- **Protocol number:** 156-08-276.
- **Document title:** A Phase 3b, Multicenter, Open-label, Randomized Withdrawal Trial of the Effects of Titrated Oral SAMSCA® (Tolvaptan) on Serum Sodium, Pharmacokinetics, and Safety in Children and Adolescent Subjects Hospitalized With Euvolemic or Hypervolemic Hyponatremia
- **Version number:** SAP Amendment 5.
- **Date of the document:** 17 Nov 2015.
- **EudraCT number:** 2013-002005-59.

Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational New Drug

OPC-41061

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

Protocol No. 156-08-276
IND No. 54,200
NDA No. 22-275
EudraCT No. 2013-002005-59

Statistical Analysis Plan

Date: 16 Aug 2017

Protocol Version 1.0: 03 Jul 2013
Protocol Amendment 01: 04 Nov 2013
Protocol Amendment 02: 19 May 2014
Protocol Amendment 03: 26 Feb 2015
Protocol Amendment 04: 07 May 2015
Protocol Amendment 05: 17 Nov 2015

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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 156-08-276. All amendments to the protocol are taken into consideration in developing this SAP.

This SAP is prepared with protocol version Amendment 5, dated 17 Nov 2015.

2 Trial Objective

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

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

3 Trial Design

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

3.1 Treatment Phase A

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

3.2 Treatment Phase B

On Day 3, responders will be randomized to either the Early Withdrawal group or the Late Withdrawal group. Subjects in the Late Withdrawal group continue tolvaptan treatment on Days 3 and 4, subjects in the Early Withdrawal group do not receive additional tolvaptan treatment on Days 3 and 4. Nonresponders will not be randomized.

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

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

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

Subjects randomized to the Early Withdrawal group will be observed to determine whether additional intervention is required to maintain appropriate serum sodium levels. Subjects whose serum sodium declines by ≥ 4 mEq/L (mmol/L) or whose overall clinical condition requires further treatment to raise serum sodium levels should be treated per local standard of care. Any intervention intended to raise serum sodium concentration during the first 48 hours of Treatment Phase B (including fluid restriction) will be defined as rescue therapy. Subjects receiving rescue therapy will be considered to have reached their clinical endpoint, and their data will be censored from that time forward.

3.3 Follow-up Phase C

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

4 Sample Size and Power Justification

4.1 Sample Size for Efficacy

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

4.2 Sample Size for Pharmacokinetic Parameters

The sample size to establish similarity between the confidence intervals (CIs) for PK parameter estimates in adults and pediatrics is based on PK data of clearance. [redacted] To be conservative, it is assumed that the coefficient of variation (CV) of clearance is 0.42. In order to establish a 95% CI within 60% and 140% of the point estimate for the geometric mean estimate of clearance in an age group (age < 10 or ≥ 10 years), under the assumption that the geometric mean estimates of clearance are equal between adult and pediatric subjects, CIs of the ratio of geometric means of pediatrics and adults will be constructed. Twenty pediatric subjects and 80 adult subjects are needed to have 90% power to establish a 95% CI of the ratio of geometric means within 0.71 and 1.40. In the actual analysis, all 81 adult subjects' data will be used.

5 Statistical Methods

5.1 Efficacy Analysis

Due to the extremely low enrollment to the trial and its early termination status, the efficacy analyses specified in the SAP do not need to be conducted in the final analysis, except providing summary statistics.

5.1.1 Data Sets Analyzed

The following samples are defined for this trial:

- Treatment Phase A Safety Sample consists of all subjects who receive at least one dose of investigational medicinal product (IMP) in Treatment Phase A of the trial.
- Treatment Phase B Safety Sample for responders consists of all randomized Late Withdrawal subjects who receive at least one dose of IMP in Treatment Phase B of the trial and all randomized Early Withdrawal subjects.
- Treatment Phase B Safety Sample for nonresponders consists of all nonresponders who receive at least one dose of IMP or standard of care in Treatment Phase B of the trial.
- Treatment Phase A Efficacy Sample consists of all subjects who are in the Treatment Phase A Safety Sample and have baseline and at least one postbaseline serum sodium evaluation in Treatment Phase A.
- Treatment Phase B Efficacy Sample for the responders is based on the intent-to-treat (ITT) principle; the full analysis dataset will be composed of all subjects who are in the Treatment Phase B Safety Sample and have both baseline and at least one postrandomization serum sodium evaluation in Treatment Phase B.

