STATISTICAL ANALYSIS PLAN

A Multicenter, Open-label, Uncontrolled Clinical Trial to Confirm the Tolerability of OPC-61815 in Patients With Congestive Heart Failure Who Have Difficulty With or Are Incapable of Oral Intake

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Otsuka Pharmaceutical Co., Ltd.

Investigational New Drug OPC-61815

Protocol No. 263-102-00004

A Multicenter, Open-label, Uncontrolled Clinical Trial to Confirm the Tolerability of OPC-61815 in Patients With Congestive Heart Failure Who Have Difficulty With or Are Incapable of Oral Intake

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AVP	Arginine vasopressin
BMI	Body mass index
BNP	Brain natriuretic peptide
CHF	Congestive heart failure
CRF	Case report form
ICD	Implantable cardioverter defibrillator
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PT	Preferred Term
QTc	QT corrected for heart rate
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

1 Introduction

This statistical analysis plan documents the details of the statistical analysis methodology to be applied in the protocol of Trial 263-102-00004.

2 Trial Objectives

To confirm the tolerability of intravenous administration of OPC-61815 at 8 or 16 mg once daily for a maximum of 5 days to congestive heart failure (CHF) patients with volume overload despite having received diuretics (injection) other than vasopressin antagonists and who have difficulty with or are incapable of oral intake.

3 Trial Design

3.1 Type/Design of Trial

This trial is a multi-center, uncontrolled, open-label trial to confirm the tolerability of intravenous administration of OPC-61815 at 8 or 16 mg once daily for a maximum of 5 days to CHF patients with volume overload despite having received diuretics (injection) other than vasopressin antagonists and who have difficulty with or are incapable of oral intake.

Subjects who meet all of the inclusion criteria and fall under none of the exclusion criteria at the screening examination will be advanced to the treatment period during which OPC-61815 will be intravenously administered at 8 or 16 mg once daily. OPC-61815 treatment will start at 8 mg, and the investigator or subinvestigator will increase the dose to 16 mg on Day 2 or 3 after confirming that the subject meets the dose escalation criteria. The procedures for dose escalation decision are shown in the protocol Section 3.2.2. The maximum treatment duration is 5 days; however, investigational medicinal product (IMP) treatment may be discontinued before Day 5 according to the rules specified in the protocol Section 3.2.3. Concomitant use of loop diuretics will continue until the end of the treatment period.

The completion assessment will be conducted on Day 6 (or the day after the final IMP administration) and the follow-up assessment will be conducted at some time between 7 and 10 days after the final IMP administration. Subjects will be hospitalized from the time of informed consent to Day 6 (or the day after the final IMP administration).

3.2 Trial Treatments

The investigator or subinvestigator will administer OPC-61815 once daily as 1-hour infusion (55 to 70 minutes allowable) according to the IMP administration procedures

specified separately. OPC-61815 treatment will start with 8 mg, and eligibility for dose escalation will be assessed on Day 2 of the treatment period (and again on Day 3 of the treatment period, if applicable) according to the protocol Section 3.2.2. If the dose escalation criteria are met, the dose will be increased to 16 mg; if the criteria are not met, administration will continue at 8 mg.

When adverse events (AEs) associated with the aquaretic effect of OPC-61815 including hypernatremia, dehydration, and thirst occur or worsen after the dose is increased to 16 mg and dose reduction is judged to be necessary by the investigator or subinvestigator, the dose will be returned to 8 mg. The dose may not be re-escalated to 16 mg once it has been reduced to 8 mg. The start time of administration on Day 2 and onward should coincide roughly (±1 hour, whenever possible) with the start time on Day 1.

3.3 Trial Population

The trial population will comprise a total of 40 Japanese male and female CHF patients aged 20 to 85, inclusive, with volume overload despite having received injection diuretics other than vasopressin antagonists and who have difficulty with or are incapable of oral intake and who are capable of being hospitalized from the time of informed consent until the end of the treatment period.

