STATISTICAL ANALYSIS PLAN

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

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

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Protocol No. 156-14-003

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Statistical Analysis Plan

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
Descriptive statistics	Number of subjects, mean, standard deviation, minimum, median, and maximum values
Frequency distribution	Number and percentage of subjects

1 Introduction

This statistical analysis plan documents the details of the statistical analysis methodology to be applied in the protocol of Trial 156-14-003.

2 Trial Objectives

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

3 Trial Design

(Refer to the corresponding sections in the trial protocol for the reference numbers indicated in this section.)

3.1 Type/Design of Trial

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

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

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

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

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

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

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

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

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

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

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

Definition of trial completion date:

The trial completion date is defined as the trial discontinuation date, or the date on which the follow-up examination is completed, whichever comes later (If 2 or more follow-up

examinations were performed, the date of the last examination will be taken as the trial completion date.)

3.2 Trial Treatments

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

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

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

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

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

3.3 Trial Population

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

At least 50% (8/16) of the above subjects should comprise subjects with serum sodium concentration of <130 mEq/L at predose on Day 1 of the treatment period. In addition, the number of subjects with SIADH due to ectopic antidiuretic hormone-producing

tumors and the number of subjects with SIADH due to other causes should not be notably different.

3.4 Handling of Timepoints

CRF Visit values at each timepoint (after the pretreatment observation period) will be used in summaries (but values at the time of discontinuation will not be used in summaries). Unscheduled Visit values will not be used for timepoint analyses.

4 Sample Size

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

Sample size determination was based on the results from patients with SIADH as the underlying disease of hyponatremia ("the SIADH subpopulation") in the efficacy analysis sets of 2 overseas phase 3, placebo-controlled, randomized, double-blind trials in patients with hyponatremia due to SIADH and other causes (Trials 156-02-235 and 156-03-238, with an optional up-titration of 15, 30, and 60 mg for 30 days). To determine the sample size of this trial, a threshold percentage was set based on the results of the placebo group in the SIADH subpopulation of the overseas trials. Considering the distribution of the point estimates which are calculated based on multiple sample sizes, in the percentage of subjects with a normalized serum sodium concentration after the final IMP administration in the tolvaptan group, a sample size for which the probability of obtaining a point estimate exceeding the threshold percentage was kept at ≥80% was sought. In addition, since this trial intends to evaluate the efficacy and safety of tolvaptan in patients with SIADH due to a variety of etiologies, and to investigate the appropriateness of the dose-titration approach adopted as the dosage regimen, the various etiologies of SIADH and the expected number of subjects at each maintenance dose level were also taken into consideration in determination of the sample size.

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

that the expected point estimate of the percentage of normalized subjects will exceed the threshold percentage is kept at ≥80% with a sample size of ≥8 subjects.

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

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

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

5 Statistical Analysis Datasets

5.1 Efficacy Analysis Set

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

5.2 Maintenance Dose-setting Set

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

5.3 Safety Analysis Set

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

5.4 Pharmacokinetic Analysis Set

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

5.5 Pharmacodynamic Analysis Set

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

5.6 Handling of Missing Data

Missing data on the day after the final IMP administration will be imputed using the last available postdose data obtained by the day after the final administration. If multiple values are available on the day of trial discontinuation, the first obtained value will be used.

6 Primary and Secondary Outcome Variables

6.1 Primary Outcome Variable

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

6.2 Secondary Outcome Variables

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

7 Disposition and Demographic Analysis

7.1 Subject Disposition

For subjects from whom informed consent has been obtained (screened subjects), the numbers of subjects with acquired informed consent and of the IMP-treated subjects as well as the numbers and percentages of subjects who completed the IMP treatment and those who discontinued the IMP treatment (using the IMP-treated subjects as the denominator) will be summarized. The number and percentage of subjects who discontinued the IMP treatment after receiving IMP will be presented and summarized by reason for discontinuation. The number of subjects receiving IMP readministration and the numbers and percentages of subjects receiving IMP readministration who completed the treatment and those who discontinued the IMP treatment after receiving IMP readministration within the specified trial period will be summarized.

For subjects receiving IMP administration, the number and percentage of subjects included in each statistical analysis set will be summarized.

7.2 Demographic and Baseline Characteristics

For the efficacy analysis set and safety analysis set, demographic and baseline characteristics will be summarized according to Table 7.2-1. The same analyses will also be performed by SIADH etiology (subjects with SIADH due to ectopic antidiuretic hormone-producing tumors/those due to other etiologies).

