STATISTICAL ANALYSIS PLAN

A Multicenter, Open-label, Dose-defining Trial to Investigate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Tolvaptan in Pediatric Heart Failure Patients With Volume Overload

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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
TEAE	Treatment-emergent adverse event
descriptive statistics	number of subjects, mean, SD, minimum, median, and maximum
frequency distributions	number of subjects, %

1 Introduction

This statistical analysis plan documents the details of the statistical analysis methodology to be applied in the protocol of Trial 156-102-00123.

2 Trial Objectives

Primary: To determine the efficacy, safety, and dose and regimen of tolvaptan in pediatric heart failure patients with volume overload

Secondary: To determine the pharmacokinetics and pharmacodynamics of tolvaptan when administered to pediatric heart failure patients with volume overload

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, open-label, uncontrolled, dose-titration trial. In this trial, an ascending dose regimen where administration is started at a low dose is employed to ensure the safety of subjects. After completion of a screening examination, subjects will be hospitalized prior to the evening meal on 3 days before start of tolvaptan administration. Tolvaptan administration will be started at 0.05 mg/kg/day, and subjects with sufficient increase in urine volume will continue administration at 0.05 mg/kg/day for 3 days. For subjects whose urine volume does not sufficiently increase, the dose may be increased to 0.15, 0.3, or 0.5 mg/kg/day according to the specification. In that case, the dose should be decided for each individual subject to obtain sufficient increase in urine volume, and administration at the decided dose will be continued for 3 days. When the dose is increased to 0.5 mg/kg/day, administration at 0.5 mg/kg/day should be continued for 3 days. After final tolvaptan administration, subjects will continue to be hospitalized for 2 days to undergo monitoring of condition. Subjects will also undergo the follow-up 5 to 7 days after final tolvaptan administration.

3.2 Trial Treatments

3.2.1 Dose and Regimen

Subjects will take tolvaptan 1% granules or tolvaptan 15-mg tablet with water once daily after breakfast.

The initial dose of tolvaptan will be 0.05 mg/kg/day. From the second day of the treatment period and onward, if necessary the dose may be increased to 0.15, 0.3, or 0.5 mg/kg/day according to the rules specified in Section 3.2.2, and then the dose decided for each individual subject will be administered for 3 days. The dose of tolvaptan 1% granules to be administered will be determined depending on the subject's body weight on the day before start of tolvaptan administration; however, the maximum dose is 15 mg/day even if the calculated dose exceeds 15 mg/day. For administration at the maximum dose of 15 mg, tolvaptan 15-mg tablet may be administered in place of tolvaptan 1% granules. If the investigator or subinvestigator judges that there are an excessive aquaresis or safety concerns of subjects, the dose may be reduced (see Section 3.2.3). For subjects who need to continue treatment after 3-day administration at the dose decided individually, extended treatment for up to 4 days is allowed if the aim is to collect data on administration for up to 7 days and if the investigator or subinvestigator considers the safety of subjects to be ensured (including ensuring safety by dose reduction) (see Section 3.2.4). The dose, the date and time of administration, and the reason for dose reduction (for dose reduction, see Section 3.2.3) will be recorded in a source document and a case report form (CRF).

3.2.2 Increasing the Dose of Tolvaptan

Tolvaptan should be administered according to the following procedure. Daily urine volume should be assessed as "insufficient increase in urine volume" when it is less than 150% of that for the pretreatment observation period (1 day before start of tolvaptan administration), and "sufficient increase in urine volume" when it is at least 150%.

1) Tolvaptan administration will be started at 0.05 mg/kg/day, and administration at 0.05 mg/kg/day will be continued for 2 days.
2) For subjects with sufficient increase in urine volume on Day 1 or Day 2 of treatment, administration at 0.05 mg/kg/day will be continued for 3 days. For subjects with an insufficient increase in urine volume on Day 1 and Day 2 of treatment, the dose will be increased to 0.15 mg/kg/day on Day 3.
3) If a sufficient increase in urine volume is observed following 2-day administration at 0.15 mg/kg/day on Day 3 or Day 4 of the treatment period, administration at 0.15 mg/kg/day will be continued for 3 days. For subjects with an insufficient increase in urine volume on Day 3 and Day 4 of the treatment period, the dose will be increased to 0.3 mg/kg/day on Day 5.
4) If a sufficient increase in urine volume is observed following 2-day administration at 0.3 mg/kg/day on Day 5 or Day 6 of the treatment period, administration at 0.3 mg/kg/day will be continued for 3 days. For subjects with an insufficient increase in urine volume on Day 5 and Day 6 of the treatment period, the dose

will be increased to 0.5 mg/kg/day on Day 7, and administration at 0.5 mg/kg/day will be continued for 3 days.

3.2.3 Reducing the Dose of Tolvaptan

If symptoms associated with excessive aquaresis such as persistent sensation of thirst, dehydration, and hypernatremia are observed or there are safety concerns in subjects, at a discretion of the investigator or subinvestigator, the dose may be reduced only to the next lower dose. In that case, however, the dose of conventional diuretics should not be changed. If the dose of tolvaptan needs to be reduced before completion of 3-day administration at the same dose, it should be administered at the reduced dose for 3 days. If the dose of tolvaptan needs to be further reduced after dose reduction to the next lower dose, the subject will be judged to have a problem with tolerability to tolvaptan and should be withdrawn from the trial.

3.2.4 Extended Treatment With Tolvaptan

If the investigator or subinvestigator judges that the safety of subjects can continue to be ensured (including ensuring safety by dose reduction) after 3-day administration at the dose decided according to the specification for increasing the dose of tolvaptan (see Section 3.2.2), administration at that dose may be continued for up to 4 days (for up to 7 days in total).

In the case of an extended treatment with tolvaptan at reduced dose, the total number of administration days should be up to 7 days, which consists of "the days of administration at the dose just before the dose requiring reduction," "the days of administration at the dose requiring reduction" and "the days of administration at the dose reduced to the next lower dose."

3.2.5 Treatment Period

According to the patterns of treatment with tolvaptan, the duration of treatment period will be 3 days at the shortest, and 13 days at the longest if tolvaptan is administered until the dose is increased to 0.5 mg/kg/day, at 0.5 mg/kg/day for 3 days, and at 0.5 mg/kg/day for additional 4 days.

