standard of care labs). 4) Administer tolvaptan. Tolvaptan will be titrated per the titration guidelines (see Section 3.2.1.2) for the assigned weight group.
3.7.3.2.3 Days 7, 14, and 21:	1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 3) 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 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). 6) Tolvaptan will be administered. Subjects and their parents/legal guardians will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation. 4) Concomitant medications will be recorded. 5) Adverse events will be assessed.	1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 7) Tolvaptan will be administered. Subjects and their parents/legal guardians will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation. 3) Concomitant medications will be recorded. 4) Adverse events will be assessed. 5) On Day 21, instruct subjects not to take the Day 30 dose of tolvaptan before coming to the clinic on Day 30.
30 (±1) Days Post-first Dose:	After 30 days of tolvaptan treatment, all subjects should discontinue treatment for assessment of continued need for	After 30 days of tolvaptan treatment, all subjects (exceptions listed in Section 2.1.2) should discontinue treatment for 2 doses to assess the continued need for tolvaptan treatment. Subjects should arrive to the

Location	Old Text	Updated Text
	tolvaptan treatment. 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 3) A blood sample for ALT, AST, and BT will be collected. 8) Tolvaptan will be administered. 4) Advise subject to skip the next 2 doses. 5) Concomitant medications will be recorded. 6) Adverse events will be assessed.	clinic prior to taking the morning dose of tolvaptan. 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 3) A blood sample for ALT, AST, and BT will be collected. 4) Tolvaptan dispensed the previous week will be returned for accountability. 9) Tolvaptan will be administered. 5) Advise subject to skip the next 2 doses. 6) Concomitant medications will be recorded. 7) Adverse events will be assessed.
3.7.3.2.5 Day 31 (-1):	New section for this amendment	The following assessments will be performed: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A clinical status assessment, including a neurological examination, will be performed. 3) A blood sample for serum sodium testing must be assessed a minimum of once per day, based on the investigator's judgment. 4) Concomitant medications will be recorded. 5) Adverse events will be assessed.
3.7.3.2.6 Day 32 (-1):	New section for this amendment	The following assessments will be performed:

Location	Old Text	Updated Text
		1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A clinical status assessment, including a neurological examination, will be performed. 3) A blood sample for serum sodium testing must be assessed a minimum of once per day, based on the investigator's judgment. 4) Concomitant medications will be recorded. 5) Adverse events will be assessed.
3.7.3.2.7 Day 33 (-1):	The following assessments will be performed: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A clinical status assessment will be performed. 3) A serum or urine pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. 4) A blood sample for serum sodium testing must be assessed to confirm the need for continuation of treatment. Refer to Figure 3.1-1 and Section 3.2.2 for the trial schematic and a description of the treatment continuation decision. 5) Tolvaptan will be administered if need for continued treatment is confirmed. Subjects who reinitiate treatment at the same dose or a lower dose of tolvaptan after discontinuation for up to 72 hours will not be required to reinitiate treatment in a hospital setting. If subjects are off tolvaptan treatment for > 72 hours, reinitiation of	The following assessments will be performed: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A clinical status assessment, including a neurological examination, will be performed. 3) A pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. 4) A blood sample for serum sodium testing must be assessed to confirm the need for continuation of treatment. Refer to Figure 3.1-1 and Section **Error! Reference source not found.** for the trial schematic and a description of the treatment continuation decision. 5) Confirm need for continuing treatment. b) If continuing treatment is needed and subjects have been off drug for up to 72 hours: • Tolvaptan will be administered. Subjects who reinitiate treatment at the same dose or a lower dose of tolvaptan after discontinuation for up to

Location	Old Text	Updated Text
	treatment, starting with titration (Section 3.2.1.2), will require reassessment of the eligibility criteria, and titration will begin in a hospital setting. Tolvaptan should be titrated with regular serum sodium assessments. 6) Concomitant medications will be recorded. 7) Adverse events will be assessed.	72 hours will not be required to reinitiate treatment in a hospital setting. However, subjects must have a 24 hour postdose serum sodium assessment on Day 34 prior to being dispensed enough medication to supply them until their next on-treatment visit (Section 3.7.3.2.4.4). c) If continuing treatment is needed and subjects have been off drug for > 72 hours: • If subjects are off tolvaptan treatment for > 72 hours (2 doses), reinitiation of treatment, starting with titration (Section 3.2.1.2), will require reassessment of the eligibility criteria, and titration will begin in a hospital setting as part of a new treatment cycle starting at the pretreatment baseline visit (Section 3.7.3.2.1). In these cases, the new treatment cycle supersedes the follow-up visits from the current treatment cycle. d) If no continuing treatment is needed: • Complete the assessments for the 7 day post-last dose visit (Section 3.7.3.2.7.2). 6) Concomitant medications will be recorded. 7) Adverse events will be assessed.
3.7.3.2.8 Day 34 (-1):	New section for this amendment	The following assessments will be performed: 1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A clinical status assessment, including a neurological examination, will be performed. 3) A blood sample for serum sodium testing must be assessed. 4) Tolvaptan will be administered. 5) Sufficient tolvaptan will be dispensed for subjects that are outpatients for QD dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to