3.4 Handling of Time Points

Case report form (CRF) Visit values at each time point (time points from baseline in the screening, treatment, and follow-up periods as specified in the protocol Table 3.7.1) 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.

According to the rules specified in the protocol Section 3.2.3, for the completion assessment of subjects who have completed treatment after a treatment period of shorter than 5 days, the CRF Visit will be set to correspond with the day of assessment for the analysis visit. Concerning interval urine samples, the daily urine volume will be calculated by summing all the interval urine volumes that constitute the daily urine volume for that day. If the interval urine sample is the last one for that day, the corresponding interval will be set as the analysis interval. The same rules also apply to fluid intake and urine electrolyte excretion. Other variables specified in the corresponding CRF Visit to be measured multiple times will be set to precede IMP administration.

Baseline and final administration time point for each variable are defined as follows.

Table 3.4-1 Handling of Time Points

Variable	Baseline	Final Administration Time Point
Clinical laboratory value	Before IMP administration on Day 1	Day after final IMP administration
Vital signs	Before IMP administration on Day 1 (Screening values will be used if the values at screening are measured on Day 1 but not measured prior to the IMP administration on that day.)	Day after final IMP administration
12-lead ECG	Before IMP administration on Day 1	Day after final IMP administration
Daily urine volume, daily fluid intake, daily fluid balance	Within 24 hours before IMP administration on Day1	-
Serum sodium concentration, serum potassium concentration, serum osmolality	Before IMP administration on Day 1	-
Daily urine sodium excretion, daily urine potassium excretion	Within 24 hours before IMP administration on Day1	-
Urine osmolality	Within 24 hours before IMP administration on Day1	-
Biomarkers (plasma AVP concentration, plasma renin activity, plasma brain natriuretic peptide [BNP] concentration, serum N-terminal pro-brain natriuretic peptide [NT-proBNP] concentration, and serum troponin I concentration)	Before IMP administration on Day 1	Day after final IMP administration
Body weight	Before IMP administration on Day 1 (Screening values will be used if the values at screening are measured on Day 1 but not measured prior to the IMP administration on that day.)	Day after final IMP administration
Congestive symptoms (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, cardiac third sound)	Screening	Day after final IMP administration
Pulmonary congestion, cardiothoracic ratio	Screening	Day after final IMP administration
Respiratory rate, paroxysmal nocturnal dyspnea, orthopnea	Screening	Day after final IMP administration
Subject-assessed dyspnea	Screening	Day after final IMP administration
NYHA classification	Screening	Day after final IMP administration

4 Sample Size

Sample size: 40 subjects (number of subjects started on OPC-61815). For a sample size of 40 subjects, the probability of AE occurring at an incidence of 5% and 4% is respectively 87% and 80%.

5 Statistical Analysis Datasets

5.1 Safety Analysis Set

The safety dataset includes all subjects who received at least one dose of IMP.

5.2 Pharmacodynamic Analysis Set

The pharmacodynamic dataset includes all subjects who received at least one dose of IMP and have postdose pharmacodynamic data.

5.3 Efficacy Analysis Set

The efficacy dataset includes all subjects who received at least one dose of IMP and have postdose efficacy data.

5.4 Handling of Missing Data

Missing data at the time of final IMP administration will be imputed using the last available data obtained by the day after the final IMP administration.

6 Primary and Secondary Outcome Variables:

6.1 Primary Outcome Variables

Primary outcome variables are not set.

6.2 Secondary Outcome Variables

Secondary outcome variables are not set.