3.3 Trial Population

Pediatric heart failure patients age 6 months to less than 15 years with volume overload despite having received conventional diuretic therapy

"Pediatric heart failure patients with volume overload despite having received conventional diuretic therapy" are defined as patients with volume overload despite

having received any of the following diuretic therapies 1) in whom sufficient effects cannot be expected even if the dose of the diuretics is increased, or 2) in whom the investigator or subinvestigator judges that increasing the dose of the diuretics is difficult due to concerns regarding electrolyte abnormalities or other side effects.

- Furosemide (oral administration) ≥ 0.5 mg/kg/day
  (Azosemide 30 mg and torasemide 4 mg will be calculated as equivalent to furosemide 20 mg.)
- Hydrochlorothiazide ≥ 2 mg/kg/day
- Trichlormethiazide ≥ 0.05 mg/kg/day
- Spironolactone ≥ 1 mg/kg/day

3.4 Handling of Time Points

Case report form (CRF) Visit values at follow-up period will be used in summaries. Unscheduled Visit values will not be used.

Baseline for each variable is defined as follows.

Table 3.4-1 Handling of Time Points

Variable	Baseline
Body weight	Before start of IMP administration on the first day of the treatment period
Edema (lower limbs, eyelids, or other sites), jugular venous distension, dyspnea, respiration rate at rest, and pulse rate (edematous symptoms)	Pretreatment observation period (final measurement)
Pulmonary congestion, pleural effusion, and cardiothoracic ratio	Pretreatment observation period
Daily urine volume, daily fluid intake, daily fluid balance, urine osmolality, daily urine sodium excretion, and daily urine potassium excretion	From the day before the start of IMP administration to the first day of the treatment period
Laboratory test values, vital signs, and serum osmolality	The day before the start of IMP administration
Serum or blood sodium concentration and serum or blood potassium concentration (pharmacodynamics)	Before start of IMP administration on the first day of the treatment period
12-lead electrocardiogram	Pretreatment observation period
Plasma arginine vasopressin (AVP) concentration	The day before the start of IMP administration

For serum or blood sodium concentration (laboratory test values and pharmacodynamic endpoint), if the values measured at withdrawal examination are used to summarize the data at each time point, those values will be handled as the values at prebreakfast (however, if the values measured at withdrawal examination are used to summarize the data on the day after the final administration, these values will not be handled as the values at prebreakfast).

4 Sample Size

For the primary endpoint, the required sample size was set by first setting the threshold value for assessment of efficacy, and then using binomial distribution to determine the number of subjects required to maintain a 90% or higher probability that the lower limit of the 95% confidence interval (CI) for the percentage of subjects achieving the primary endpoint will be above the threshold value.

As reference information for the threshold value and binomial distribution parameter required to set the sample size for the trial, a threshold of 0.3 and a binomial distribution parameter of 0.5 to 0.6 were used based on interviews with clinicians, since no clinical trial results for administration of tolvaptan in pediatric patients have been obtained either in Japan or other countries.

Based on the above, the required number of subjects was calculated to be a minimum of 68 for a parameter of 0.5 and a minimum of 30 for a parameter of 0.6.

A sample size of 30 to 68 subjects was therefore considered to be appropriate, and in view of feasibility the number of subjects for the trial was set at 60.

5 Statistical Analysis Datasets

5.1 Full Analysis Set (FAS)

The full analysis set (FAS) includes all subjects who received at least 1 dose of the IMP and have postdose data on body weight and daily urine volume.

5.2 Dose Maintenance Analysis Set

The dose maintenance analysis set includes all subjects who received administration at same dose for at least 3 days in the full analysis set.

5.3 Safety Analysis Set (SAS)

The safety analysis set (SAS) includes all subjects who received at least 1 dose of the IMP.

5.4 Pharmacokinetic Analysis Set

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

5.5 Pharmacodynamic Analysis Set

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

5.6 Handling of Missing Data

If data on body weight and edematous symptoms cannot be obtained for assessment on (the day after) the third day of administration at the evaluation dose, the missing data will be imputed using the last available data obtained by that day.

If data on body weight on the day after the third day of administration at the evaluation dose cannot be obtained for the primary endpoint, the definition of the primary endpoint, "the mean daily urine volume for the 3 days of treatment at the evaluation dose" (Section 6.1), will be changed to "the mean daily urine volume from the start of administration at the evaluation dose to the day on which the imputed data on body weight is obtained."

If data on body weight, edematous symptoms, and safety endpoints cannot be obtained even on the day of (or the day after) the final administration at the evaluation dose and the day of (or the day after) the final administration, the missing data will be imputed using the last previous data obtained.

The missing data will be imputed when there are data after the administration at the evaluation dose for (the day after) the third day of administration at the evaluation dose and the day of (or the day after) the final administration at the evaluation dose, or after the IMP administration for the day of (or the day after) the final administration ('after the administration at the evaluation dose' for the analysis with baseline as the first day or immediately before the start of administration at the evaluation dose).

5.7 Definition of Evaluation Dose

Of the doses administered as specified in Section 3.2.2 and Section 3.2.3, the dose meeting the following criteria is defined as an evaluation dose.

1) If sufficient increase in urine volume was obtained during the course of dose escalation, or if the dose was increased to 0.5 mg/kg/day because sufficient increase in urine volume was not obtained:

- If the dose was not subsequently reduced, then that dose
- If the dose was reduced without having been administered for 3 days, then the reduced dose
- If the dose was reduced after having been administered for 3 days, then the dose before reduction

2) If IMP administration was discontinued before sufficient increase in urine volume was obtained during the course of dose increase:

- The dose at final IMP administration

6 Primary and Secondary Outcome Variables:

6.1 Primary Outcome Variables

The percentage of subjects who satisfy the following condition:

- Body weight on the day after the third day of treatment with tolvaptan at the evaluation dose (see Section 7.4) is decreased by 1.7% or more from the weight measured before breakfast on the first day of the treatment period

However, mean daily urine volume for the 3 days of treatment with tolvaptan at the evaluation dose must be higher than the daily urine volume for the pretreatment observation period. For subjects whose treatment period at evaluation dose is less than 3 days, mean daily urine volume at the time of the treatment at evaluation dose must be higher than the daily urine volume for the pretreatment observation period.