Table 7.2-1 Demographic and Baseline Characteristics

Variable	Timepoint	Method	Level
Age (years)	Informed consent acquisition	Descriptive statistics	-
		Frequency distribution	20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-85
			<65, ≥65
Sex	-	Frequency distribution	Male, Female
Height (cm)	Screening	Descriptive statistics	-
Body weight (kg)	Screening	Descriptive statistics	-
BMI (kg/m^2)	Screening	Descriptive statistics	-
Race	-	Frequency distribution	Asian
Ethnicity	-	Frequency distribution	Not Hispanic or Latino
Presence of complication	Screening	Frequency distribution	Yes, No
Presence of medical history	Screening	Frequency distribution	Yes, No
Etiology of SIADH	Screening	Frequency distribution	Ectopic, Other
Disease duration of SIADH*	Screening	Descriptive statistics	-

*Number of days from the date on which the latest diagnosis of SIADH was made (or the date on which hyponatremia requiring treatment was diagnosed) to the date of acquisition of informed consent.

7.3 Baseline Disease Evaluation

For the efficacy analysis set and safety analysis set, each variable at baseline will be calculated. The same analyses will also be performed by SIADH etiology (subjects with SIADH due to ectopic antidiuretic hormone-producing tumors/those due to other etiologies).

Table 7.3-1 Baseline Disease Evaluation		
Variable	**Method**	**Level**
Serum sodium concentrations	Descriptive statistics	-
	Frequency distribution	<130 mEq/L ≥130 mEq/L
Clinical symptoms associated with hyponatremia • Anorexia • Vomiting • Headache	Frequency distribution	Nothing, Grade 1, Grade 2, Grade 3, Unknown
Clinical symptoms associated with hyponatremia • Consciousness disturbed	Frequency distribution	Nothing, 1, 2, 3, 10, 20, 30, 100, 200, 300, Unknown
Clinical symptoms associated with hyponatremia • Malaise	Frequency distribution	Nothing, Grade 1, Grade 2, Unknown

7.4 Treatment Compliance

The frequency distribution of days with missed doses occurring between Day 1 of the treatment period and the completion or discontinuation of treatment will be determined in the efficacy and safety analysis sets, and subjects who are readministered with the IMP.

7.5 Prior and Concomitant Medications

Prior and concomitant medications will not be tabulated in this trial.

7.6 Protocol Deviations

Protocol deviations will not be tabulated in this trial.

8 Efficacy Analysis

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

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

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

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

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

8.1 Primary Efficacy Endpoint

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

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

8.1.1 Primary Efficacy Analysis

The number, percentage, and 2-sided 95% CI (exact) of subjects with normalized serum sodium concentration on the day of fixing the maintenance dose and on the day after final IMP administration will be calculated. The number and percentage of subjects will also be calculated for each timepoint after start of IMP administration.

8.2 Secondary Efficacy Endpoints

8.2.1 Change in Serum Sodium Concentration

Descriptive statistics (the number of subjects and the mean, standard deviation, minimum, median, and maximum values) and 2-sided 95% CI (based on the t distribution) for measured values for serum sodium concentration and the change from baseline (predose on Day 1 of the treatment period) on the day of fixing the maintenance dose and on the day after final IMP administration will be calculated. Descriptive statistics at each timepoint after start of IMP administration will also be calculated.

8.2.2 Time Course of Serum Sodium Concentration

The individual time courses of measured values and changes from baseline for serum sodium concentration will be plotted with the horizontal axis representing timepoints (days of trial period). The individual time courses of measured values and changes from

baseline for serum sodium concentration will be plotted for the periods from the day of initial IMP administration to the follow-up visit and from the day of fixing the maintenance dose to the day after the final IMP administration.

8.2.3 Changes in Clinical Symptoms Associated With Hyponatremia

Shift tables of the changes in clinical symptom gradings (anorexia, vomiting, headache, consciousness disturbed, and malaise) from baseline (pretreatment observation) to the day of fixing the maintenance dose and from baseline to the day after final IMP administration will be generated. Shift tables of consciousness disturbed will be generated for high categories (I, II, and III) and for low categories (1, 2, 3, 10, 20, 30, 100, 200, and 300) from baseline (pretreatment observation) to the day of fixing the maintenance dose and from baseline to the day after final IMP administration. Shift tables of the changes at each postdose timepoint will be generated in the same way.

8.3 Subgroup Analyses and the Analysis by Dose

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

For maintenance dose-setting set, a similar analysis will also be conducted by the dose administered at determination of the maintenance dose (7.5, 15, 30, and 60 mg) and the final dose.