Location	Old Text	Updated Text
		return any remaining tolvaptan at the next visit for dose reconciliation. 6) Concomitant medications will be recorded. 7) Adverse events will be assessed.
3.7.3.2.9 Treatment Cycle Month 2: Every 2 Weeks (± 2 days):	1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 3) A blood sample for ALT, AST, and BT will be collected (at the end of Treatment Cycle Month 2). 4) For each treatment cycle, a single PK blood sample will be collected after 8 consecutive weeks of tolvaptan dosing for the determination of tolvaptan and metabolites plasma concentrations. 5) A clinical status assessment will be performed. 6) A serum or urine pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started (at the end of Treatment Cycle Month 2 only). 7) Tolvaptan will be administered.	1) Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has been supine for ≥ 3 minutes. Vital signs should be assessed prior to blood draws. 2) A blood sample for serum sodium testing must be assessed at 24 (± 4) hours post-previous dose with the results reviewed prior to subsequent tolvaptan dosing. 3) A blood sample for ALT, AST, and BT will be collected (at the end of Treatment Cycle Month 2). 4) For each treatment cycle, a single PK blood sample will be collected after 8 consecutive weeks of tolvaptan dosing for the determination of tolvaptan and metabolites plasma concentrations. 5) A clinical status assessment will be performed. 6) A pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started (at the end of Treatment Cycle Month 2 only). 7) Tolvaptan dispensed the previous week will be returned for accountability. 8) Tolvaptan will be administered
3.7.3.2.10.1 Treatment Cycle Month 3 (and every month thereafter) (± 2 days):	1) A serum or urine pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. 2) A directed physical examination will be performed.	1) A pregnancy test will be performed at each visit on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started. 2) A directed physical examination will be performed. 3) A clinical status assessment will be performed. 4) A blood sample for ALT, AST, and BT will be collected every

Location	Old Text	Updated Text
	3) A clinical status assessment will be performed. 4) A blood sample for ALT, AST, and BT will be collected every month. 5) A blood sample for serum sodium testing should be taken at each visit. 6) Tolvaptan will be administered. 7) Sufficient tolvaptan will be dispensed for subjects that are outpatients for QD dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation. 8) If a PK sample has not been taken at the end of the Treatment Cycle Month 2 visits, a single PK blood sample will be collected after 8 consecutive weeks of tolvaptan dosing for the determination of tolvaptan and metabolites plasma concentrations. 9) Concomitant medications will be recorded. 10) Adverse events will be assessed. Tolvaptan treatment cycles may be repeated per a subject's clinical need and the discretion of the investigator. Subjects may be evaluated for continued need for tolvaptan treatment at additional clinical trial site visits per the investigator's discretion. After discontinuation of tolvaptan, serum sodium concentrations will be assessed at 24 (± 4) hours and at 7 (+ 1) days post-last dose.	month. 5) A blood sample for serum sodium testing should be taken at each visit. 6) Tolvaptan dispensed the previous week will be returned for accountability. 7) Tolvaptan will be administered. 8) Sufficient tolvaptan will be dispensed for subjects that are outpatients for QD dosing until their next scheduled visit. Subjects and their parents/legal guardians will be instructed to return any remaining tolvaptan at the next visit for dose reconciliation. 9) If a PK sample has not been taken at the end of the Treatment Cycle Month 2 visits, a single PK blood sample will be collected after 8 consecutive weeks of tolvaptan dosing for the determination of tolvaptan and metabolites plasma concentrations. 10) Concomitant medications will be recorded. 11) Adverse events will be assessed. Tolvaptan treatment cycles may be repeated per a subject's clinical need and the discretion of the investigator. Subjects may be evaluated for continued need for tolvaptan treatment at additional clinical trial site visits per the investigator's discretion. After discontinuation of tolvaptan, serum sodium concentrations will be assessed at 24 (± 4) hours and at 7 (+ 1) days post-last dose. Subjects who elect to opt out of treatment within a treatment cycle should immediately proceed to the Follow-up Phase.
3.7.3.2.11.1 First Follow-up: 24 (± 4) hours post-last dose:	3) A serum or urine pregnancy test will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started (if not done within the last 30 days).	3) A pregnancy test will be performed on female subjects ≥ 12 years of age and female subjects < 12 years of age if menstruation has started (if not done within the last 30 days).