6.3 Safety Outcome Variables

Adverse events, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), and 12-lead electrocardiogram (ECG)

6.4 Pharmacodynamic Outcome Variables

Urine volume, fluid intake, fluid balance, serum sodium concentration, serum potassium concentration, serum osmolality, urine sodium excretion, urine potassium excretion, urine osmolality, and biomarkers (plasma concentrations of AVP and brain natriuretic peptide

[BNP], plasma renin activity, and serum concentrations of N-terminal pro BNP [NTproBNP] and troponin I)

6.5 Efficacy Outcome Variables

- Body weight
- Congestive symptoms

Lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, cardiac third sound, cardiothoracic ratio, and pulmonary congestion

- Dyspnea

Respiratory rate, paroxysmal nocturnal dyspnea, orthopnea, and subject-assessed dyspnea

- New York Heart Association (NYHA) classification

7 Disposition and Demographic Analysis

7.1 Subject Disposition

For subjects from whom informed consent was obtained (screened subjects), the number of subjects and subjects administered IMP and the numbers and percentages of completed subjects after IMP administration, and discontinued subjects after IMP administration (the denominator indicates the number of subjects administered IMP) will be summarized. For discontinued subjects after IMP administration, the number and percentage of subjects by reason for discontinuation will be summarized. Of the completed subjects after IMP administration, the number and percentage of those who completed treatment in less than a 5-day treatment period (as in Section 3.2.3 in the protocol) will be summarized by reason.

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

7.2 Demographic and Baseline Characteristics

For the safety analysis set and efficacy analysis set, distributions (number of subjects, %) or descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) will be calculated according to Table 7.2-1

Table 7.2-1 Demographic and Other Baseline Characteristics

Variable	Time point	Method	Level
Age	Informed consent acquisition	Descriptive statistics	-
		Distribution	20-29, 30-39,

Table 7.2-1 Demographic and Other Baseline Characteristics			
Variable	**Time point**	**Method**	**Level**
			40-49, 50-59, 60-69, 70-79, 80-85
			<65, ≥65
Sex	-	Distribution	Female, Male, Undifferentiated
Height (cm)	Screening	Descriptive statistics	-
Body weight (kg)	Screening	Descriptive statistics	-
BMI (kg/m^2)	Screening	Descriptive statistics	-
Country	-	Distribution	JAPAN
Race	-	Distribution	Asian
Ethnicity	-	Distribution	Not Hispanic or Latino
Primary illness (multiple selection) • Ischemic heart disease • Cardiomyopathy • Valvular disease • Hypertensive heart disease • Arrhythmia	Screening	Distribution	Yes, No
Type of heart failure	Screening	Distribution	Right Heart Failure, Left Heart Failure, Bi-ventricular Failure, Unspecified
Presence of arrhythmia	Screening	Distribution	Yes, No
Use of Pacemaker	Screening	Distribution	Yes, No
Use of ICD	Screening	Distribution	Yes, No
Complication (multiple selection) • Hypertension • Angina pectoris • Diabetes mellitus • Renal impairment	Screening	Distribution	Yes, No
Presence of complication	Screening	Distribution	Yes, No
Presence of medical history	Screening	Distribution	Yes, No
Reason why oral intake was judged difficult or impossible (multiple selection)	Screening	Distribution	Ongoing NPPV therapy, Risk of aspiration, Reduced swallowing function, Other