Except for the time course of serum sodium concentration, data obtained at fixing of maintenance dose and the day after the final IMP administration will be analyzed in the subgroup analyses and the analysis by dose administered at determination of the maintenance dose, and data obtained at the day after the final IMP administration will be analyzed in the analysis by the final dose.

9 Safety Analyses

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

9.1 Extent of Exposure

The frequency distribution of subjects will be determined by the number of days of IMP administration (1 - 7 days, 8 - 14 days, 15 - 21 days, 22 - 29 days, and 30 days) during the period from Day 1 of the treatment period to the completion or discontinuation of treatment. In addition, the number of days of IMP administration will be summarized using descriptive statistics, and the frequency distribution of subjects will be determined

by maintenance dose, final dose, and highest dose. Similar analyses will be performed in subjects with the IMP readministration.

9.2 Adverse Events

All adverse events (AEs) will be coded by system organ class (SOC) and preferred term (PT) (Medical Dictionary for Regulatory Activities [MedDRA]). The incidence of the following events will be summarized for all events, by SOC, and by PT.

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

If there are multiple occurrences of the same event in the same period in the same subject, the event with the highest severity will be selected. The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

In addition to summarization of the data collected over the entire period of the trial, AE data will be summarized by time period ("during the treatment period [including the day after the final IMP administration]," "from the day of the initial IMP administration to the day after the maintenance dose is determined," "from 2 days after the maintenance dose is determined to the day after the final IMP administration," and "from 2 days after the final IMP administration to the follow-up examination"). Adverse events occurring from the day of the initial IMP administration to the day after the final IMP administration in subjects whose maintenance dose has not been determined will be classified in the time period "from the day of the initial IMP administration to the day after the maintenance dose is determined."

9.3 Clinical Laboratory Data

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

9.4 Vital Sign Data

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

9.5 Electrocardiogram Data

For 12-lead electrocardiographic parameters and QTcF (rounded to the nearest integer data in msec, QTcF = $QT/RR^{0.33}$, RR = 60/heart rate), measured values and changes from baseline (pretreatment observation period) on the day after final IMP administration and at each timepoint will be summarized using descriptive statistics.

The numbers and percentages of subjects who have a QTcF interval of >450, >480, or >500 ms at any postdose timepoint from start of IMP administration through the day after the final IMP administration will be calculated. In addition, the numbers and percentages of subjects who have a change in QTcF interval from baseline of >30 and >60 ms at any postdose timepoint from start of IMP administration through the day after the final IMP administration will be calculated. The numbers and percentages at baseline and each postdose timepoint will be calculated in the same way.

Shift tables for QTcF interval interpretation (normal or abnormal) will be prepared from baseline through each timepoint and the day after the final IMP administration.

9.6 Liver Function Tests

The numbers and percentages of subjects who have a serum total bilirubin value of ≥2 times the upper limit of normal (ULN), and AST or ALT value of ≥3 times the ULN, at any postdose timepoint will be calculated.

Subgroup Analyses and the Analysis by Dose

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

For subjects in the safety analysis set for whom maintenance doses of the IMP were determined, a similar analysis will also be conducted by the dose administered at determination of the maintenance dose (7.5, 15, 30, and 60 mg) and the final dose.

Except for adverse events and liver function tests, data obtained at the day after the final IMP administration will be analyzed in the subgroup analyses and the analysis by dose administered.

10 Pharmacokinetic Analyses

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

11 Pharmacodynamic Analyses

Pharmacodynamic analyses will be performed in the pharmacodynamic analysis set. For the parameters below, measured values and changes from baseline (at predose on Day 1 of the treatment period for serum osmolality and plasma AVP concentration or at 24 hours predose on Day 1 of the treatment period for other parameters) at each timepoint will be summarized using descriptive statistics.

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

12 Pharmacogenomic Analyses

Pharmacogenomic analyses will not be tabulated in this trial.

13 Interim Analysis

No interim analysis will be performed in this trial.

14 Changes in the Planned Analyses

- To correct an entry omission in Section 7.3 of the Trial Protocol, the description “will be imputed using the last available data obtained by the day after the final administration” to “will be imputed using the last available postdose data obtained by the day after the final administration.”
- Section 7.4 of the Trial Protocol specified as follows: “In patients receiving readministration with the IMP, similar analyses using the data immediately before treatment was resumed as baseline data will performed, as well as a comparison of efficacy between initial treatment and readministration to demonstrate the absence of

significant differences (For details, see the "Statistical Analysis Plan")." However, these analyses were cancelled and limited to the individual assessment, because only 1 subject received readministration of the IMP.