Location	Old Text	Updated Text
3.7.4.1.1 Pretreatment Baseline Visit:	All subjects should have blood samples collected for serum sodium assessment at the baseline visit or transferred from the last visit of the previous trial. Within 48 hours prior to tolvaptan administration, 2 blood samples will be collected at least 12 hours apart for assessment of baseline serum sodium to determine subject eligibility for tolvaptan treatment. A third serum sodium sample should be drawn within 2 to 4 hours prior to dosing; the results must be verified to be < 130 mEq/L (mmol/L) prior to the first dose in each treatment cycle.	All subjects should have blood samples collected for serum sodium assessment at a prior visitor transferred from the last visit of the previous trial. Within 48 hours prior to tolvaptan administration, 2 blood samples will be collected at least 12 hours apart for assessment of baseline serum sodium to determine subject eligibility for tolvaptan treatment. A third serum sodium sample (STAT) should be drawn within 2 to 4 hours prior to dosing; the results must be verified to be < 130 mEq/L (mmol/L) prior to the first dose in each treatment cycle.
3.7.4.1.2 Initial Titration Phase and Month 1:	During the Titration Phase (the first 30 days of treatment) subjects should have serum sodium assessments at a minimum of QD on Day 1 up to Day 4 of treatment, and at a minimum of once weekly thereafter (ie, on Days 7, 14, 21, and 28 of Month 1). On Day 1, a serum sodium sample should be collected STAT and recorded in the CRF at a minimum of 8 hours post-first dose and 24 (± 4) hours post-previous dose.	During the Titration Phase (the first 30 days of treatment) subjects should have serum sodium assessments at a minimum of QD on Day 1 up to Day 4 of treatment, and at a minimum of once weekly thereafter (ie, on Days 7, 14, 21, and 28 of Month 1). On Day 1, a serum sodium sample should be collected STAT and recorded in the CRF at a minimum of 8 hours post-first dose and 24 (± 4) hours post-previous dose. 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).
3.7.4.2 Quality of Life AssessmentsL	The assessment time points are at Baseline, Month 2, Month 4, and at Month 6 or Early Termination during the	The assessment time points during the Core Safety Follow-up Component are at Baseline, Month 2, Month 4, and at Month 6 or Early Termination.

Location	Old Text	Updated Text
	Core Safety Follow-up Component.	
3.7.5.2 Clinical Laboratory Tests: Core Safety Follow-up Component:	For all subjects enrolled in the core safety follow-up component, serum sodium assessments and LFTs will either be performed at baseline or transferred from the last visit of the previous trial. At Months 2, 4, and 6, serum sodium will be assessed. At Month 2 or at ET, if ET occurs before the Month 2 Visit, ALT, AST, and BT will be measured. No further laboratory assessments are required per protocol except as needed for the follow-up of AEs.	For all subjects enrolled in the core safety follow-up component, LFT assessments will either be performed at baseline or transferred from the last visit of the previous trial, as long as not more than 1 month prior to previous trial. Serum sodium assessment is required during the baseline visit in the Core Safety Follow-up Component. At Months 2, 4, and 6, serum sodium will be assessed. At Month 2 or at ET, if ET occurs before the Month 2 Visit, ALT, AST, and BT will be measured. No further laboratory assessments are required per protocol except as needed for the follow-up of AEs.
3.7.5.3 Clinical Laboratory Tests: Optional Tolvaptan Treatment Component:	If these results are to be obtained as part of the standard of care for the subject, the timing should be coordinated per the schedule of assessments (Section 3.7.3), whenever possible, to minimize the number of blood draws for the subject **while at the same time ensuring that liver function tests are monitored on a monthly basis while continuing treatment with tolvaptan.**	If these results are to be obtained as part of the standard of care for the subject, the timing should be coordinated per the schedule of assessments (Section 3.7.3), whenever possible, to minimize the number of blood draws for the subject **while at the same time ensuring that liver function tests are monitored on a monthly basis while continuing treatment with tolvaptan.** For the schedule of laboratory assessments, please refer to Appendix 6.
Table 3.7.5.3-1:	Clinical Laboratory Tests During Tolvaptan Treatment	Clinical Laboratory Tests During Optional Tolvaptan Treatment
3.7.5.5 Tanner Staging:	The collection of Tanner Staging data is required for all subjects in the core safety follow-up component at the Month 6 Visit. Every attempt should be made to collect this information. ...A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging.	The collection of Tanner Staging data is required for all subjects in the core safety follow-up component at the baseline and the Month 6 Visit. Every attempt should be made to collect this information. ...A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging and the same stage will be carried forward to any subsequent visits.
3.7.5.6 Hyponatremia	Each subject's hyponatremia medical history will be recorded at baseline. The hyponatremia history should	Each subject's hyponatremia medical history will be recorded at the baseline visit of the core safety follow-up component as well as at the pre-

Location	Old Text	Updated Text
History:	include the etiology of subject's hyponatremia (including tests per protocol) and what treatment was administered before trial enrollment. Symptoms potentially attributable to hyponatremia should be specifically assessed for prior history. The hyponatremia assessment at baseline will consist of documentation of hyponatremia etiology (eg, SIADH, hepatocellular disease [including cirrhosis], heart failure, or 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.	treatment baseline visit of the optional tolvaptan component. The hyponatremia history should include the etiology of subject's hyponatremia (including tests per protocol) and what treatment was administered before trial enrollment. Symptoms potentially attributable to hyponatremia should be specifically assessed for prior history. The hyponatremia assessment at baseline will consist of documentation of hyponatremia etiology (eg, SIADH, hepatocellular disease [including cirrhosis], heart failure, or 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.
3.7.6.1 Blood Collection Times:	For subjects undergoing treatment with tolvaptan for at least 8 consecutive weeks for each initiation or reinitiation of therapy, a single blood sample to measure tolvaptan and metabolite concentrations at steady state will be obtained for each cycle. The date and time of the PK sample and the date and time of the dose given immediately prior to the PK sample will be recorded on the CRFs. For each subject all samples will be collected according to local guidelines and best practices for pediatric care. If a sample is missing because of limitations in allowable blood volumes based on local regulations or local practice this will not count as a protocol deviation.	For subjects undergoing treatment with tolvaptan for at least 8 consecutive weeks (short interruptions of < 72 hours is still considered consecutive treatment) for each initiation or reinitiation of therapy, a single blood sample to measure tolvaptan and metabolite concentrations at steady state will be obtained for each cycle. The date and time of the PK sample and the date and time of the dose given immediately prior to the PK sample will be recorded on the CRFs. For each subject all samples will be collected according to local guidelines and best practices for pediatric care.
3.7.9 Independent Data Monitoring Committee:	New section for this amendment	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