6.2 Secondary Outcome Variables

- Body weight
- Edematous symptoms (edema [lower limbs, eyelids, etc], dyspnea, jugular venous distension, pulmonary congestion, cardiothoracic ratio, respiration rate at rest, pulse rate, and pleural effusion), central venous pressure (only subjects with central venous catheterization), and retention of pericardial effusion (only subjects requiring echocardiography to confirm retention of pericardial effusion prior to tolvaptan administration)
- Daily urine volume

7 Disposition and Demographic Analysis

7.1 Subject Disposition

In the subjects who provided informed consent (screened subjects), the number of subjects who provided informed consent and received IMP administration, as well as the number and percentage (the denominator is the number of subjects treated with IMP administration) of completed subjects after IMP administration and discontinued subjects after IMP administration will be presented. The number and percentage of discontinued subjects after IMP administration will be presented by reason for discontinuation. The

number and percentage of subjects receiving extended treatment and those receiving a reduced dose will be presented.

The number and percentage of subjects included in and excluded from each analysis set in those treated with the IMP will be presented.

7.2 Demographic and Baseline Characteristics

For the full analysis set and safety analysis set, each variable will be calculated based on Table 7.2-1.

Table 7.2-1 Demographic and Baseline Characteristics

Variable	Time point	Method	Level
Age (years)	At the time of informed consent	Descriptive statistics	-
		Frequency distribution	6 months to less than 2 years, 2 years to less than 7 years, 7 years to less than 15 years
Gender	-	Frequency distribution	Female, Male, Undifferentiated
Height (cm)	Screening	Descriptive statistics	-
Body weight (kg)	Screening	Descriptive statistics	-
BMI (kg/m^2)[a]	Screening	Descriptive statistics	-
Race	-	Frequency distribution	American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other
Presence/absence of complications	Screening	Frequency distribution	Yes, No
Presence/absence of a medical history	Screening	Frequency distribution	Yes, No
Presence/absence of a history of surgery	Screening	Frequency distribution	Yes, No

[a]BMI = body weight (kg)/(height [m] × height [m])

7.3 Baseline Disease Evaluation

For the full analysis set and safety analysis set, each variable at baseline will be calculated.

Table 7.3-1 Baseline Disease Evaluation		
Variable	**Method**	**Level**
Edema • Lower limbs	Frequency distribution	None, Mild, Moderate, Severe
Edema • Eyelids	Frequency distribution	Present, Absent
Dyspnea	Frequency distribution	Present, Absent
Jugular venous distension	Frequency distribution	Present, Absent
Respiration rate at rest (times/minute)	Descriptive statistics	-
Pulse rate (times/minute)	Descriptive statistics	-
Pulmonary congestion	Frequency distribution	None, Mild, Moderate, Severe
Cardiothoracic ratio (%)	Descriptive statistics	-
Pleural effusion	Frequency distribution	Present, Absent

7.4 Treatment Compliance

For the full analysis set and safety analysis set, the frequency distributions for the presence/absence of days on which the IMP is not administered from the first day of the treatment period to the completion or discontinuation of the IMP administration will be calculated.

7.5 Prior and Concomitant Medications

For the full analysis set and safety analysis set, frequency distributions for usage of concomitant medication on the initial IMP administration day will be calculated.

Table 7.5-1 Usage of Concomitant Medication on the Initial IMP Administration Day	
Variable	**Level**
Category of diuretic *Concomitant use of diuretic drugs other than loop diuretic, thiazide diuretic, and anti-aldosterone drug is not summarized.	Monotherapy with loop diuretic, Loop diuretic + thiazide diuretic, Loop diuretic + anti-aldosterone drug, Loop diuretic + thiazide diuretic + anti-aldosterone drug
Thiazide diuretic	No, Yes
Anti-aldosterone drug	No, Yes
Drugs for heart failure other than diuretics	No, Yes
CYP3A4 inducers	No, Yes
CYP3A4 inhibitors	No, Yes

7.6 Protocol Deviations

For subjects administered IMP, frequency distributions for presence or absence of serious deviations in each CRF classification (Dosing, Inclusion/Exclusion Criteria, Met Withdrawal Criteria But Was Not Withdrawn, Prohibited Concomitant Medications) will be calculated. Frequency distributions of subjects with at least one serious deviation will also be calculated.

8 Efficacy Analysis

The following analyses will be performed in the full analysis set and the dose maintenance analysis set.

Efficacy will be comprehensively assessed based on the results of primary and other endpoints.

8.1 Primary Efficacy Endpoint

The definition of the primary endpoint is presented in Section 6.1.

8.1.1 Primary Efficacy Analysis

The number and percentage of subjects as well as the exact 95% CI based on binomial distribution will be calculated. The same calculations will be performed for body weight on the day after the final administration at the evaluation dose and the day after the final administration. The number and percentage of subjects will also be calculated for each

time point after the start of administration at the evaluation dose (the data to be summarized are from the first day of administration at the evaluation dose to the day after the final administration at the evaluation dose and follow-up period; the same shall apply hereinafter).

Analysis will also be performed using data collected on the first day of administration at the evaluation dose as the baseline.

8.2 Secondary Efficacy Endpoints

8.2.1 Percent Change in Body Weight

For body weight measured on the day after the third day of administration at the evaluation dose, the day after the final administration at the evaluation dose, and the day after the final administration, and their percent changes from baseline, the descriptive statistics (the number of subjects, mean, standard deviation, minimum, median, and maximum) will be calculated, and the 95% CI (based on t-distribution) of the percent changes from baseline in body weight will be calculated. The descriptive statistics will also be calculated for each time point after the start of administration at the evaluation dose.

Analysis will also be performed using data collected on the first day of administration at the evaluation dose as the baseline. In addition, data will be summarized by the number of days that had elapsed since the start of administration (the data to be summarized are from the initial IMP administration day to the day after the final administration; the same shall apply hereinafter).

The figure of percent changes in body weight from baseline will be prepared in individual subjects according to the number of days elapsed (with a reference line of −1.7%).