7.3 Baseline Disease Evaluation

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

Table 7.3-1 Baseline Pathologic Evaluation

Variable	Method	Level
Cardiothoracic ratio (%)	Descriptive statistics	-
NYHA classification	Distribution	Class I, Class II, Class III, Class IV
Severity of lower limb edema	Distribution	None, Mild, Moderate, Severe
Pulmonary congestion	Distribution	None, Mild, Moderate, Severe
Presence of jugular venous distension	Distribution	Yes, No
Jugular venous distension (cm)	Descriptive statistics	-
Presence of jugular venous distension (value at baseline)	Distribution	Yes, No
Jugular venous distension (cm) (subjects with baseline value)	Descriptive statistics	-
Presence of hepatomegaly	Distribution	Yes, No
Hepatomegaly (cm)	Descriptive statistics	-
Presence of hepatomegaly (value at baseline)	Distribution	Yes, No
Hepatomegaly (cm) (subjects with baseline value)	Descriptive statistics	-
Pulmonary rales	Distribution	Yes, No
Third cardiac sound	Distribution	Yes, No
Respiratory rate (breaths/min)	Descriptive statistics	-
Orthopnea	Distribution	Present, Absent
Paroxysmal nocturnal dyspnea	Distribution	Present, Absent
Subject-assessed dyspnea (presence of symptoms)	Distribution	Present, Absent
Daily urine volume	Distribution	<1500 mL, ≥1500 mL
Creatinine	Distribution	<2 mg/dL, ≥2 mg/dL
Plasma AVP concentration	Distribution	≤3.1 pg/mL, >3.1 pg/mL

Table 7.3-1 Baseline Pathologic Evaluation		
Variable	**Method**	**Level**
Albumin	Distribution	<3 g/dL, ≥3 g/dL

7.4 Treatment Compliance

Treatment compliance will be summarized for the safety analysis set and efficacy analysis set. Distributions for presence or absence of discontinuation during IMP (injection) administration will be calculated. Distributions for presence or absence of days of incomplete IMP (injection) administration as well as days on which the duration from start to end of IMP administration is outside the allowable range (55 to 70 minutes) will also be calculated.

7.5 Prior and Concomitant Medications

No prior and concomitant medications analysis will be performed in this trial.

7.6 Protocol Deviations

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

8 Efficacy Analysis

The following analyses will be conducted on the efficacy dataset. The same analyses will also be conducted for subjects categorized by the presence or absence of dose escalation (ie, subjects with dose increased to 16 mg and subjects with dose maintained at 8 mg without dose escalation) based on the dose escalation criteria.

8.1 Primary Efficacy Endpoint

Primary efficacy endpoint are not set.

8.2 Key Secondary Efficacy Endpoint

Key secondary endpoint are not set.

8.3 Efficacy Analyses

8.3.1 Body Weight

Descriptive statistics and two-sided 95% confidence intervals (based on t-distribution) will be calculated for measured values and changes from baseline at the time of final IMP administration, and descriptive statistics will be calculated for the percent changes. At each time point, descriptive statistics will be calculated.

8.3.2 Congestive Symptoms

8.3.2.1 Lower Limb Edema and Pulmonary Congestion

The number, and proportion with the two-sided 95% confidence intervals (exact) will be calculated for the improvement rate and the resolution rate at the time of final IMP administration. The improvement rate is defined as the proportion of subjects in whom a symptom is present at baseline and then markedly improves or improves after IMP administration (for the improvement category, see Table 8.3.2.1-1). The resolution rate is defined as the proportion of subjects in whom a symptom is present at baseline and then resolves after IMP administration.

Shift tables for the severity of the symptoms will be prepared at each on-treatment time point and at the time of final IMP administration compared with baseline.

Table 8.3.2.1-1 Improvement Category of Lower Limb Edema and Pulmonary Congestion

	Improvement category	Assessment criteria
1	Markedly improved	The symptom resolved or improved by ≥2 categories.
2	Improved	The symptom improved by one category. (Symptom resolution will be categorized as “markedly improved.”)
3	Unchanged	The symptom remained unchanged or was absent throughout the trial period.
4	Deteriorated	The symptom worsened by ≥1 category.

8.3.2.2 Jugular Venous Distension, Hepatomegaly and Cardiothoracic Ratio

Descriptive statistics and two-sided 95% confidence intervals (based on t-distribution) will be calculated for measured values and changes from baseline at the time of final IMP administration. Descriptive statistics will also be calculated at each time point after IMP administration. Note that the absence of jugular venous distension and hepatomegaly will be indicated as 0 cm. The above data on jugular venous distension and hepatomegaly will also be summarized in the same manner for subjects with baseline value. For the presence of jugular venous distension and hepatomegaly, shift tables in changes from baseline at

the final IMP administration and at each time point following IMP administration will be prepared.