- Treatment Phase B Efficacy Sample for the nonresponders consists of all subjects who are in the Treatment Phase B Safety Sample for nonresponders and have both baseline and at least one postbaseline serum sodium evaluation in Treatment Phase B.

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

5.1.2 Handling of Missing Data

For the primary endpoint analysis, missing data will be handled by analysis of mixed-model repeated measures (MMRM) methodology under the assumption of missing at random. The MMRM analysis will be performed based on the observed cases (OC) data. In order to assess sensitivity of results due to missing data, the last observation carried forward (LOCF) analysis will be performed as a sensitivity analysis. In contrast to the OC dataset, which will consist of the actual observations recorded at each visit, the LOCF dataset will include data recorded at a scheduled visit (ie, all OC data, or, if no observation is recorded at that visit, data carried forward from the previously scheduled visit). Baseline data will not be carried forward to impute missing values for the LOCF dataset.

5.1.3 Randomization

Eligible subjects will be randomized in a 1:1 ratio to either the Early Withdrawal group or the Late Withdrawal group. Randomization will be stratified by age [redacted], serum sodium response [redacted], and underlying hyponatremia etiology [redacted].

5.1.4 Baseline Characteristics and Baseline Comparability

In general, baseline measurements of efficacy and safety variables are defined as their last measurements prior to the first dose of IMP in the corresponding phases.

Demographic characteristics and medical history at Screening will be summarized by descriptive statistics, eg, proportion, mean, median, SD, minimum and maximum values. Use of concomitant medications prior to the start of IMP will be summarized by number and percentage of users by treatment group. These summary statistics will be reviewed to identify any potential lack of balance between the treatment groups.

Baseline characteristics will be summarized for Treatment Phase A and Treatment Phase B, respectively. Baseline characteristics by age categories [redacted]

[redacted] and by disease etiology [redacted] will also be provided.

5.1.5 Treatment Compliance

Treatment compliance will be calculated by dividing the total dose taken by the total dose the subjects are scheduled to take during the trial. For the Early Withdrawal subjects, the subjects are not scheduled to take the IMP in Treatment Phase B, the compliance will be 100% for these subjects unless they accidentally take the IMP.

5.1.6 Protocol Deviations

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

5.1.7 Primary Outcome Analysis

5.1.7.1 Analysis of the Primary Outcome Endpoint

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

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

The MMRM analysis with an unstructured variance covariance structure based on the OC dataset will be performed on the primary endpoint. The MM[redacted]clude

fixed effect of treatment, age subgroup [redacted], serum sodium response subgroup [redacted], underlying etiology [redacted], visit, treatment visit interaction, and covariate of baseline and baseline visit interaction. A statistical test of the least squares (LS) mean differences between treatment groups at the end of Treatment Phase B of the MMRM analysis will serve as the primary analysis.

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

5.1.7.2 Technical Computational Details for Primary Outcome Analysis

1) Baseline for Treatment Phase B is the last evaluation of serum sodium at the end of Treatment Phase A.
2) For the Early Withdrawal group, the serum sodium collected at 72 hours post-last dose on the CRF will be used to define the endpoint of Treatment Phase B. For the Late Withdrawal group, the serum sodium collected at 24 hours post-dose (Trough) of Day 4 on the CRF will be used to define the endpoint of Treatment Phase B.
3) The MMRM analysis for the primary endpoint will be analyzed using PROC MIXED of SAS (with default REML option). Specifically, the following SAS statements will be used for the primary analysis:

   ```
   proc mixed;
   class treatment visit  subject agesubgrp responsesubgrp etiologysubgrp;
   model change =agesubgrp responsesubgrp etiologysubgrp treatment  visit
   treatment*visit  baseline baseline*visit/ s ddfm=kr;
   repeated visit / type=un sub=subject;
   lsmeans treatment*visit / pdiff cl alpha=0.05;
   run;
   ```

4) In case there is a convergence problem in the MMRM model with the unstructured variance covariance matrix, the following variance covariance matrix structures will be used in the order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry. The first (co)variance structure which does not have a convergence problem will be the one used for the analysis. If a structured covariance has to be used, the "sandwich" estimator of the variance covariance matrix of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix.
5) Medications for rescue therapy (with indication of hyponatremia) include:

   Rescue therapy is defined as any level of fluid restriction, hypertonic saline, isotonic saline (with or without diuretic for purpose of increasing the serum sodium level), plasmapheresis/dialysis, demeclocycline, urea, lithium, commercially available

vaptans, or any treatment intended to raise the level of serum sodium at any time during the trial.