8.2.2 Edematous Symptoms (Edema [Lower Limbs, Eyelids, or Other Sites], Dyspnea, Jugular Venous Distension, Pulmonary Congestion, Cardiothoracic Ratio, Respiration Rate at Rest, Pulse Rate, and Pleural Effusion), Central Venous Pressure (Only Subjects With Central Venous Catheterization), and Retention of Pericardial Effusion (Only Subjects Requiring Echocardiography)

8.2.2.1 Edema (Lower Limbs, or Other Sites) and Pulmonary Congestion

A shift table will be prepared for changes in the degree of edema (lower limbs) from baseline to the third day of administration at the evaluation dose, the day of the final administration at the evaluation dose, and the day of the final administration. Another shift table will also be prepared for each time point after the start of administration at the

evaluation dose. Analysis will also be performed using data collected immediately before the start of administration at the evaluation dose as the baseline. In addition, data will be summarized by the number of days elapsed since the start of administration.

In addition, the number and percentage of subjects as well as the exact 95% CI based on binomial distribution will be calculated for the improvement rate (the percentage of subjects who had symptoms at baseline and showed remarkable improvement or improvement after the IMP administration; the same shall apply hereinafter) and the disappearance rate (the percentage of subjects who had symptoms at baseline and whose symptoms resolved after the IMP administration; the same shall apply hereinafter) on the third day of administration at the evaluation dose, the day of the final administration at the evaluation dose, and the day of the final administration. Analysis will also be performed using data collected immediately before the start of administration at the evaluation dose as the baseline (the phrase "after the IMP administration" for the improvement and disappearance rates is read as that of "after the start of administration at the evaluation dose"; the same shall apply hereinafter).

A shift table will be prepared for changes in the degree of pulmonary congestion from baseline through the day after the final administration.

The number and percentage of subjects as well as the exact 95% CI based on the binomial distribution will be calculated for the improvement and disappearance rates on the day after the final administration.

Table 8.2-1 Degree of Improvement of Lower Limb Edema, Other Edema, and Pulmonary Congestion

	Degree of improvement	Criterion
1	Remarkable improvement	Symptom resolution or improvement to at least 2 grades better
2	Improvement	Symptom improvement to 1 grade better (symptom resolution should be assessed as remarkable improvement)
3	No change	No change in the degree of symptom, or no symptom observed throughout the trial period
4	Worsening	Symptom worsening to at least 1 grade worse

8.2.2.2 Edema (Eyelids), Jugular Venous Distension, Dyspnea, and Pleural Effusion

A shift table will be prepared for changes in the degree of edema (eyelids), jugular venous distension, and dyspnea from baseline to the third day of administration at the evaluation dose, the day of the final administration at the evaluation dose, and the day of the final administration. Another shift table will also be prepared for each time point after the start of administration at the evaluation dose. Analysis will also be performed using

data collected immediately before the start of administration at the evaluation dose as the baseline. In addition, data will be summarized by the number of days elapsed since the start of administration.

The number and percentage of subjects as well as the exact 95% CI based on the binomial distribution will be calculated for the disappearance rate on the third day of administration at the evaluation dose, the day of the final administration at the evaluation dose, and the day of the final administration. Analysis will also be performed using data collected immediately before the start of administration at the evaluation dose as the baseline.

A shift table will be prepared for changes in the degree of pleural effusion from baseline through the day after the final administration.

The number and percentage of subjects as well as the exact 95% CI based on the binomial distribution will be calculated for the disappearance rate on the day after the final administration.

8.2.2.3 Cardiothoracic Ratio, Respiration Rate at Rest, and Pulse Rate

For respiration rate at rest and pulse rate measured on the third day of administration at the evaluation dose, the day of the final administration at the evaluation dose, and the day of the final administration, and their changes from baseline, the descriptive statistics will be calculated and the 95% CI (based on the t-distribution) of changes from baseline will be calculated. The descriptive statistics will also be calculated for each time point after the start of administration at the evaluation dose. Analysis will also be performed using data collected immediately before the start of administration at the evaluation dose as the baseline. In addition, data will be summarized by the number of days elapsed since the start of administration.

For the cardiothoracic ratio measured on the day after the final administration and the changes from baseline, the descriptive statistics will be calculated and the 95% CI (based on the t-distribution) of changes from baseline will be calculated.

8.2.2.4 Central Venous Pressure

A list will be prepared.

8.2.2.5 Retention of Pericardial Effusion

A list will be prepared.

8.2.3 Daily Urine Volume

The data based on which the accurate daily volume is measured will be used.

Descriptive statistics of measured values and changes from baseline will be calculated for each time point after start of administration at evaluation dose. An analysis will also be performed using data collected immediately before start of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

The percent changes from baseline will also be summarized in the same manner.

8.3 Subgroup Analyses and Analysis by Evaluation Dose

As a subgroup analysis, the items will also be analyzed for each age group (young age, 6 months to less than 2 years; middle age, 2 years to less than 7 years; and old age, 7 years to less than 15 years).

The same analysis will be performed for each evaluation dose (0.05, 0.15, 0.3, and 0.5 mg/kg/day, a classification entered in a CRF; the same shall apply hereinafter) (in the entire and each age group).

Subgroup analyses and analyses by the evaluation dose of the primary endpoint, percent changes in body weight, and edematous symptoms will be performed for (the day after) the third day of administration at the evaluation dose, the day of (or the day after) the final administration at the evaluation dose, and the day of (or the day after) the final administration (except for the summarization by the number of days that had elapsed since the start of administration).

9 Safety Analyses

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

9.1 Extent of Exposure

Frequency distributions of the number of subjects for each number of days of administration from the first day of the treatment period to the completion or discontinuation of the IMP administration (1 to 3 days, 4 to 5 days, 6 to 7 days, 8 to 9 days, and 10 to 13 days) will be calculated. Descriptive statistics will be calculated for the number of days of administration. To be calculated for the entire and by the evaluation dose.

Frequency distributions will be calculated for the evaluation dose.

9.2 Adverse Events

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

The above AEs will also be summarized by evaluation dose. In addition, summaries of AEs by the evaluation dose after the start of administration at the evaluation dose will be prepared. Summarization for each age group (young age, 6 months to less than 2 years; middle age, 2 years to less than 7 years; and old age, 7 years to less than 15 years) will also be prepared.