8.3.2.3 Pulmonary Rales and Cardiac Third Sound

The number, and proportion with the two-sided 95% confidence intervals (exact) will be calculated for the resolution rates of pulmonary rales and cardiac third sound at the time of final IMP administration. The resolution rate is defined as the proportion of subjects in whom a symptom is present at baseline and disappears after IMP administration.

Shift tables showing whether the symptom is present will be prepared at each on-treatment time point and at the time of final IMP administration compared with baseline.

8.3.3 Dyspnea

8.3.3.1 Respiratory Rate

Descriptive statistics and two-sided 95% confidence intervals (based on t-distribution) will be calculated for measured values and changes from baseline at the time of final IMP administration. At each time point, descriptive statistics will be calculated.

8.3.3.2 Orthopnea and Paroxysmal Nocturnal Dyspnea

The number, and proportion with the two-sided 95% confidence intervals (exact) will be calculated for the resolution rates of orthopnea and paroxysmal nocturnal dyspnea at the time of final IMP administration. The resolution rate is defined as the proportion of subjects in whom a symptom is present at baseline and then disappears after IMP administration.

Shift tables showing whether each symptom is present will be prepared at each postdose time point and at the time of final IMP administration compared with baseline.

8.3.3.3 Subject-assessed Dyspnea

The number, and proportion with the two-sided 95% confidence intervals (exact) will be calculated for the improvement rate at the time of final IMP administration. The improvement rate is defined as the proportion of subjects in whom a symptom is present at baseline and then mildly improved, moderately improved or markedly improved after IMP administration.

The frequencies at each postdose time point and at the time of final IMP administration will be summarized.

8.3.4 NYHA Classification

A shift table showing the NYHA classification will be prepared at each on-treatment time point and at the time of final IMP administration compared to baseline.

For subjects in Class II and higher, the number and proportion with two-sided 95% confidence intervals (exact) will be calculated for subjects who have improved from baseline by 1 class or more at the final IMP administration.

8.4 Subgroup Analyses

Subgroup analyses will not be performed in this trial.

9 Safety Analyses

The following analyses will be conducted on the safety dataset. The same analyses will also be conducted for subjects categorized by the presence or absence of dose escalation (ie, subjects with dose increased to 16 mg and subjects with dose maintained at 8 mg without dose escalation) based on the dose escalation criteria.

9.1 Extent of Exposure

Distributions of the number of subjects on each number of administration days will be calculated. Descriptive statistics of the number of administration days will be calculated. The number of subjects at each daily dose (8 or 16 mg) will be counted on each administration day. The combination of number of administration days for each daily dose will be summarized in a cross table.

9.2 Adverse Events

All AEs will be coded by system organ class (SOC) and ICH Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT). 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. IMP-related TEAEs will be summarized in the same manner as shown above.

For TEAEs, a summary table will also be created for any TEAE that occurs in more than 2 subjects in any group.

9.3 Clinical Laboratory Data

Clinical laboratory data obtained from central measurements will be used for analyses. For clinical laboratory test parameters other than qualitative urinalysis, measured values and changes from baseline at each time point and at the time of final IMP administration will be summarized using descriptive statistics. For qualitative urinalysis parameters, shift tables will be prepared at each time point and at the time of final IMP administration compared with baseline. In addition, measured values of clinical laboratory test parameters other than qualitative urinalysis will be categorized as below, within, or above the normal range, and shift tables will be prepared at each postdose time point and at the time of final IMP administration compared with baseline.

The numbers and percentages of subjects who have a visit with serum total bilirubin value of ≥2 times the upper limit of normal (ULN), and an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value of ≥3 times the ULN at any postdose time point will be calculated.

The numbers and percentages of subjects experiencing the following events after IMP administration will be calculated.