5.1.7.3 Subgroup Analysis of the Primary Outcome Endpoint

Subgroup analysis of the primary efficacy endpoint will be conducted by gender and race (white and all other races), using similar analysis of the primary analysis. The subgroup analysis by 3 stratification factors will also be provided for the primary endpoint. Subgroup analysis by additional age categories [redacted] will also be provided for the primary endpoint.

5.1.8 Secondary Outcome Analyses

5.1.8.1 Analysis of the Key Secondary Endpoint

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

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

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

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

5.1.8.2 Analyses of Other Secondary Endpoints

Other secondary endpoints include:

- Percentage of subjects with an overly rapid increase in serum sodium level [redacted].
- Change in serum sodium level from 24 hours post-last dose to 7 days post-last dose.
- Percentage of subjects requiring rescue therapy (other than fluid restriction) during Treatment Phase A and Treatment Phase B.
- Percentage of subjects requiring fluid restriction during Treatment Phase A and Treatment Phase B.
- Pharmacodynamic endpoints are fluid intake, urine output, and fluid balance (intake minus output) every 6 hours on Days 1 and 2 in Treatment Phase A.

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

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

Urine volume will be summarized by 6-hour intervals using descriptive statistics. Fluid intake and the calculated value of fluid balance will be summarized for each 6-hour period and for the 24-hour daily interval on Days 1 and 2 in Treatment Phase A using descriptive statistics. A subgroup analysis by the disease etiology of hyponatremia or by fluid status (euvolemic, hypervolemic) may be conducted if there are sufficient subjects in each category.

5.1.8.3 Technical Computational Details for the Analysis of the Secondary Efficacy Endpoints

1) Percentage of subjects with an overly rapid increase in serum sodium level will only apply to the Treatment Phase A Efficacy Sample.
2) Change in serum sodium level from 24 hours post-last dose to 7 days post-last dose will only apply to the Treatment Phase B Efficacy Sample for responders.

5.1.9 Exploratory Efficacy Analysis

5.1.9.1 Analysis of Exploratory Efficacy Endpoints

Exploratory analyses will include:

- Change in Serum Sodium level from baseline at the end of Treatment Phase B compared to the end of Treatment Phase A for nonresponders continuing on tolvaptan therapy
- Quality of life (QoL) assessments
- In all subjects, 24-hour excretion of sodium, creatinine, and osmolality on Days 1 and 2
- 24-hour sodium clearance on Day 1

A paired Student's t-test will be applied to the change from baseline in serum sodium concentration for nonresponders continuing on tolvaptan therapy.

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 by the paired Student's t-test for the responders. For the

QoL MFS, the QoL MFS total score will be analyzed by the paired Student's t-test for the responders.

For the responders, the change from baseline at the end of Treatment Phase A to the end of the Treatment Phase B will be compared between the Early Withdrawal group and the Late Withdrawal group using the same MMRM analysis that is used for the primary endpoint.

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

5.1.9.2 Technical Computational Details for the Analysis of the Exploratory Efficacy Endpoints

1) In Treatment Phase A, subjects achieving an increase in serum sodium concentration of ≥ 4 mEq/L (mmol/L) by end of Day 2 (or 2a) will be defined as responders. If subjects do not achieve an increase in serum sodium concentration of ≥ 4 mEq/L (mmol/L) by end of Day 2 (or 2a), they will be defined as nonresponders.
2) 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 to 100 scale, so that higher scores indicate better HRQOL (Health-Related Quality of Life).

   To reverse score, transform the 0 to 4 scale items to 0 to 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.
3) 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 to 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.

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

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

5.1.10 Analysis of Pharmacokinetic Parameters

To establish similarity between the CIs for PK parameter estimates between adults and pediatrics based on PK data of clearance, the clearance data of at least 20 pediatric subjects from this trial and 81 adult subjects from an existing tolvaptan trial will be used. An analysis of variance model will be performed on the natural log transformed PK parameters using the MIXED procedure in SAS, in which only one fixed effect of subject group (pediatric and adult groups) is included in the model. From each analysis, least squares means, their difference, and the 90% CI for their difference will be derived. Then, the antilogs of the difference and the confidence limits will provide the estimate and 90% CI for the ratio of the geometric means of the 2 treatments (pediatric vs adult). The similarity of PK parameter estimates between adults and pediatrics will be claimed if the 90% CI for the ratio of the population geometric means—based on the analysis of the log-transformed data—is contained within the confidence limits of 0.60 to 1.40.