- To correct an error in writing in Section 7.6.1 of the Trial Protocol, the description regarding the summarization by time period "(during the treatment period, from the day of the initial IMP administration to the day after the maintenance dose is determined, from 2 days after the maintenance dose is determined to the day after the final IMP administration, and from 2 days after the final IMP administration to the follow-up examination)" was changed to "("during the treatment period [including the day after the final IMP administration]," "from the day of the initial IMP administration to the day after the maintenance dose is determined", and "from 2 days after the maintenance dose is determined to the day after the final IMP administration," and "from 2 days after the final IMP administration to the follow-up examination")."
- To correct an error in writing in Section 7.6.5 of the Trial Protocol the description "The numbers and percentages of subjects who have a serum total bilirubin value of ≥2 times the ULN, or an AST or ALT value of ≥3 times the ULN, at any timepoint after start of IMP administration will be calculated." was changed to "The numbers and percentages of subjects who have a serum total bilirubin value of ≥2 times the upper limit of normal (ULN), and an AST or ALT value of ≥3 times the ULN, at any postdose timepoint will be calculated."
- To correct an error in writing in Section 6.1 of the Trial Protocol the description "on Day 21, at discontinuation of treatment, and on the day after the final IMP administration" was changed to "on Day 21 and the day after the final IMP administration."

References

None.

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CT-6.1.3 Descriptive Statistics for Change from Baseline in Serum Sodium Concentration by Underlying Disease Leading to SIADH for Efficacy Analysis Set

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CT-6.3.6 Shift Tables of the Changes in Clinical Symptom Associated with Hyponatremia by baseline sodium level for Maintenance Dose-setting Set (Consiousness Disorder - Mainscale)

CT-6.3.7 Shift Tables of the Changes in Clinical Symptom Associated with Hyponatremia by Maintenance Dose for Maintenance Dose-setting Set (Consiousness Disorder - Mainscale)

CT-6.3.8 Shift Tables of the Changes in Clinical Symptom Associated with Hyponatremia by Final Dose for Maintenance Dose-setting Set (Consiousness Disorder - Mainscale)

CT-6.4.1 Shift Tables of the Changes in Clinical Symptom Associated with Hyponatremia for Efficacy Analysis Set (Consiousness Disorder - Subscale)

CT-6.4.2 Shift Tables of the Changes in Clinical Symptom Associated with Hyponatremia for Maintenance Dose-setting Set (Consiousness Disorder - Subscale)

CT-6.4.3 Shift Tables of the Changes in Clinical Symptom Associated with Hyponatremia by Underlying Disease Leading to SIADH for Efficacy Analysis Set (Consiousness Disorder - Subscale)

CT-6.4.4 Shift Tables of the Changes in Clinical Symptom Associated with Hyponatremia by Underlying Disease Leading to SIADH for Maintenance Dose-setting Set (Consiousness Disorder - Subscale)

CT-6.4.5 Shift Tables of the Changes in Clinical Symptom Associated with Hyponatremia by baseline sodium level for Efficacy Analysis Set (Consiousness Disorder - Subscale)

CT-6.4.6 Shift Tables of the Changes in Clinical Symptom Associated with Hyponatremia by baseline sodium level for Maintenance Dose-setting Set (Consiousness Disorder - Subscale)

CT-6.4.7 Shift Tables of the Changes in Clinical Symptom Associated with Hyponatremia by Maintenance Dose for Maintenance Dose-setting Set (Consiousness Disorder - Subscale)

CT-6.4.8 Shift Tables of the Changes in Clinical Symptom Associated with Hyponatremia by Final Dose for Maintenance Dose-setting Set (Consiousness Disorder - Subscale)

CT-7.1 Extent of Exposure to Investigational Medicinal Product (Safety Analysis Set)

CT-7.2.1 Treatment Compliance (Safety Analysis Set)

CT-7.2.2 Treatment Compliance (Efficacy Analysis Set)

CT-8.1 Overall Summary of Adverse Events (Safety Analysis Set)

CT-8.2.1.1 Incidences of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.2.1.2 Incidences of Treatment-emergent Adverse Events occurring in >= 2 subjects by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.2.2 Incidences of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-8.2.3 Incidences of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Baseline Sodium Level (Safety Analysis Set)

CT-8.2.4 Incidences of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.2.5 Incidences of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.3.1 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.3.2 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-8.3.3 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Baseline Sodium Level (Safety Analysis Set)

CT-8.3.4 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.3.5 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.4.1 Incidences of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.4.2 Incidences of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-8.4.3 Incidences of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Baseline Sodium Level (Safety Analysis Set)

CT-8.4.4 Incidences of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.4.5 Incidences of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.5.1 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.5.2 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-8.5.3 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Baseline Sodium Level (Safety Analysis Set)