- A serum sodium concentration >147 mEq/L
- A >10 mEq/L increase in serum sodium concentration within 24 hours after the start of IMP administration

9.4 Vital Sign Data

For vital signs (blood pressure, pulse rate, and body temperature), measured values and changes from baseline at each time point and at the time of final IMP administration will be summarized using descriptive statistics.

9.5 Physical Examination Data

No physical examination data analysis will be performed in this trial.

9.6 Electrocardiogram Data

For 12-lead ECG parameters, measured values and changes from baseline will be summarized at each time point and at the time of final IMP administration using descriptive statistics.

The numbers and percentages of subjects who have a QT corrected for heart rate (QTc) interval of >450, >480, or >500 msec at any postdose time point until the time of final IMP administration will be calculated. The numbers and percentages of subjects who have a change in QTc interval from baseline of >30 and >60 msec at any postdose time point or at the time of final IMP administration will be calculated. Also at baseline and at each postdose time point, the numbers and percentages of subjects will be calculated in the same manner as described above.

A shift table showing interpretation (normal or abnormal) will be prepared at each postdose time point and at the time of final IMP administration compared to baseline. Interpretation (normal or abnormal) assessments by the trial site (investigator or subinvestigator) will be used.

9.7 Other Safety Data

None.

10 Pharmacokinetic Analyses

No pharmacokinetic analysis will be performed in this trial.

11 Pharmacodynamic Analyses

A pharmacodynamic analysis will be conducted on the pharmacodynamic dataset. The same analysis will also be conducted for subjects categorized by the presence or absence of dose escalation (ie, subjects with dose increased to 16 mg and subjects with dose maintained at 8 mg without dose escalation) based on the dose escalation criteria (excluding analysis regarding the day of IMP dose escalation).

11.1 Urine Volume, Fluid Intake, Fluid Balance

Descriptive statistics for measured values and changes from baseline at each time point will be calculated for daily urine volume, daily fluid intake, and daily fluid balance (0 to 24 hours).

Descriptive statistics for measured values at each time point will be calculated for interval urine volume, interval fluid intake, and interval fluid balance (0 to 1 hour, 1 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, and 8 to 24 hours) on Day 1 and for interval urine volume, interval fluid intake, and interval fluid balance (0 to 4 hours, 4 to 8 hours, and 8 to 24 hours) on the day of IMP dose escalation (Day 2 or Day 3).

Descriptive statistics for measured values at each time point will be calculated for cumulative urine volume, cumulative fluid intake, and cumulative fluid balance (0 to

1 hour, 0 to 2 hours, 0 to 4 hours, 0 to 6 hours, 0 to 8 hours, and 0 to 24 hours) on Day 1 and for cumulative urine volume, cumulative fluid intake, and cumulative fluid balance (0 to 4 hours, 0 to 8 hours, and 0 to 24 hours) on the day of IMP dose escalation (Day 2 or Day 3).

Note that a fluid balance will be calculated by subtracting the "urine volume" from the "fluid intake."

11.2 Serum Sodium Concentration, Serum Potassium Concentration, Serum Osmolality

Descriptive statistics will be calculated for measured values and changes from baseline at each time point.

For subjects with dose escalation to 16 mg on Day 2 or Day 3, descriptive statistics will be calculated for measured values and changes from before IMP administration on the day of IMP dose escalation at each time point (from before IMP administration on the day of dose escalation to before IMP administration on the next day).

For serum sodium concentration, central laboratory measurements will be used.

11.3 Biomarkers (Plasma AVP Concentration, Plasma Renin Activity, Plasma BNP Concentration, Serum NT-proBNP Concentration, and Serum Troponin I Concentration)

Descriptive statistics will be calculated for measured values and changes from baseline at each time point and at the time of final IMP administration.