Location	Old Text	Updated Text
		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.
3.8.3 Individual Subject:	...In addition, subjects on tolvaptan treatment who meet the following criteria should have results confirmed with a repeat test. ...If subjects consent, the investigator will continue to contact those who discontinue tolvaptan every 3 months through the final completion date of the trial or thereafter if needed to determine outcomes ie, vital status.	...In addition, subjects on tolvaptan treatment who meet the following criteria should have results confirmed with a repeat test. Sodium tests should be done either STAT or through bedside monitoring. ...If subjects consent, the investigator will continue to contact those who stop tolvaptan treatment and those who complete the Core Safety Follow-up Component every 3 months through the final completion date of the trial or thereafter if needed to determine outcomes ie, vital status. ...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 (Core Safety Follow-up Component and Optional Treatment Component, as applicable), or to discontinue trial visits in the Core Safety Follow-up Component while still allowing for telephone contacts, or (if enrolled in the Optional Treatment Component) to withdraw from IMP while still continuing in the Core Safety Follow-up Component.
3.8.3 Individual Subject:	The investigator will notify the sponsor promptly when a subject is withdrawn.	The investigator will notify the sponsor promptly when a subject is withdrawn. If subjects consent, the investigator will continue to contact those who discontinue tolvaptan every 3 months through the final completion date of the trial or thereafter if needed to determine outcomes ie, vital status.

Location	Old Text	Updated Text
3.10 Definition of Completed Subjects:	...Any visits beyond the Month 6 Visit will be considered "follow-up" visits for the purpose of evaluating safety and efficacy for those subjects who require treatment with tolvaptan. Prior to the end of the trial, each subject's final visit should be documented, including the date of the last dose and the number of treatment cycles.	...Any visits beyond the Month 6 Visit will be considered "follow-up" visits for the purpose of evaluating safety and efficacy for those subjects who require treatment with tolvaptan and safety for those subjects who do not receive treatment. Upon the sponsor's decision to terminate the trial, each subject's final visit should be documented, including the date of the last dose and the number of treatment cycles. The core safety follow-up component of the trial is expected to continue until all enrolled subjects from Trials 156-08-276, 156-13-207, or 156-12-205 have been followed for 6 months. For subjects in the optional tolvaptan treatment component, the length of participation for each individual subject will vary depending on duration of treatment required and the need for repeated treatments. The opportunity to participate in the Optional Tolvaptan Treatment Component is planned to remain open until the last subject completes the Core Safety Follow-up Component.
4.1 Prohibited Medications:	...Since tolvaptan is a weak CYP3A4 substrate, subjects weighing ≥ 20 kg and taking moderate inhibitors of CYP3A4 will be administered a half-dose of tolvaptan.	...Since tolvaptan is a sensitive CYP3A4 substrate, subjects weighing ≥ 20 kg and taking moderate inhibitors of CYP3A4 will be administered a half-dose of tolvaptan.
4.2 Other Restrictions:	The use of saline in this population should be closely monitored. The use of hypertonic saline (3% or greater) within 8 hours of the initial screening laboratory collection prior to tolvaptan treatment is prohibited. The use of hypertonic saline (3% or greater) is *highly discouraged* during tolvaptan treatment. Please see Section 4.1 for the list of prohibited medications during tolvaptan treatment. The use of normal saline (0.9%) is allowed during the Pretreatment baseline Period until the beginning of	The use of saline in this population should be closely monitored. The use of hypertonic saline (3% or greater) within 8 hours of the initial screening laboratory collection prior to tolvaptan treatment 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. Please see Section 4.1 for the list of

Location	Old Text	Updated Text
	treatment; normal saline use can resume during the follow-up period. 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.	prohibited medications during tolvaptan treatment. The use of normal saline (0.9%) is allowed during the Pretreatment baseline Period until the beginning of treatment; normal saline use can resume during the follow-up period. 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.
5.4.1.1 Criteria for Discontinuation From the Optional Tolvaptan Treatment Component of the Trial due to Liver Transaminase Elevations:	...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 it.	...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 treatment options.
5.5 Pregnancy:	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	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 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

Location	Old Text	Updated Text
	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 vasectomy and tubal ligation, may fail, leading to pregnancy. 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: • 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 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. During the trial, all female subjects of childbearing	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), 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 with spermicide, or sponge with spermicide. 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 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

Location	Old Text	Updated Text
	potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). If a subject or investigator suspects that the subject may be 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. (Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the trial medical monitor.) 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. Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray trials). Other	parent/guardian. A urine and/or serum pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening on all WOCBPand female subjects ≥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 the Clinical Safety and Pharmacovigilance department [see Appendix 1 for contact information]) The investigator must immediately notify the sponsor 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 the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Location	Old Text	Updated Text
	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.	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.
9.1 Source Documents:	...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.	...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:	• Documentation of the informed consent process, including any revised consents; • 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, and duration of any AEs and the investigator's assessment of relationship to tolvaptan 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 all clinicians who made an entry in the progress notes.	• 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 tolvaptan 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 tolvaptan 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.