CT-8.5.4 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.5.5 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.7.1 Incidences of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period (Safety Analysis Set)

CT-8.7.2 Incidences of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-8.7.3 Incidences of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Baseline Sodium Level (Safety Analysis Set)

CT-8.7.4 Incidences of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.7.5 Incidences of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.8.1 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period (Safety Analysis Set)

CT-8.8.2 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-8.8.3 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Baseline Sodium Level (Safety Analysis Set)

CT-8.8.4 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.8.5 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.9.1 Incidences of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Period (Safety Analysis Set)

CT-8.9.2 Incidences of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Period by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-8.9.3 Incidences of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Period by Baseline Sodium Level (Safety Analysis Set)

CT-8.9.4 Incidences of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Period by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.9.5 Incidences of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Period by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.10.1 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Period (Safety Analysis Set)

CT-8.10.2 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Period by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-8.10.3 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Period by Baseline Sodium Level (Safety Analysis Set)

CT-8.10.4 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Period by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-8.10.5 Incidences of Potentially Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Period by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.1.1 Incidences of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-9.1.2 Incidences of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.1.3 Incidences of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Baseline Sodium Level (Safety Analysis Set)

CT-9.1.4 Incidences of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.1.5 Incidences of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.2.1 Incidences of Potentially Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-9.2.2 Incidences of Potentially Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.2.3 Incidences of Potentially Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Baseline Sodium Level (Safety Analysis Set)

CT-9.2.4 Incidences of Potentially Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.2.5 Incidences of Potentially Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.3.1 Incidences of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-9.3.2 Incidences of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.3.3 Incidences of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Baseline Sodium Level (Safety Analysis Set)

CT-9.3.4 Incidences of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.3.5 Incidences of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.4.1 Incidences of Potentially Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-9.4.2 Incidences of Potentially Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.4.3 Incidences of Potentially Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Baseline Sodium Level (Safety Analysis Set)

CT-9.4.4 Incidences of Potentially Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.4.5 Incidences of Potentially Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.5.1 Incidences of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-9.5.2 Incidences of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.5.3 Incidences of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Baseline Sodium Level (Safety Analysis Set)

CT-9.5.4 Incidences of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.5.5 Incidences of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.6.1 Incidences of Potentially Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-9.6.2 Incidences of Potentially Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.6.3 Incidences of Potentially Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Baseline Sodium Level (Safety Analysis Set)

CT-9.6.4 Incidences of Potentially Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.6.5 Incidences of Potentially Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.7.1 Incidences of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Period (Safety Analysis Set)

CT-9.7.2 Incidences of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Period by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.7.3 Incidences of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Period by Baseline Sodium Level (Safety Analysis Set)

CT-9.7.4 Incidences of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Period by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.7.5 Incidences of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Period by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.8.1 Incidences of Potentially Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Period (Safety Analysis Set)

CT-9.8.2 Incidences of Potentially Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Period by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.8.3 Incidences of Potentially Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Period by Baseline Sodium Level (Safety Analysis Set)

CT-9.8.4 Incidences of Potentially Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Period by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.8.5 Incidences of Potentially Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Period by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.9.1 Incidences of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period (Safety Analysis Set)

CT-9.9.2 Incidences of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.9.3 Incidences of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Baseline Sodium Level (Safety Analysis Set)

CT-9.9.4 Incidences of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.9.5 Incidences of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.10.1 Incidences of Potentially Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period (Safety Analysis Set)

CT-9.10.2 Incidences of Potentially Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.10.3 Incidences of Potentially Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Baseline Sodium Level (Safety Analysis Set)

CT-9.10.4 Incidences of Potentially Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.10.5 Incidences of Potentially Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Period by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.11.1 Incidences of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Period (Safety Analysis Set)

CT-9.11.2 Incidences of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Period by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.11.3 Incidences of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Period by Baseline Sodium Level (Safety Analysis Set)

CT-9.11.4 Incidences of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Period by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.11.5 Incidences of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Period by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.12.1 Incidences of Potentially Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Period (Safety Analysis Set)

CT-9.12.2 Incidences of Potentially Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Period by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-9.12.3 Incidences of Potentially Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Period by Baseline Sodium Level (Safety Analysis Set)

CT-9.12.4 Incidences of Potentially Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Period by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.12.5 Incidences of Potentially Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Period by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-9.13 Listing of Deaths (Safety Analysis Set)

CT-9.14 Listing of Serious Adverse Events Other Than Death (Safety Analysis Set)

CT-9.15 Listing of Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration (Safety Analysis Set)

CT-10.1.1 Mean Change from Baseline in Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) (Safety Analysis Set)