11.4 Urine Sodium Excretion, Urine Potassium Excretion, Urine Osmolality

Descriptive statistics for measured values and changes from baseline at each time point will be calculated for daily urine sodium excretion and daily urine potassium excretion (0 to 24 hours).

Descriptive statistics for measured values at each time point will be calculated for interval urine sodium excretion and interval urine potassium excretion (0 to 4 hours, 4 to 8 hours, and 8 to 24 hours) on Day 1 and the day of dose escalation (Day 2 or Day 3).

Descriptive statistics for measured values at each time point will be calculated for cumulative urine sodium excretion and cumulative urine potassium excretion (0 to 4 hours, 0 to 8 hours, and 0 to 24 hours) on Day 1 and the day of dose escalation (Day 2 or Day 3).

Descriptive statistics for measured values and changes from baseline at each time point will be calculated for urine osmolality.

Note that urine sodium excretion and urine potassium excretion will be calculated by multiplying the urine sodium concentration and the urine potassium concentration obtained at the central laboratory, respectively, by urine volume.

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

Regarding IMP dose escalation based on the dose escalation criteria, the subject distribution was found to be different than had originally been expected. Therefore it was decided not to conduct the analysis "by timing of dose escalation (ie, subjects achieving a dose escalation to 16 mg on Day 2, those achieving a dose escalation to 16 mg on Day 3, and those achieving no dose escalation to 16 mg)" in Section 7.4.1, Section 7.4.2, and Section 7.4.3 in the protocol, but to add analysis "by presence or absence of dose escalation (ie, subjects with dose increased to 16 mg and subjects with dose maintained at 8 mg without dose escalation)" to Section 8, Section 9, and Section 11 of the Statistical Analysis Plan.

15 References

None.

Appendix 1 List of Summary Tables

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CT-8.1	Overall Summary of Adverse Events (Safety Analysis Set)
CT-8.2	Incidence of Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.3	Incidence of Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.4	Incidence of Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.5	Incidence of Drug-related Treatment-emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.6	Incidence of Treatment-emergent Adverse Events Occurring in >= 2 subjects of All Subjects by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-8.7	Incidence of Drug-related Treatment-emergent Adverse Events Occurring in >= 2 subjects of All Subjects by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-9.1	Incidence of Treatment-emergent Adverse Events with an outcome of death by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-9.2	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-9.3	Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-9.4	Incidence of Drug-related Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)
CT-9.5	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-9.6	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-9.7	Listing of Deaths (IMP Administered Subjects)
CT-9.8	Listing of Serious Adverse Events Other Than Death (IMP Administered Subjects)
CT-9.9	Listing of Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration (IMP Administered Subjects)
CT-10.1.1	Mean Change from Baseline in Clinical Laboratory Test Results (Serum Chemistry) (Safety Analysis Set)
CT-10.1.2	Mean Change from Baseline in Clinical Laboratory Test Results (Hematology) (Safety Analysis Set)

CT-10.1.3	Mean Change from Baseline in Clinical Laboratory Test Results (Urinalysis) (Safety Analysis Set)
CT-10.2	Shift Tables of Clinical Laboratory Test Results (Qualitative Urinalysis) (Safety Analysis Set)
CT-10.3.1	Shift Tables of Clinical Laboratory Test Results (Serum Chemistry) (Safety Analysis Set)
CT-10.3.2	Shift Tables of Clinical Laboratory Test Results (NA, K) (Safety Analysis Set)
CT-10.3.3	Shift Tables of Clinical Laboratory Test Results (Hematology) (Safety Analysis Set)
CT-10.3.4	Shift Tables of Clinical Laboratory Test Results (Urinalysis) (Safety Analysis Set)
CT-10.4.1	Listing of Abnormal Laboratory Findings (IMP Administered Subjects)
CT-10.4.2	Listing of Abnormal Laboratory Findings Potential Drug-Induced Liver Injury (IMP Administered Subjects)
CT-10.5	Incidence of Potential Drug-Induced Liver Injury (Safety Analysis Set)
CT-10.6	Incidence of Sodium Related Events (Safety Analysis Set)
CT-11	Mean Change from Baseline in Vital Signs (Safety Analysis Set)
CT-12.1	Mean Change from Baseline in Electrocardiogram Results (Safety Analysis Set)
CT-12.2.1	Shift Table of 12-Lead ECG Findings (Normal/Abnormal Assessments) (Safety Analysis Set)
CT-12.3.1	Incidence of Categorical Changes in Electrocardiogram Results (Post baseline any visit) (Safety Analysis Set)
CT-12.3.2	Incidence of Categorical Changes in Electrocardiogram Results (Each Visit) (Safety Analysis Set)
PDT-1.1	Descriptive Statistics for Daily Urine Volume (mL) (Pharmacodynamic Analysis Set)
PDT-1.2.1	Descriptive Statistics for Interval Urine Volume (mL) (Pharmacodynamic Analysis Set)