5.2 Safety Analysis

The safety analysis will be conducted based on the Safety Samples, which are defined in Section 5.1.1. 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.

Safety analyses will be performed for Treatment Phase A and Treatment Phase B separately. Safety analyses by age categories [redacted] will be provided as well.

5.2.1 Duration of Exposure to Trial Medication

Duration of exposure to each treatment of each subject will be summarized by treatment group. A subject's duration of exposure is defined as the IMP end date − IMP 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 IMP in this trial that was not present prior to IMP 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.

Safety variables of analysis include:

- Proportion of subjects with TEAEs
- Proportions of subjects with TEAEs by preferred term
- Proportion of subjects with severe TEAEs
- Proportion of subjects with serious TEAEs
- Proportion of subjects with TEAEs leading to death
- Proportion of subjects with potentially drug-related TEAEs
- Proportion of subjects with TEAEs that result in trial termination

Analysis of special interested AEs include:

- Proportion of subjects with absolute serum sodium level ≥ 145 mEq/L
- Proportion of subjects with overly rapid rise in serum sodium defined as an increase in serum sodium of [redacted] or a rate of increase in serum sodium that the investigator deems too rapid
- Proportion of subjects with neurological symptoms or other signs or symptoms suggestive of osmotic demyelination
- Proportions of subjects with worsening symptoms of hyponatremia
- Proportion of subjects with hypovolemia or hypotension requiring intervention

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 postbaseline visits, and summary statistics of changes from baseline to each visit will be presented by treatment group. Shift tables will be produced, assessing low-normal-high (at baseline) to low-normal-high (at postbaseline visit).

The incidence of treatment-emergent potentially clinically significant abnormal laboratory results will also be summarized by treatment groups. Listings of potentially clinically significant abnormalities will also be provided.

According to the Food and Drug Administration (FDA) 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 by treatment group, for both vital signs and change from baseline in vital signs. The incidence of treatment-emergent potentially clinically significant vital sign results will also be summarized by treatment groups. Listings of potentially clinically significant abnormalities will also be provided.

For a subject with repeat measures in either vital signs or laboratory 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 ECG data will be collected at the screening visit only.

5.2.6 Postbaseline Concomitant Medications

Concomitant medications used postbaseline will be summarized in two categories of time interval: during the IMP period and after the IMP period. In each case, the use of concomitant medications will be summarized by number and percentage of users by treatment group.

5.3 Sample Size Re-estimation

It was recommended by the FDA that the sample size should be re-estimated when approximately 90% of the subjects had finished the trial. The sample size re-estimation will assess the variability of change from Day 2 (or 2a) at the end Treatment Phase A to the end of Treatment Phase B in serum sodium level by using the pooled variance of the 2 treatment groups. At the trial planning stage, an SD of 5 was used to detect a treatment difference of 4, resulting in a sample size of 70 with a 2-sided alpha of 0.05 and 90% power. In case the variance ratio (equal to the observed pooled variance divided by 25, the square of 5 as an SD used in the sample size calculation) is ≤ 1, no sample size increase will be made, and the trial will proceed to finish enrollment of 70 randomized subjects. In case the variance ratio is > 1, the sample size re-estimation will be equal to 70 multiplied by the variance ratio, then rounded up to the nearest even number. Table 5.3-1 provides an example of the sample size re-estimation under different variance ratios.

Table 5.3-1 Sample Size Re-estimation

Variance Ratio	Sample Size
1.1	78
1.2	84
1.3	92
1.4	78
1.5	106

6 Monitoring of Safety Data

Safety monitoring will be performed by the Independent Data Monitoring Committee (IDMC). Reference is made to the IDMC Charter for details of constituents and roles and responsibilities of IDMC. The independent statistician at Theorem will work closely with the IDMC and will assist the IDMC in the retrieval and analysis of safety and efficacy data. The DMC will review the data periodically. Summary tables will be produced by OPDC (Otsuka Pharmaceutical Development & Commercialization) Biometrics.

7 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.

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Document Name: P15608276_SAP

Document Number: 0001127440

Document Version: 6.0

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[redacted]	Biostatistics Approval	28-Aug-2017 18:03 GMT+00