CT-10.1.2 Mean Change from Baseline in Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-10.1.3 Mean Change from Baseline in Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) by Baseline Sodium Level (Safety Analysis Set)

CT-10.1.4 Mean Change from Baseline in Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-10.1.5 Mean Change from Baseline in Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-10.2.1 Shift Tables of Clinical Laboratory Test Results (Qualitative Urinalysis) (Safety Analysis Set)

CT-10.2.2 Shift Tables of Clinical Laboratory Test Results (Qualitative Urinalysis) by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-10.2.3 Shift Tables of Clinical Laboratory Test Results (Qualitative Urinalysis) by Baseline Sodium Level (Safety Analysis Set)

CT-10.2.4 Shift Tables of Clinical Laboratory Test Results (Qualitative Urinalysis) by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-10.2.5 Shift Tables of Clinical Laboratory Test Results (Qualitative Urinalysis) by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-10.3.1.1 Shift Tables of Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) (Safety Analysis Set)

CT-10.3.1.2 Shift Tables of Clinical Laboratory Test Results (Serum Sodium) (Safety Analysis Set)

CT-10.3.1.3 Shift Tables of Clinical Laboratory Test Results (Liver Function) (Safety Analysis Set)

CT-10.3.2.1 Shift Tables of Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-10.3.2.2 Shift Tables of Clinical Laboratory Test Results (Serum Sodium) by Underlying Disease Leading to SIADH at Central Laboratory (Safety Analysis Set)

CT-10.3.2.3 Shift Tables of Clinical Laboratory Test Results (Liver Function) by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-10.3.3.1 Shift Tables of Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) by Baseline Sodium Level (Safety Analysis Set)

CT-10.3.3.2 Shift Tables of Clinical Laboratory Test Results (Serum Sodium) by Baseline Sodium Level (Safety Analysis Set)

CT-10.3.3.3 Shift Tables of Clinical Laboratory Test Results (Liver Function) by Baseline Sodium Level (Safety Analysis Set)

CT-10.3.4.1 Shift Tables of Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-10.3.4.2 Shift Tables of Clinical Laboratory Test Results (Serum Sodium) by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-10.3.4.3 Shift Tables of Clinical Laboratory Test Results (Liver Function) by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-10.3.5.1 Shift Tables of Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-10.3.5.2 Shift Tables of Clinical Laboratory Test Results (Serum Sodium) by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-10.3.5.3 Shift Tables of Clinical Laboratory Test Results (Liver Function) by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-10.4 Listing of Abnormal Laboratory Findings (Safety Analysis Set)

CT-11.1 Mean Change from Baseline in Vital Signs (Safety Analysis Set)

CT-11.2 Mean Change from Baseline in Vital Signs by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-11.3 Mean Change from Baseline in Vital Signs by Baseline Sodium Level (Safety Analysis Set)

CT-11.4 Mean Change from Baseline in Vital Signs by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-11.5 Mean Change from Baseline in Vital Signs by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-12.1.1 Mean Change from Baseline in ECG Evaluations (Safety Analysis Set)

CT-12.1.2 Mean Change from Baseline in ECG Evaluations by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-12.1.3 Mean Change from Baseline in ECG Evaluations by Baseline Sodium Level (Safety Analysis Set)

CT-12.1.4 Mean Change from Baseline in ECG Evaluations by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-12.1.5 Mean Change from Baseline in ECG Evaluations by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-12.2.1 Shift Table of 12-Lead ECG Findings (Normal/Abnormal Assessments) (Safety Analysis Set)

CT-12.2.2 Shift Table of 12-Lead ECG Findings (Normal/Abnormal Assessments) by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-12.2.3 Shift Table of 12-Lead ECG Findings (Normal/Abnormal Assessments) by Baseline Sodium Level (Safety Analysis Set)

CT-12.2.4 Shift Table of 12-Lead ECG Findings (Normal/Abnormal Assessments) by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-12.2.5 Shift Table of 12-Lead ECG Findings (Normal/Abnormal Assessments) by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-12.3.1 Incidence of Categorical Changes in ECG Evaluations (Safety Analysis Set)

CT-12.3.2 Incidence of Categorical Changes in ECG Evaluations by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-12.3.3 Incidence of Categorical Changes in ECG Evaluations by Baseline Sodium Level (Safety Analysis Set)

CT-12.3.4 Incidence of Categorical Changes in ECG Evaluations by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-12.3.5 Incidence of Categorical Changes in ECG Evaluations by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-12.3.6 Incidence of Categorical Changes in ECG Evaluations (Each Visit) (Safety Analysis Set)