9.3 Clinical Laboratory Data

For clinical laboratory tests other than qualitative urinalysis (except for pH and specific gravity in urinalysis), descriptive statistics of the measured values and changes from baseline at each time point after the start of administration at the evaluation dose and on the day after the final administration will be calculated. For qualitative urinalysis parameters, shift tables at each time point after the start of administration at the evaluation dose and on the day after the final administration compared with baseline will be prepared (except for color). For clinical laboratory test parameters other than qualitative urinalysis, a specified site reference range will be used to classify the measurements into measurements “within the reference range,” “below the reference range,” or “above the reference range,” and shift tables of classifications at each time point after the start of administration at the evaluation dose and on the day after the final administration compared with baseline will be prepared.

An analysis will also be performed using data collected immediately before start of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

For ALP, the value calculated by the IFCC method will be used for the descriptive statistics (for the measured values by the JSCC method, a conversion factor of 0.35 will be used to summarize the converted values).

9.4 Vital Sign Data

For vital signs, descriptive statistics of measured values and changes from baseline at each time point after the start of administration at the evaluation dose and on the day after the final administration will be calculated.

An analysis will also be performed using data collected immediately before start of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

9.5 Electrocardiogram Data

For each 12-lead ECG parameter, descriptive statistics of measured values and changes from baseline will be calculated on the day after the final administration and the follow-up period.

For QTc interval (QTcB, QTcF), the number and percentage of subjects with a QTc interval of > 450, > 480, or > 500 msec measured at baseline, on the day after the final administration and in the follow-up period will be calculated. The number and percentage of subjects with a change in QTc interval from baseline of > 30 or > 60 msec on the day after the final administration and the follow-up period will also be calculated. A shift table for QTc interpretation (normal or abnormal) will be prepared from baseline through the day after the final administration and follow-up period. The QTc interpretation (normal or abnormal) by the site (the investigator or subinvestigator) will be used rather than that of the central ECG measurement facility.

10 Pharmacokinetic Analyses

In the pharmacokinetic analysis set, the plasma concentrations of OPC-41061 and its metabolites (DM-4103 and DM-4107) will be summarized by descriptive statistics, in the following 2 ways. The doses used for tabulation (0.05, 0.15, 0.3, and 0.5 mg/kg/day) will be those on the date of blood sampling (the classification entered in the CRF).

- Summarization for each compound, time point of blood sampling, and dose
- Summarization for each compound, time point of blood sampling, dose, and age group (young age, 6 months to less than 2 years; middle age, 2 years to less than 7 years; and old age, 7 years to less than 15 years)

Descriptive statistics to be determined are the number of subjects, mean, standard deviation, coefficient of variation, minimum, median, and maximum.

For OPC-41061, a figure of changes in the plasma concentration will also be prepared for each subject by dose. The actual time points of blood sampling ("0 (zero)" before administration) will be used for the horizontal axis (X axis) of the figure.

When calculating descriptive statistics and preparing figures, plasma drug concentrations below the lower limit of quantitation will be handled as "0 (zero)" until the first quantitative value after administration is obtained and as missing values after the quantitative value.

11 Pharmacodynamic Analyses

A pharmacodynamic analysis will be performed in the pharmacodynamic analysis set.

For urine osmolality, daily urine sodium excretion, and daily urine potassium excretion, the data of the daily volume of the complete urine collection will be used.

As a subgroup analysis, the items will also be analyzed for each age group (young age, 6 months to less than 2 years; middle age, 2 years to less than 7 years; and old age, 7 years to less than 15 years).

The same analysis will be performed for each evaluation dose (0.05, 0.15, 0.3, and 0.5 mg/kg/day) (in the entire and each age group).

For the items listed below, descriptive statistics of measured values and changes from baseline at each time point after start of administration at evaluation dose will be determined.

An analysis will also be performed using data collected immediately before start of administration at evaluation dose as a baseline. In addition, data will be summarized by the number of days elapsed since start of administration.

- Daily fluid intake
- Daily fluid balance
- Serum osmolality
- Serum or blood sodium concentration
- Serum or blood potassium concentration
- Urine osmolality
- Daily urine sodium excretion
- Daily urine potassium excretion

For the plasma AVP concentration, descriptive statistics of measured values and changes from baseline will be calculated on the day after the final administration (CRF Visit).

12 Pharmacogenomic Analyses

No pharmacogenomic analysis will be performed in this trial.

13 Interim Analysis

No interim analysis will be performed in this trial.

14 Changes in the Planned Analyses

- Since it was a clerical error, the following description in Section 6.2 in the protocol was not to be performed: “In the subgroup analysis and the analysis by the evaluation dose, data collected on the day after the third day of administration at the evaluation dose, the day after the final administration at the evaluation dose, and the day after the final administration will be analyzed.” Since it was a clerical error, the following description for the plasma AVP concentration was added separately: “For the plasma AVP concentration, descriptive statistics of measured values and changes from baseline will be calculated on the day after the final administration (CRF Visit).”
- A summary of percent changes from baseline was added to the summary in Section 7.5.2.3 in the protocol to consider the effect of baseline values.
- Since it was a clerical error, the summarization at each time point after the start of administration at the evaluation dose and the summarization by the number of days elapsed since the start of administration in Section 7.7.4 in the protocol were not to be performed.
- Since it was considered difficult to assess several sites collectively, other edema in Section 7.5.2.2.1 in the protocol was not to be summarized.
- For edema, dyspnea, jugular venous distention, respiration rate at rest, and pulse rate among the items of edematous symptoms, the schedule for assessment was when possible after the IMP administration on each date of assessment, and the assessment on the day after extended treatment would not be that on the third day of administration at the evaluation dose. Therefore, the assessment “on the day after the third day of administration at the evaluation dose, the day after the final administration at the evaluation dose, and the day after the final administration” in each section of Section 7.5.2.2 in the protocol was regarded as that “on the third day of administration at the evaluation dose, the day of the final administration at

the evaluation dose, and the day of the final administration." In accordance with this, Section 7.3 in the protocol was also corrected to the corresponding description.

