- **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: 2.0**
- **Date of the document: 19 October 2017**
- **NCT number: NCT02020278**

Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational New Drug

OPC-41061

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

Statistical Analysis Plan

Date: 19 Oct 2017

Protocol: 31 Oct 2013
Protocol Amendment 1: 05 Sep 2014
Protocol Amendment 2: 26 Feb 2015
Protocol Amendment 3: 09 Nov 2015

Table of Contents

1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of efficacy and safety data of Trial 156-11-294. All amendments to the protocol are taken into consideration in developing this SAP.

2 Trial Objective

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

This trial consists of 2 components, a 6-month safety follow-up trial, and an embedded optional tolvaptan treatment trial for eligible subjects.

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.

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 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.

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.

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

4 Sample Size and Power Justification

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

5 Statistical Methods

5.1 Efficacy Analysis

Due to the early termination status, not all planned analyses will be provided due to lack of data. For an example, no subject received optional Tolvaptan treatment, the efficacy analyses specified in the SAP will not be applied to Optional Tolvaptan Treatment Component.

5.1.1 Data Sets Analyzed

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.

5.1.2 Handling of Missing Data

The primary dataset for efficacy analyses will be the observed cases (OC) dataset. The OC dataset will consist of the actual observations recorded at each visit so that no imputation of missing values will be made.

5.1.3 Baseline Characteristics and Baseline Comparability

Demographic characteristics and medical history at baseline will be summarized by descriptive statistics, e.g., proportion, mean, median, standard deviation(SD), minimum and maximum values.

Baseline characteristics by age categories ($\geq$ 4 weeks to < 4 years, $\geq$ 4 years to < 8 years, $\geq$ 8 years to < 12 years, $\geq$ 12 years to < 18 years) will also be provided. Baseline characteristics by underlying etiology (heart failure, hepatocellular disease, syndrome of inappropriate antidiuretic hormone secretion (SIADH) or other diseases) will be provided as well.

5.1.4 Treatment Compliance

For subjects participating in the Optional Tolvaptan Treatment Component, treatment compliance will be calculated for each cycle by dividing the total dosage taken during the cycle by the total dosage the subjects are scheduled to take during the cycle based on the Study Medication panel of the case report form (CRF). The overall treatment compliance across cycles will be provided

5.1.5 Protocol Deviations

Protocol deviations data will be summarized by type of deviations (e.g., deviations in entry criteria, dosing, concomitant medication, procedural, etc.) by center and treatment group. In addition, a subject listing will be provided describing the deviations for each subject.

5.1.6 Primary Outcome Analyses

5.1.6.1 Analysis of Primary Outcome Endpoint

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. The descriptive statistics will be provided for the primary endpoint.

The primary endpoint will be analyzed by age groups ($\geq$ 4 weeks to < 4 years, $\geq$ 4 years to < 8 years, $\geq$ 8 years to < 12 years, $\geq$ 12 years to < 18 years).

5.1.6.2 Technical Computational Details for Primary Outcome Analysis

1) Baseline for the primary endpoint is the last evaluation of serum sodium prior to the first dose at each cycle in the Optional Tolvaptan Treatment Component.
2) For safety purpose, additional unscheduled serum sodium between scheduled efficacy endpoints may be collected measured in the local hospital labs. These assessments of serum sodium will not be included in the primary efficacy analysis.
3) The primary analysis will be only performed on the Optional Treatment Efficacy Sample.

5.1.7 Secondary Outcome Analysis

5.1.7.1 Analyses of Secondary Outcome Variables

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 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

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
- 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.

5.1.7.2 Technical Computational Details for the Analysis of the Secondary Endpoints

1) Baseline for the continuous secondary endpoints of the subjects receiving tolvaptan in the Optional Tolvaptan Treatment Component is the last evaluation prior to the first dose at each cycle in the Optional Tolvaptan Treatment Component. This applies to ALT, AST and BT.
2) Baseline for the continuous secondary endpoints except QoL and serum sodium of the subjects participating in the Core Safety Follow-up Component is the last evaluations from the previous trial , if the last evaluation was done in previous trials within one month of this trial starts. If more than one month passes between trials, the baseline will be the evaluations at the baseline visit of this trial.

   The baseline for QoL and serum sodium of the subjects in the Core Safety Follow-up Component is the evaluations at the baseline visit.
3) The QoL assessment includes the PedsQL Generic Core Scale (QoL GCS) and PedsQL Multidimensional Fatigue Scale (QoL MFS). For the QoL GCS, the change from baseline in QoL GCS total score, physical health summary score, and psychosocial health summary score will be analyzed using the descriptive statistics. For the QoL MFS, the QoL MFS total score will be analyzed using the descriptive statistics.
4) The QoL GCS scale consists of 23 items encompassing physical, emotional, social, and school domains.

   For ease of interpretability, items are reversed scored and linearly transformed to a 0-100 scale, so that higher scores indicate better HRQOL (Health-Related Quality of Life).

To reverse score, transform the 0-4 scale items to 0-100 as follows: 0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0.

To create scale scores, the mean is computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the scale scores should not be computed. If 50% or more items are completed, then impute missing scores by the mean of the completed items in a scale.