CT-12.3.7 Incidence of Categorical Changes in ECG Evaluations by Underlying Disease Leading to SIADH (Each Visit) (Safety Analysis Set)

CT-12.3.8 Incidence of Categorical Changes in ECG Evaluations by Baseline Sodium Level (Each Visit) (Safety Analysis Set)

CT-12.3.9 Incidence of Categorical Changes in ECG Evaluations by Maintenance Dose (Each Visit) (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-12.3.10 Incidence of Categorical Changes in ECG Evaluations by Final Dose (Each Visit) (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-13.1 Percentage of subjects with Abnormal Liver Function Test (Safety Analysis Set)

CT-13.2 Percentage of subjects with Abnormal Liver Function Test by Underlying Disease Leading to SIADH (Safety Analysis Set)

CT-13.3 Percentage of subjects with Abnormal Liver Function Test by Baseline Sodium Level (Safety Analysis Set)

CT-13.4 Percentage of subjects with Abnormal Liver Function Test by Maintenance Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

CT-13.5 Percentage of subjects with Abnormal Liver Function Test by Final Dose (Subjects in The Safety Analysis Set for whom Maintenance Doses of The IMP were Determined)

PDT-1	Descriptive Statistics for Daily Urine Volume (mL) (Pharmacodynamics Analysis Set)
PDT-2	Descriptive Statistics for Daily Fluid Intake (mL) (Pharmacodynamics Analysis Set)
PDT-3	Descriptive Statistics for Daily Fluid Balance (mL) (Pharmacodynamics Analysis Set)
PDT-4	Descriptive Statistics for Serum Osmolality (mOsm/kg) (Pharmacodynamics Analysis Set)
PDT-5	Descriptive Statistics for Urine Osmolality (mOsm/kg) (Pharmacodynamics Analysis Set)
PDT-6	Descriptive Statistics for Daily Urine Excretion of Sodium (mEq) (Pharmacodynamics Analysis Set)
PDT-7	Descriptive Statistics for Plasma AVP Concentration (ng/L) (Pharmacodynamics Analysis Set)
CF-1.1	Transition Diagram for Serum Sodium Concentration for Efficacy Analysis Set
CF-1.2.1	Transition Diagram for Serum Sodium Concentration for Maintenance Dose- setting Set
CF-1.2.2	Transition Diagram for Serum Sodium Concentration After Maintenance Dose Determination for Maintenance Dose-setting Set
CF-1.3	Transition Diagram for Serum Sodium Concentration by Underlying Disease Leading to SIADH for Efficacy Analysis Set
CF-1.4.1	Transition Diagram for Serum Sodium Concentration by Underlying Disease Leading to SIADH for Maintenance Dose-setting Set
CF-1.4.2	Transition Diagram for Serum Sodium Concentration After Maintenance Dose Determination by Underlying Disease Leading to SIADH for Maintenance Dose-setting Set
CF-1.5	Transition Diagram for Serum Sodium Concentration by baseline sodium level for Efficacy Analysis Set
CF-1.6.1	Transition Diagram for Serum Sodium Concentration by baseline sodium level for Maintenance Dose-setting Set

CF-1.6.2 Transition Diagram for Serum Sodium Concentration After Maintenance Dose Determination by baseline sodium level for Maintenance Dose-setting Set

CF-1.7.1 Transition Diagram for Serum Sodium Concentration by Maintenance Dose for Maintenance Dose-setting Set

CF-1.7.2 Transition Diagram for Serum Sodium Concentration After Maintenance Dose Determination by Maintenance Dose for Maintenance Dose-setting Set

CF-1.7.3 Transition Diagram for Serum Sodium Concentration by Final Dose for Maintenance Dose-setting Set

CF-1.8 Transition Diagram for Change from Baseline in Serum Sodium Concentration for Efficacy Analysis Set

CF-1.9.1 Transition Diagram for Change from Baseline in Serum Sodium Concentration for Maintenance Dose-setting Set

CF-1.9.2 Transition Diagram for Change from Baseline in Serum Sodium Concentration After Maintenance Dose Determination for Maintenance Dose-setting Set

CF-1.10 Transition Diagram for Change from Baseline in Serum Sodium Concentration by Underlying Disease Leading to SIADH for Efficacy Analysis Set

CF-1.11.1 Transition Diagram for Change from Baseline in Serum Sodium Concentration by Underlying Disease Leading to SIADH for Maintenance Dose-setting Set

CF-1.11.2 Transition Diagram for Change from Baseline in Serum Sodium Concentration After Maintenance Dose Determination by Underlying Disease Leading to SIADH for Maintenance Dose-setting Set