- In light of the schedule of assessments (only when the assessment point after the IMP administration is on the day after the final administration) for pulmonary congestion, cardiothoracic ratio, and pleural effusion among the items of edematous symptoms, the assessment "on the day after the third day of administration at the evaluation dose, the day after the final administration at the evaluation dose, and the day after the final administration" in each section of Section 7.5.2.2 in the protocol was regarded as only that "on the day after the final administration."
- Summarization of data from Section 7.5.2.2.4 and Section 7.5.2.2.5 in the protocol was limited to the preparation of a list because the data were not collected at the specified time point.

15 References

None.

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CT-6.7.4.3 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Age Category (Full Analysis Set)

CT-6.7.4.4 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Age Category (Dose Maintenance Set)

CT-6.7.4.5 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Evaluation Dose (Full Analysis Set)

CT-6.7.4.6 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Evaluation Dose (Dose Maintenance Set)

CT-6.7.4.7 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Evaluation Dose by Age Category (Full Analysis Set)

CT-6.7.4.8 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Evaluation Dose by Age Category (Dose Maintenance Set)

CT-6.7.5.1 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume with Day of Just Before Start of Evaluation Dose as Baseline (Full Analysis Set)

CT-6.7.5.2 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume with Day of Just Before Start of Evaluation Dose as Baseline (Dose Maintenance Set)

CT-6.7.5.3 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume with Day of Just Before Start of Evaluation Dose as Baseline by Age Category (Full Analysis Set)

CT-6.7.5.4 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume with Day of Just Before Start of Evaluation Dose as Baseline by Age Category (Dose Maintenance Set)

CT-6.7.5.5 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume with Day of Just Before Start of Evaluation Dose as Baseline by Evaluation Dose (Full Analysis Set)

CT-6.7.5.6 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume with Day of Just Before Start of Evaluation Dose as Baseline by Evaluation Dose (Dose Maintenance Set)

CT-6.7.5.7 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume with Day of Just Before Start of Evaluation Dose as Baseline by Evaluation Dose by Age Category (Full Analysis Set)

CT-6.7.5.8 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume with Day of Just Before Start of Evaluation Dose as Baseline by Evaluation Dose by Age Category (Dose Maintenance Set)

CT-6.7.6.1 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Days after the start of IMP administration (Full Analysis Set)

CT-6.7.6.2 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Days after the start of IMP administration (Dose Maintenance Set)

CT-6.7.6.3 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Days after the start of IMP administration by Age Category (Full Analysis Set)

CT-6.7.6.4 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Days after the start of IMP administration by Age Category (Dose Maintenance Set)

CT-6.7.6.5 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Days after the start of IMP administration by Evaluation Dose (Full Analysis Set)

CT-6.7.6.6 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Days after the start of IMP administration by Evaluation Dose (Dose Maintenance Set)

CT-6.7.6.7 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Days after the start of IMP administration by Evaluation Dose by Age Category (Full Analysis Set)

CT-6.7.6.8 Descriptive Statistics for Change Rate from Baseline in Daily Urine Volume by Days after the start of IMP administration by Evaluation Dose by Age Category (Dose Maintenance Set)

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

CT-7.2.1 Treatment Compliance (Full Analysis Set)

CT-7.2.2 Treatment Compliance (Safety Analysis Set)

CT-8.1.1 Overall Summary of Adverse Events (Safety Analysis Set)

CT-8.1.2.1 Incidence of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.1.2.2 Incidence of Treatment-emergent Adverse Events occurring in >= 2 subjects by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.1.3 Incidence of Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.1.4 Incidence of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.1.5 Incidence of Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.2.1 Overall Summary of Adverse Events by Age Category (Safety Analysis Set)

CT-8.2.2 Incidence of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Age Category (Safety Analysis Set)

CT-8.2.3 Incidence of Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Age Category (Safety Analysis Set)

CT-8.2.4 Incidence of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Age Category (Safety Analysis Set)

CT-8.2.5 Incidence of Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Age Category (Safety Analysis Set)

CT-8.3.1 Overall Summary of Adverse Events by Evaluation Dose (Safety Analysis Set)

CT-8.3.2 Incidence of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Evaluation Dose (Safety Analysis Set)

CT-8.3.3 Incidence of Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Evaluation Dose (Safety Analysis Set)

CT-8.3.4 Incidence of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Evaluation Dose (Safety Analysis Set)

CT-8.3.5 Incidence of Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term by Evaluation Dose (Safety Analysis Set)

CT-8.4.1 Overall Summary of Adverse Events after Start of Evaluation Dose Administration by Evaluation Dose (Safety Analysis Set)

CT-8.4.2 Incidence of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term after Start of Evaluation Dose Administration by Evaluation Dose (Safety Analysis Set)

CT-8.4.3 Incidence of Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term after Start of Evaluation Dose Administration by Evaluation Dose (Safety Analysis Set)

CT-8.4.4 Incidence of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term after Start of Evaluation Dose Administration by Evaluation Dose (Safety Analysis Set)

CT-8.4.5 Incidence of Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term after Start of Evaluation Dose Administration by Evaluation Dose (Safety Analysis Set)

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

CT-9.1.3 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-9.1.4 Incidence of Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-9.1.5 Incidence 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-9.1.6 Incidence of 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-9.2.1 Incidence of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Age Category (Safety Analysis Set)

CT-9.2.2 Incidence of Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Age Category (Safety Analysis Set)

CT-9.2.3 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Age Category (Safety Analysis Set)

CT-9.2.4 Incidence of Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Age Category (Safety Analysis Set)

CT-9.2.5 Incidence of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Age Category (Safety Analysis Set)

CT-9.2.6 Incidence of Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Age Category (Safety Analysis Set)

CT-9.3.1 Incidence of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Evaluation Dose (Safety Analysis Set)

CT-9.3.2 Incidence of Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term by Evaluation Dose (Safety Analysis Set)

CT-9.3.3 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Evaluation Dose (Safety Analysis Set)

CT-9.3.4 Incidence of Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Evaluation Dose (Safety Analysis Set)

CT-9.3.5 Incidence of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Evaluation Dose (Safety Analysis Set)

CT-9.3.6 Incidence of Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Evaluation Dose (Safety Analysis Set)

CT-9.4.1 Incidence of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term after Start of Evaluation Dose Administration by Evaluation Dose (Safety Analysis Set)