To create the Psychosocial Health Summary Score, the mean is computed as the sum of the items divided by the number of items answered in the Emotional, Social, and School Functioning Scales. The Physical Health Summary Score is the same as the Physical Functioning Scale Score.

To create the total scale score, the mean is computed as the sum of all the items divided by the number of items answered on all the scales.

Child self-reported data for subjects with age ≥ 5 years will be used in the analysis, while for subjects with age < 4 years, parent-reported data will be used.

5) The QoL MFS scale consists of 18 items in 3 subscales: general fatigue, sleep/rest fatigue, and cognitive fatigue.

Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0.

To create scale scores for each dimension, the mean is computed as the sum of the items divided by the number of items answered.

The total QoL MFS score will be calculated by summing up all the items divided by the number of items answered on all the scales.

If more than 50% of the items in the scale are missing, the scale scores should not be computed. If 50% or more items are completed, then impute missing scores by the mean of the completed items in a scale.

Child self-reported data for subjects with age ≥ 5 years will be used in the analysis, while for subjects with age < 4 years, parent-reported data will be used.

5.2 Safety Analysis

Due to the early termination status, not all planned safety analyses will be provided due to lack of data. For an example, no subject received optional Tolvaptan treatment, the safety analyses specified in the SAP will not be applied to Optional Tolvaptan Treatment Component.

Safety variables to be analyzed include adverse events (AEs), clinical laboratory data, and vital signs. In general, summary statistics will be provided for safety variables based on all available data.

Baseline of the subjects receiving tolvaptan in the Optional Tolvaptan Treatment Component is the last evaluation prior to the first dose at each cycle in the Optional Tolvaptan Treatment Component. Baseline of the subjects participating in the Core Safety Follow-up Component is the last evaluations from the previous trial (tolvaptan in Trial 156-08-276), if the last evaluation was done in previous trials within one month of this trial starts. If more than one month passes between trials, the baseline will be the evaluations at the baseline visit of this trial.

Safety analyses by age categories (≥ 4 weeks to < 4 years, ≥ 4 years to < 8 years, ≥ 8 years to < 12 years, ≥ 12 years to < 18 years) will be provided. Safety analysis by underlying etiology (heart failure, hepatocellular disease, SIADH/other) will also be provided.

5.2.1 Duration of Exposure to Trial Medication

Duration of exposure to each treatment of each subject will be summarized for subjects who enrolled in Optional Tolvaptan Treatment Component. A subject's duration of exposure is defined as the trial medication end date - trial medication start date + 1.

5.2.2 Adverse Events

Definitions:

- A treatment-emergent adverse event (TEAE) is an event that is observed or reported after administration of trial medication in this trial that was not present prior to trial medication administration or an event that represents the exacerbation of a pre-existing event. Exacerbation includes any event that increases in frequency or severity or becomes classified as serious after the start of treatment in this trial.
- An adverse withdrawal is a subject who withdrew from the trial due to an AE.
- A serious adverse event (SAE) is an AE that is classified as serious according to the criteria specified in the trial protocol.

The incidence of the following events will be summarized:

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

All AEs will be coded by MedDRA (Medical Dictionary for Regulatory Activities) system organ class and preferred term.

5.2.3 Laboratory Test Results

Summary statistics for the clinical laboratory measurements at baseline and post-baseline visits, and summary statistics of changes from baseline to each visit will be presented. Shift tables will be produced, assessing low-normal-high (at baseline) to low-normal-high (at post-baseline visit).

The incidence of potentially clinically significant abnormal lab results will also be summarized. Listings of potentially clinically significant abnormalities will also be provided.

According to FDA (Food and Drug Administration) Guidance,[1] laboratory measurements that signal the potential for drug-induced liver injury (DILI) will be reported. An incidence table and a listing will be provided for subjects who meet one or combinations of the following criteria:

1) ALT (alanine transaminase) or AST (aspartate transaminase) ≥ 3x upper limit of normal (ULN) (or baseline value for subjects with abnormal baseline)
2) Increase in bilirubin ≥ 2x ULN (or baseline value for subjects with abnormal baseline)

5.2.4 Vital Signs Data

Descriptive statistics will be provided for both vital signs and change from baseline in vital signs. The incidence of potentially clinically significant vital sign results will also be summarized. Listings of potentially clinically significant abnormalities will also be provided.

For a subject with repeat measures in either vital signs or lab tests at a visit, the last repeat will be used in the by visit summary. However, for outlier analysis (such as clinically significant abnormalities), data from all visits, no matter they are from the original visits, repeats, or unscheduled visits, will be included.

5.2.5 Electrocardiogram Data

Electrocardiogram (ECG) data will not be summarized since there are no trial mandated ECGs.

5.2.6 Post-baseline Concomitant Medications

Concomitant medications used post-baseline will be summarized in two categories of time interval: during the trial medication period and after the trial medication period. In each case, the use of concomitant medications will be summarized by number and percentage of users.

6 SAP References

[1] Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation. US Department of Health and Human Services, Food and Drug Administration, and Center for Drug Evaluation and Research (CDER), July 2009.

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

OPC-41061

SIGNATURE PAGE

Document Name: SAP1561129414

Document Number: 0001163416

Document Version: 2.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Clinical Approval	23-Oct-2017 16:23 GMT+00
	Biostatistics Approval	23-Oct-2017 21:09 GMT+00