Location	Old Text	Updated Text
	...Changes will be made by striking a single line through erroneous 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.	...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.
9.3 File Management at the Trial Site:	The investigator will ensure that the trial center file is maintained in accordance with Section 8 of the ICH Guideline for GCP 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 and as required by applicable local regulations.
9.4 Records Retention at the Trial Site:	• A period of at least 2 years following the date on which approval to market the drug is obtained (or if tolvaptan development is discontinued, the date of discontinuation); OR ...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.	• A period of at least 2 years following the date on which approval to market the drug is obtained (or if tolvaptan development is discontinued, the date regulatory authorities were notified of discontinuation); OR ...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.
10.1 Monitoring:	The sponsor has ethical, legal, and scientific obligations to follow this trial carefully 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	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

Location	Old Text	Updated Text
	telephone and written communications.	and ongoing training for this particular trial, and this training will be clearly documented.
10.2 Auditing:	The sponsor's Quality Management Unit (or representative) may conduct trial site audits. Audits will include but are not 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 limited to, drug supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents.
11 Ethics and Responsibility:	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, the ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Sciences (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.
12 Confidentiality:	...However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All supplies of tolvaptan, 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 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.	...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 supplies of tolvaptan, 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 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.

Location	Old Text	Updated Text
13 Amendment Policy:	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 the tolvaptan tablets 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. 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.	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 the tolvaptan tablets 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	New section for this amendment	

Location	Old Text	Updated Text
Requirements:		
Appendix 2:	**Medical Monitor:** PPD PPD INC Research 580 Union Square Drive New Hope, Pennsylvania 18938 US Phone PPD Mobile PPD E-Mail PPD	**Medical Monitor:** PPD PPD 3210 Beechleaf Ct., Suite 600 Raleigh, North Carolina 27604, USA Phone PPD Mobile PPD Fax: PPD E-Mail: PPD
Appendix 2:	New contact information added with this amendment.	**IDMC Support** Theorem Clinical Research 1016 West Ninth Avenue King of Prussia, PA, 19406, USA Phone: PPD Fax: PPD

Old Text: Appendix 5 Optional Tolvaptan Treatment Component: Eligibility Criteria

Subjects will be eligible for tolvaptan treatment if they meet the criteria outlined in the table below.

Eligibility Criteria for Optional Tolvaptan Treatment	
1.	Male or female subjects ≥ 4 weeks (or ≥ 44 weeks adjusted gestational age) to < 18 years old
2.	The subject must have been off treatment with the investigational medicinal product (IMP) for 7 days following the end of treatment in the previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) to assess the subject's clinical need for dosing
3.	Persistent dilutional (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 to 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 the pretreatment baseline for this trial 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 tolvaptan for sexually active females of childbearing potential

Subjects will be ineligible for tolvaptan treatment if they meet any of the following criteria:

Ineligibility Criteria for Tolvaptan Treatment	
25.	Subjects < 2 years of age, weight <10 kg, or who cannot swallow an oral tablet are excluded until an oral liquid formulation becomes available

New Text: Appendix 5 Optional Tolvaptan Treatment Component: Eligibility Criteria

Subjects will be eligible for tolvaptan treatment if they meet the criteria outlined in the table below.

Eligibility Criteria for Optional Tolvaptan Treatment	
1.	Male or female subjects ≥ 4 weeks (or ≥ 44 weeks adjusted gestational age)
2.	The subject must have been off treatment with the investigational medicinal product (IMP) for at least 7 days following the end of treatment in the previous trial of titrated oral IMP (tolvaptan in Trial 156-08-276, tolvaptan or placebo in Trials 156-13-207 and 156-12-205) to assess the subject's clinical need for dosing
3.	Persistent dilutional (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 to 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 the pretreatment baseline for this trial 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 tolvaptan for sexually active females of childbearing potential

Ineligibility Criteria for Tolvaptan Treatment	
25.	Subjects < 2 years of age, weight < 10 kg, or who cannot swallow an oral tablet are excluded until an alternate formulation becomes available

Old Text: Appendix 6 Optional Tolvaptan Treatment Component: Laboratory Assessment Schedule

Frequency of Recurring Laboratory Assessments			
Treatment Phase	**Serum Sodium**	**LFTs (ALT, AST, BT)**	**PK[a]**
Pretreatment Baseline doses	Day -1 to Day -4: assessments ≤ 130 mEqL (mmol/L) ≥ 12 hours apart		
Month 1: Titration[b]	Once daily		
Month 6, End of Treatment or Early Termination	24 (±4) hours and 7 (±1) days		

New Text: Appendix 6 Optional Tolvaptan Treatment Component: Laboratory Assessment Schedule