CT-9.4.2 Incidence of Drug-related Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term after Start of Evaluation Dose Administration by Evaluation Dose (Safety Analysis Set)

CT-9.4.3 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term after Start of Evaluation Dose Administration by Evaluation Dose (Safety Analysis Set)

CT-9.4.4 Incidence of Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term after Start of Evaluation Dose Administration by Evaluation Dose (Safety Analysis Set)

CT-9.4.5 Incidence of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term after Start of Evaluation Dose Administration by Evaluation Dose (Safety Analysis Set)

CT-9.4.6 Incidence of Drug-related Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by

	MedDRA System Organ Class and Preferred Term after Start of Evaluation Dose Administration by Evaluation Dose (Safety Analysis Set)
CT-9.7	Listing of Deaths (Safety Analysis Set)
CT-9.8	Listing of Serious Adverse Events Other Than Death (Safety Analysis Set)
CT-9.9	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) with Day of Just Before Start of Evaluation Dose as Baseline (Safety Analysis Set)
CT-10.1.3	Mean Change from Baseline in Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) by Days after the start of IMP administration (Safety Analysis Set)
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) with Day of Just Before Start of Evaluation Dose as Baseline (Safety Analysis Set)
CT-10.2.3	Shift Tables of Clinical Laboratory Test Results (Qualitative Urinalysis) by Days after the start of IMP administration (Safety Analysis Set)
CT-10.3.1	Shift Tables of Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) (Safety Analysis Set)
CT-10.3.2	Shift Tables of Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) with Day of Just Before Start of Evaluation Dose as Baseline (Safety Analysis Set)
CT-10.3.3	Shift Tables of Clinical Laboratory Test Results (Serum Chemistry, Hematology, Urinalysis) by Days after the start of IMP administration (Safety Analysis Set)
CT-10.4.1	Shift Tables of Clinical Laboratory Test Results (NA, K) (Safety Analysis Set)

CT-10.4.2	Shift Tables of Clinical Laboratory Test Results (NA, K) with Day of Just Before Start of Evaluation Dose as Baseline (Safety Analysis Set)
CT-10.4.3	Shift Tables of Clinical Laboratory Test Results (NA, K) by Days after the start of IMP administration (Safety Analysis Set)
CT-10.5	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 with Day of Just Before Start of Evaluation Dose as Baseline (Safety Analysis Set)
CT-11.3	Mean Change from Baseline in Vital Signs by Days after the start of IMP administration (Safety Analysis Set)
CT-12.1	Mean Change from Baseline in ECG Evaluations (Safety Analysis Set)
CT-12.2	Shift Table of 12-Lead ECG Findings (Normal/Abnormal Assessments) (Safety Analysis Set)
CT-12.3	Incidence of Categorical Changes in ECG Evaluations (Safety Analysis Set)
PKT-1.1	Individual and Summary of OPC-41061 Plasma Concentration on the Third Day of Administration at Each Dose and Day After Final Administration (Pharmacokinetics Analysis Set)
PKT-1.2	Individual and Summary of DM-4103 Plasma Concentration on the Third Day of Administration at Each Dose and Day After Final Administration (Pharmacokinetics Analysis Set)
PKT-1.3	Individual and Summary of DM-4107 Plasma Concentration on the Third Day of Administration at Each Dose and Day After Final Administration (Pharmacokinetics Analysis Set)
PKT-2.1	Individual and Summary of OPC-41061 Plasma Concentration on the Third Day of Administration at Each Dose and Day After Final Administration by Age Category (Pharmacokinetics Analysis Set)
PKT-2.2	Individual and Summary of DM-4103 Plasma Concentration on the Third Day of Administration at Each Dose and Day After Final Administration by Age Category (Pharmacokinetics Analysis Set)

PKT-2.3 Individual and Summary of DM-4107 Plasma Concentration on the Third Day of Administration at Each Dose and Day After Final Administration by Age Category (Pharmacokinetics Analysis Set)

PDT-1.1.1 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium (Pharmacodynamics Analysis Set)

PDT-1.1.2 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium by Age Category (Pharmacodynamics Analysis Set)

PDT-1.1.3 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium by Evaluation Dose (Pharmacodynamics Analysis Set)

PDT-1.1.4 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium by Evaluation Dose by Age Category (Pharmacodynamics Analysis Set)

PDT-1.2.1 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium with Day of Just Before Start of Evaluation Dose as Baseline (Pharmacodynamics Analysis Set)

PDT-1.2.2 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium with Day of Just Before Start of Evaluation Dose as Baseline by Age Category (Pharmacodynamics Analysis Set)

PDT-1.2.3 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium with Day of Just Before Start of Evaluation Dose as Baseline by Evaluation Dose (Pharmacodynamics Analysis Set)

PDT-1.2.4 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium with Day of Just Before Start of Evaluation Dose as Baseline by Evaluation Dose by Age Category (Pharmacodynamics Analysis Set)

PDT-1.3.1 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium by Days after the start of IMP administration (Pharmacodynamics Analysis Set)

PDT-1.3.2 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium by Days after the start of IMP administration by Age Category (Pharmacodynamics Analysis Set)

PDT-1.3.3 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium by Days after the start of IMP administration by Evaluation Dose (Pharmacodynamics Analysis Set)

PDT-1.3.4 Descriptive Statistics for Daily Fluid Intake, Daily Fluid Balance, Urine Osmolality, Daily Urine Excretion of Sodium and Potassium by Days after the start of IMP administration by Evaluation Dose by Age Category (Pharmacodynamics Analysis Set)

PDT-2.1.1 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration (Pharmacodynamics Analysis Set)

PDT-2.1.2 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration by Age Category (Pharmacodynamics Analysis Set)

PDT-2.1.3 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration by Evaluation Dose (Pharmacodynamics Analysis Set)

PDT-2.1.4 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration by Evaluation Dose by Age Category (Pharmacodynamics Analysis Set)

PDT-2.2.1 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration with Day of Just Before Start of Evaluation Dose as Baseline (Pharmacodynamics Analysis Set)

PDT-2.2.2 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration with Day of Just Before Start of Evaluation Dose as Baseline by Age Category (Pharmacodynamics Analysis Set)