CF-1.12 Transition Diagram for Change from Baseline in Serum Sodium Concentration by baseline sodium level for Efficacy Analysis Set

CF-1.13.1 Transition Diagram for Change from Baseline in Serum Sodium Concentration by baseline sodium level for Maintenance Dose-setting Set

CF-1.13.2 Transition Diagram for Change from Baseline in Serum Sodium Concentration After Maintenance Dose Determination by baseline sodium level for Maintenance Dose-setting Set

CF-1.14.1 Transition Diagram for Change from Baseline in Serum Sodium Concentration by Maintenance Dose for Maintenance Dose-setting Set

CF-1.14.2 Transition Diagram for Change from Baseline in Serum Sodium Concentration After Maintenance Dose Determination by Maintenance Dose for Maintenance Dose-setting Set

CF-1.14.3 Transition Diagram for Change from Baseline in Serum Sodium Concentration by Final Dose for Maintenance Dose-setting Set

Appendix 2 List of Subject Data Listings

DREAS-1	Discontinued Subjects and Reason for Discontinuation (IMP Administered Subjects)
SUBEX-1	Subjects Excluded From Analysis Set (IMP Administered Subjects)
DEMOG-1	Demographic and Baseline Characteristics (IMP Administered Subjects)
SMED-1	Investigational Medicinal Product Compliance (IMP Administered Subjects)
PDEV-1	Protocol Deviations (IMP Administered Subjects)
AE-1	Adverse Events (IMP Administered Subjects)
AE-2	Adverse Events Observed Before Start of Investigational Medicinal Product Administration (IMP Administered Subjects)
LAB-1	Laboratory Test Results - Serum Chemistry (IMP Administered Subjects)
LAB-2	Laboratory Test Results - Hematology (IMP Administered Subjects)
LAB-3	Laboratory Test Results - Urinalysis (IMP Administered Subjects)
PDATA-1	Study Completion Status and Reason for Discontinuation (IMP Administered Subjects)
PDATA-2	Inclusion Criteria and Exclusion Criteria Not Met (Screened Subjects)
PDATA-3	Medical History and Complications (IMP Administered Subjects)
PDATA-4.1	Concomitant Medications (IMP Administered Subjects)
PDATA-4.2	Concomitant Therapy (IMP Administered Subjects)
PDATA-4.3	Treatment for Hyponatremia in SIADH Prior to Trial (IMP Administered Subjects)
PDATA-4.4	Concomitant Medications (Antineoplastic Agents) (IMP Administered Subjects)
PDATA-4.5	Concomitant Medications (Saline) (IMP Administered Subjects)
PDATA-4.6	Concomitant Medications (Infusion Solution other than Saline) (IMP Administered Subjects)
PDATA-4.7	Concomitant Medications (Sodium Chloride) (IMP Administered Subjects)

PDATA-4.8	Concomitant Medications (Affects Sodium Concentration) (IMP Administered Subjects)
PDATA-5	Vital Signs (IMP Administered Subjects)
PDATA-6	Electrocardiogram Results (IMP Administered Subjects)
PDATA-7	Pharmacokinetic Blood Draw Time and Plasma Drug Concentration (IMP Administered Subjects)
PDATA-8	Screen Failures
PDATA-9	Serum Osmolality and Plasma AVP Concentration at Central Laboratory (IMP Administered Subjects)
PDATA-10	Serum Osmolality and Plasma AVP Concentration at Each Center (IMP Administered Subjects)
PDATA-11	Daily Urine Volume, Daily Fluid Intake, Daily Fluid Balance, Urine Sodium Concentration, Daily Urine Excretion of Sodium and Urine Osmolality (IMP Administered Subjects)
PDATA-12	Past medical history of bilateral oophorectomy or hysterectomy (IMP Administered Subjects)
PDATA-13	Information on Hospitalization (IMP Administered Subjects)
PDATA-14	Subject lost to Follow-up (IMP Administered Subjects)
PDATA-15	Fluid Intake Restriction Compliance (IMP Administered Subjects)
EFF-1.1	Serum Sodium Concentration Measured at Central Laboratory (IMP Administered Subjects)
EFF-1.2	Serum Sodium Concentration Measured at Each Center (IMP Administered Subjects)
EFF-1.3	Serum Sodium Concentration Measured at Each Center Diagnosis and Treatment of SIADH Prior to Trial (IMP Administered Subjects)
EFF-2.1	Clinical Symptom Associated with Hyponatremia (IMP Administered Subjects)
EFF-2.2	Clinical Symptom Associated with Hyponatremia Diagnosis and Treatment of SIADH Prior to Trial (IMP Administered Subjects)