Frequency of Recurring Laboratory Assessments			
Treatment Phase	**Serum Sodium**	**LFTs (ALT, AST, BT)**	**PK[a]**
Pretreatment Baseline doses	Day -1 to Day -4: assessments ≤ 130 mEqL (mmol/L) ≥ 12 hours apart	Required at Baseline if not done within the previous month	
Month 1: Titration[b]	Once daily efficacy assessment and additional safety assessments 4 to 6 hours and 18 hours postdose		
Post-last dose Follow-up each cycle	24 (±4) hours and 7 (±1) days		

Location	Old Text	Updated Text
Agreement:	...and in the sponsor's (or designee's) Clinical Research Agreement. ...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). ...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. ...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	...and in the sponsor's (or designee's) Clinical Trial Agreement. ...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 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 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. _____ Principal Investigator

	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. _____ Principal or Coordinating Investigator Signature and Date _____ Sponsor Representative Signature and Date	_____ Print Name _____ Signature _____ Date

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

Amendment Number: 3
Issue Date: 9 November 2015

PURPOSE:

The main intent of the amendment is to streamline text within the protocol by providing administrative clarifications, removing duplicative language, and ensuring consistency across sections. Efficiencies have been established in the Schedule of Assessments between the core safety and optional tolvaptan treatment components. This amendment is also intended to reduce burden on the subject, including the replacement of Months 2 and 4 in-clinic visits with telephone assessments. Therefore assessments required for in-clinic visits on these months have been removed.

BACKGROUND

This is a pediatric trial required by the EMA under the Pediatric Investigational Plan (PIP). The changes implemented within this protocol amendment continue to address the key binding elements of the PIP.

GENERAL CHANGES:

Description of Change	Rationale for Change	Sections Affected by Change
General Changes		
Removed study-specific parent trial numbers in the eligibility criteria for optional tolvaptan treatment to generalize the enrollment criteria from previous tolvaptan pediatric trials for hyponatremia.	To generalize trial entry criteria.	Synopsis, Section 2 (Trial Rationale and Objectives), Section 2.3 (Trial Objectives), Section 3.1.1 (Core Safety Follow-up Component), Section 3.3.1 (Core Safety Follow-up Component), Section 3.4.1 ((Informed Consent/Assent), Section 3.4.2 (Inclusion Criteria), Section 3.7.1 (Core Safety Follow-up Component), Table 3.7.1-1 (Core Safety Follow-up Component - Schedule of Assessments for All Subjects), Section 3.7.2 (Optional Tolvaptan Treatment Component), Section 3.7.3.1.1 (Baseline), Section 3.10 (Definition of Completed Subjects), Section 7.1 (Sample Size)
Added percentage of subjects who have recurrence of hyponatremia while on tolvaptan as a secondary efficacy endpoint	To align with Pediatric Investigational Plan requirements.	Synopsis, Section 3.5.2.1
Reduced the sample size from approximately 140 to approximately 100 male or female subjects.	EMA required safety follow-up data for at least 100 subjects.	Synopsis, Section 3.3.1 (Core Safety Follow-up Component), Section 7.1 (Sample Size)
Removed Tanner Staging analysis method	Tanner Staging will not be analyzed using the Cochran-Mantel-Haenszel row mean scores differ test controlling for subjects.	Synopsis, Section 7.4.2
Updated protocol with trial data, exposure, and references from IB edition 21.	Updated with current information on Health Canada and EMA approvals for tolvaptan in ADPKD, on updated tolvaptan exposure and reference information.	Section 1 (Introduction)
Updated safety outcome variables applicable in core safety component to indicate that they apply to all subjects.	All subjects participating in this trial will be evaluated for safety, as the optional tolvaptan treatment component is a subgroup of the core safety component. It was preferred not to differentiate this component.	Section 3.5 (Outcome Variables), Section 7.4 (Primary and Secondary Outcome Analysis)
Removed exploratory outcomes related to neurocognitive battery assessments.	There was no requirement in the Pediatric Investigational Plan to conduct neurocognitive assessments. They were therefore removed.	Section 3.5.3 (Exploratory Variables), Section 7.4.3 (Exploratory Outcome Analyses)