PDT-2.2.3 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration with Day of Just Before Start of

Evaluation Dose as Baseline by Evaluation Dose (Pharmacodynamics Analysis Set)

PDT-2.2.4 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration with Day of Just Before Start of Evaluation Dose as Baseline by Evaluation Dose by Age Category (Pharmacodynamics Analysis Set)

PDT-2.3.1 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration by Days after the start of IMP administration (Pharmacodynamics Analysis Set)

PDT-2.3.2 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration by Days after the start of IMP administration by Age Category (Pharmacodynamics Analysis Set)

PDT-2.3.3 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration by Days after the start of IMP administration by Evaluation Dose (Pharmacodynamics Analysis Set)

PDT-2.3.4 Descriptive Statistics for Serum or Blood Sodium Concentration and Serum or Blood Potassium Concentration by Days after the start of IMP administration by Evaluation Dose by Age Category (Pharmacodynamics Analysis Set)

PDT-3.1.1 Descriptive Statistics for Serum Osmolality (Pharmacodynamics Analysis Set)

PDT-3.1.2 Descriptive Statistics for Serum Osmolality by Age Category (Pharmacodynamics Analysis Set)

PDT-3.1.3 Descriptive Statistics for Serum Osmolality by Evaluation Dose (Pharmacodynamics Analysis Set)

PDT-3.1.4 Descriptive Statistics for Serum Osmolality by Evaluation Dose by Age Category (Pharmacodynamics Analysis Set)

PDT-3.2.1 Descriptive Statistics for Serum Osmolality with Day of Just Before Start of Evaluation Dose as Baseline (Pharmacodynamics Analysis Set)

PDT-3.2.2 Descriptive Statistics for Serum Osmolality with Day of Just Before Start of Evaluation Dose as Baseline by Age Category (Pharmacodynamics Analysis Set)

PDT-3.2.3 Descriptive Statistics for Serum Osmolality with Day of Just Before Start of Evaluation Dose as Baseline by Evaluation Dose (Pharmacodynamics Analysis Set)

PDT-3.2.4 Descriptive Statistics for Serum Osmolality with Day of Just Before Start of Evaluation Dose as Baseline by Evaluation Dose by Age Category (Pharmacodynamics Analysis Set)

PDT-3.3.1 Descriptive Statistics for Serum Osmolality by Days after the start of IMP administration (Pharmacodynamics Analysis Set)

PDT-3.3.2 Descriptive Statistics for Serum Osmolality by Days after the start of IMP administration by Age Category (Pharmacodynamics Analysis Set)

PDT-3.3.3 Descriptive Statistics for Serum Osmolality by Days after the start of IMP administration by Evaluation Dose (Pharmacodynamics Analysis Set)

PDT-3.3.4 Descriptive Statistics for Serum Osmolality by Days after the start of IMP administration by Evaluation Dose by Age Category (Pharmacodynamics Analysis Set)

PDT-4.1 Descriptive Statistics for Plasma AVP Concentration (Pharmacodynamics Analysis Set)

PDT-4.2 Descriptive Statistics for Plasma AVP Concentration by Age Category (Pharmacodynamics Analysis Set)

PDT-4.3 Descriptive Statistics for Plasma AVP Concentration by Evaluation Dose (Pharmacodynamics Analysis Set)

PDT-4.4 Descriptive Statistics for Plasma AVP Concentration by Evaluation Dose by Age Category (Pharmacodynamics Analysis Set)

CF-1.1 Individual Transition Diagram for Change Rate from Baseline in Body Weight (Full Analysis Set)

CF-1.2 Individual Transition Diagram for Change Rate from Baseline in Body Weight (Dose Maintenance Set)

CF-2.1 Individual Transition Diagram for Change Rate from Baseline in Body Weight by Age Category (Full Analysis Set)

CF-2.2 Individual Transition Diagram for Change Rate from Baseline in Body Weight by Age Category (Dose Maintenance Set)

CF-3.1 Individual Transition Diagram for Change Rate from Baseline in Body Weight by Evaluation Dose (Full Analysis Set)

CF-3.2 Individual Transition Diagram for Change Rate from Baseline in Body Weight by Evaluation Dose (Dose Maintenance Set)

CF-4.1 Individual Transition Diagram for Change Rate from Baseline in Body Weight by Evaluation Dose by Age Category (Full Analysis Set)

CF-4.2 Individual Transition Diagram for Change Rate from Baseline in Body Weight by Evaluation Dose by Age Category (Dose Maintenance Set)

PKF-1.1 Individual OPC-41061 Plasma Concentrations on the Third Day of Administration at Each Dose (Pharmacokinetics Analysis 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 Other Than Medication (IMP Administered Subjects)
PDATA-5	Vital Signs (IMP Administered Subjects)
PDATA-6	Electrocardiogram Results (IMP Administered Subjects)
PDATA-7	Pharmacokinetic Blood Draw Time (IMP Administered Subjects)
PDATA-8	Screen Failures
PDATA-9	Serum Sodium Concentration, Serum Potassium Concentration (IMP Administered Subjects)
PDATA-10	Serum Osmolality, Plasma AVP Concentration (IMP Administered Subjects)

PDATA-11	Daily Urine Volume, Daily Fluid Intake, Daily Fluid Balance (IMP Administered Subjects)
PDATA-12	Urine Sodium Concentration, Urine Osmolality, Urine Potassium Concentration, Daily Urine Excretion of Sodium and Potassium (IMP Administered Subjects)
EFF-1	Body Weight (IMP Administered Subjects)
EFF-2	Congestive Symptoms (Lower Limb Edema, Eyelids Edema, Dyspnea, Juglar Venous Distension, Respiration Rate at Rest, Pulse Rate, Pleural Effusion) (IMP Administered Subjects)
EFF-3	Congestive Symptoms (Other Edema) (IMP Administered Subjects)
EFF-4	Chest X-ray (Pulmonary Congestion, Cardiothoracic Ratio) (IMP Administered Subjects)
EFF-5	Congestive Symptoms (Central Venous Pressure) (IMP Administered Subjects)
EFF-6	Congestive Symptoms (Retention of Pericardial Effusion) (IMP Administered Subjects)