Description of Change	Rationale for Change	Sections Affected by Change
Replaced trial tolvaptan references to IMP, where applicable.	In Amendment #2, there were references to tolvaptan rather than IMP. However, to differentiate between commercial use of tolvaptan, IMP will be referenced in this trial.	Throughout protocol.
Updated adverse events reporting protocol language.	AE wording revised to match current protocol template language	Section 5.1 (Definitions)
Updated SAE reporting guidelines related to hospitalization.	SAE wording revised to match current protocol template language	Section 5.1 (Definitions)
Updated IRE reporting guidelines related to potential drug induced liver injury cases.	The protocol template has been updated to no longer isolate Hy's Law cases for IRE reporting. Potential DILIs must be reported as an IRE.	Section 5.4 (Potential Drug-induced Liver Injury)
Updated Trial Design Schematic	To align with changes made to the Schedule of Assessments.	Figure 3.1-1
Core Safety Follow-up Component Changes		
Modified the requirements for in-clinic visits vs. telephone assessments for each of the visits in the 6 month core safety component.	To reduce subject burden, several of the clinic visits were replaced by telephone visits. Subsequently, in-clinic visits were removed from the Month 2 and Month 4 visits.	Synopsis, Figure 3.1-1 (Trial Design Schematic), Section 3.1.1 (Core Safety Follow-up Component), Section 3.7.1 (Core Safety Follow-up Component), Table 3.7.1-1 (Core Safety Follow-up Component - Schedule of Asessments for All Subjects), Section 3.7.3.1 (Core Safety Follow-up Component)
Clarified which assessments and time points from the previous tolvaptan trial will serve as baseline assessments.	To reduce subject burden, assessment data could be applied from the previous trial if they were performed within 30 days of baseline.	Section 3.1.1 (Core Safety Follow-up Component), Section 3.7.1 (Core Safety Follow-up Component), Table 3.7.1-1 (Core Safety Follow-up Component - Schedule of Assessments for All Subjects), Section 3.7.3.1.1 (Baseline)
Clarified that subjects who do not enroll directly from the parent trial into Trial 156-11-294 will still be eligible to enroll.	Amendment 2 was not clear about whether there could be a lapse between the parent trial and enrollment into this trial. Further clarification was provided that allowed a lapse to occur.	Synopsis, Section 3.1.1 (Core Safety Follow-up Component), Section 3.7.1 (Core Safety Follow-up Component)
Clarified requirements for a full versus directed physical examination and neurological examination. Added a fontanelle assessment as age appropriate.	To reduce subject burden while evaluating examination requirements with any lapse between the previous tolvaptan trial.	Table 3.7.1-1 (Core Safety Follow-up Component - Schedule of Assessments), Section 3.7.3.1.1 (Baseline), Section 3.7.3.1.3 (Month 6/Early Termination), Section 3.7.5.4 (Physical Examination and Vital Sign Assessments)

Description of Change	Rationale for Change	Sections Affected by Change
Removed Neurocognitive Assessments.	There was no requirement in the Pediatric Investigational Plan to conduct neurocognitive assessments so they were deleted from the protocol.	Table 3.7.1-1 (Core Safety Follow-up Component: Schedule of Assessments for All Subjects), Section 3.7.3.1.1 (Baseline), Section 3.7.3.1.3 (Months 2, 4 and 6/Early Termination), Section 3.7.7 (Exploratory Assessments).
Clarified timepoint to obtain consent and assent prior to conducting trial-level procedures.	In amendment 2, allowance was given to obtain the ICF/assent in the parent trial in advance of the rollover trial participation. Given that the ICF/assent is a baseline assessment, it is more appropriate to obtain it at this timepoint.	Section 3.4.1 (Informed Consent/Assent)
Summarized required laboratory tests in Table 3.7.5.2-1.	For ease of site use, this was added to the protocol.	Table 3.7.5.2-1.
Removed collection of serum sodium as a safety variable in the core safety follow-up population.	To reduce subject burden.	Synopsis, Section 3.5.2.2 (Safety Variables), Table 3.7.1-1 (Core Safety Follow-up Component - Schedule of Assessments for All Subjects), Section 7.4.2 (Secondary Outcome Variables)
Clarified liver function test collection requirements at baseline, Month 1 and Month 2.	For ease of site use, this was clarified in the protocol.	Figure 3.1-1 (Trial Design Schematic), Section 3.1.1 (Core Safety Follow-up Component), Section 3.7.1 (Core Safety Follow-up Component), Section 3.7.5 (Safety Assessments)
Added vital status assessment at Month 6 for subjects who discontinue the trial but consent to continued telephone contact.	To make every attempt to verify safety of patients who participate in this protocol throughout the duration of their expected participation at 6 months	Section 3.7.1-1 (Core Safety Follow-up Component - Schedule of Assessments for All Subjects), Section 3.7.3 (Schedule of Assessments), Section 3.7.3.1.3 (Month 6/Early Termination)
Remove hyponatremia history at Month 6.	Not applicable.	Table 3.7.1-1, Section 3.7.3.1.3.
Optional Tolvaptan Treatment Component Changes		
Limited optional tolvaptan treatment up to a maximum of 6 months participation in the core safety component.	In amendment 2, the optional treatment was indefinate. The protocol has been updated to provide a finite timepoint, the duration not to exceed the core safety Month 6 visit.	Synopsis, Section 2.1.2 (Optional Tolvaptan Treatment Component), Section 3.1.2 (Optional Tolvaptan Treatment Component)
Updated eligibility criteria of optional tolvaptan treatment #1.	Due to unavailability of an age appropriate formulation, the entrance criteria for the lower age groups is being modified to allow subjects ≥ 4 years of age (or per local Health Authority age restrictions) and ≥ 10 kg.	Appendix 5, Section 3.2.1.2.

Description of Change	Rationale for Change	Sections Affected by Change
Updated eligibility criteria of optional tolvaptan treatment #2	Clarify that the clinical need for optional tolvaptan dosing is not contingent for general trial enrollment.	Appendix 5
Updated eligibility criteria of optional tolvaptan treatment #4.	Modification made for ability to swallow tablets due to unavailability of an age appropriate formulation.	Appendix 5
Updated ineligibility criteria for tolvaptan treatment #17.	Removed IRE form completion requirement due to change in IRE definition.	Appendic 5
Updated ineligibility criteria for tolvaptan treatment #18.	Clarified entry requirement related to cirrhosis.	Appendix 5
Updated ineligibility criteria for tolvaptan treatment #24.	Removed specific drug trial numbers to make more general.	Appendix 5
Updated ineligibility criteria for tolvaptan treatment #25.	Due to unavailability of an age appropriate formulation, the ineligibility criteria was modified to exclude subjects < 4 years of age (or per local Health Authority age restrictions), weight < 10 kg and who are unable to swallow tablets.	Appendix 5
Specified that the optional tolvaptan treatment component objective duration is up to 6 months.	In amendment 2, the optional treatment was indefinate. The protocol has been updated to provide a finite timepoint, the duration not to exceed the core safety Month 6 visit.	Synopsis, Section 2.3 (Trial Objectives)
Provided guidelines regarding how to proceed with the treatment interruption period on Days 31 – 34.	In amendment 2, the optional tolvaptan treatment dosing interruption period, days 31-32 included - 1 day visit window. However, many logistical questions were raised, particularly with the IWRS and the mandatory requirement to reinitiate treatment after 72 hours off treatment. Therefore, in this amendment, the visit windows were removed during the interruption period.	Figure 3.1-1 (Trial Design Schematic), Table 3.7.2-1 (Schedule of Assessments for Each Treatment Cycle), Section 3.7.3.2 (Optional Tolvaptan Treatment Component)
Clarified that a new treatment cycle is required if a subject is off tolvaptan treatment for ≥ 72 hours.	In this amendment, subjects who have been off tolvaptan for ≥ 72 hours are required to retitrate in a hospital setting, rather than > 72 hours as in the previous version.	Synopsis, Section 3.1.2 (Optional Tolvaptan Treatment Component), Section 3.2.1 (Optional Tolvaptan Treatment Component), Table 3.7.2-1 (Schedule of Assessments for Each Treatment Cycle), Section 3.7.3.2.4.3 (Day 33)

Description of Change	Rationale for Change	Sections Affected by Change
Removed Table 3.2.2-1.	To streamline the dosing section, the table was removed since this information was provided elsewhere in the protocol.	Table 3.2.2-1
Added trial day numbers associated with Month 2+ visits to further clarify time point data collection.	The trial day numbers are clarified in Sections 3.7.3.2.5 and 3.7.3.2.6, and in the Schedule of Assessments.	Section 3.7.3.2.5 (Treatment Cycle Month 2), Section 3.7.3.2.6 (Maintenance Phase), Table 3.7.2-1 (Schedule of Assessments for Each Treatment Cycle)
Clarified urine vs. serum pregnancy test requirements.	In amendment 2, there was no clear specification of whether the pregnancy test would be assessed from urine or serum. This is clarified in the Schedule of Assessments and Section 5.5 that the investigator can chose either one, as long as a serum pregnancy test is done if the urine pregnancy is positive.	Section 5.5 (Pregnancy), Table 3.7.2-1 (Schedule of Assessments for Each Treatment Cycle)
Added serum creatinine assessment as a safety variable	Additional safety monitoring of the subjects	Section 3.5.2.2 (Safety Variables), Table 3.7.2-1 (Schedule of Assessments for Each Treatment Cycle), Section 3.7.3.2.1 (Pretreatment Baseline Visit), Section 3.7.3.2.4 (Day 30 Interruption (± 1) Days Post-first Dose, Section 3.7.3.2.5 (Treatment Cycle Month), Section 3.7.3.2.6.1 (Treatment Cycle Month 3), Section 3.7.3.2.7.1 (First Follow-up: 24 (± 4) hours Post last Dose) , Table 3.7.5.3-1 (Clinical Laboratory Tests During Optional Tolvaptan Treatment), Section 7.4.2 (Secondary Outcome Measures).
Clarified that initial dosing should be given and all titrations should occur in a hospital setting.	Additional wording was added to clarify these requirements.	Synopsis, Section 3.1.2.1 (Treatment Interruption on Day 30), Section 3.2.1.2 (Titration Guidelines for the Optional Tolvlaptan Treatment Component)
Added table for serum sodium assessments for efficacy and safety (supplemental)	For ease of site use, this was added to the protocol.	Table 3.7.4.1.2-1 (Serum Sodium Assessments During the Optional Tolvaptan Component)
Clarified requirements for a full versus directed physical examination and neurological examination. Added a fontanelle assessment as age appropriate.	Provide further clarity to the examination requirements during the treatment cycle and giving the investigator the option to complete a neurological examination if there are any positive findings on the clinical status assessment.	Table 3.7.2-1, Section 3.7.3, and 3.7.5.4, Section 3.7.5.5

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 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.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

Otsuka Pharmaceutical Development & Commercialization, Inc.
This page is a manifestation of an electronically captured signature

OPC-41061

SIGNATURE PAGE

Document Name: Protocol 156-11-294 Amendment 3

Document Number: 0000835721

Document Version: 8.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Clinical Pharmacology	10-Nov-2015 14:24 GMT+00
	Clinical Approval	10-Nov-2015 16:10 GMT+00
	Biostatistics Approval	10-Nov-2015 16:33 GMT+00