PDT-1.2.2 Descriptive Statistics for Interval Urine Volume (mL) by Dose Escalation (Pharmacodynamic Analysis Set)

PDT-1.3.1 Descriptive Statistics for Cumulative Urine Volume (mL) (Pharmacodynamic Analysis Set)

PDT-1.3.2 Descriptive Statistics for Cumulative Urine Volume (mL) by Dose Escalation (Pharmacodynamic Analysis Set)

PDT-2.1 Descriptive Statistics for Daily Fluid Intake (mL) (Pharmacodynamic Analysis Set)

PDT-2.2.1 Descriptive Statistics for Interval Fluid Intake (mL) (Pharmacodynamic Analysis Set)

PDT-2.2.2 Descriptive Statistics for Interval Fluid Intake (mL) by Dose Escalation (Pharmacodynamic Analysis Set)

PDT-2.3.1 Descriptive Statistics for Cumulative Fluid Intake (mL) (Pharmacodynamic Analysis Set)

PDT-2.3.2 Descriptive Statistics for Cumulative Fluid Intake (mL) by Dose Escalation (Pharmacodynamic Analysis Set)

PDT-3.1 Descriptive Statistics for Daily Fluid Balance (mL) (Pharmacodynamic Analysis Set)

PDT-3.2.1 Descriptive Statistics for Interval Fluid Balance (mL) (Pharmacodynamic Analysis Set)

PDT-3.2.2 Descriptive Statistics for Interval Fluid Balance (mL) by Dose Escalation (Pharmacodynamic Analysis Set)

PDT-3.3.1 Descriptive Statistics for Cumulative Fluid Balance (mL) (Pharmacodynamic Analysis Set)

PDT-3.3.2 Descriptive Statistics for Cumulative Fluid Balance (mL) by Dose Escalation (Pharmacodynamic Analysis Set)

PDT-4.1 Descriptive Statistics for Serum Sodium Concentration (mEq/L) (Pharmacodynamic Analysis Set)

PDT-4.2 Descriptive Statistics for Serum Sodium Concentration (mEq/L) for Dose Escalated Subjects (Pharmacodynamic Analysis Set)

PDT-5.1 Descriptive Statistics for Serum Potassium Concentration (mEq/L) (Pharmacodynamic Analysis Set)

PDT-5.2 Descriptive Statistics for Serum Potassium Concentration (mEq/L) for Dose Escalated Subjects (Pharmacodynamic Analysis Set)

PDT-6.1 Descriptive Statistics for Serum Osmolality (mOsm/kg) (Pharmacodynamic Analysis Set)

PDT-6.2 Descriptive Statistics for Serum Osmolality (mOsm/kg) for Dose Escalated Subjects (Pharmacodynamic Analysis Set)

PDT-7 Descriptive Statistics for Plasma AVP Concentration (pg/mL) (Pharmacodynamic Analysis Set)

PDT-8 Descriptive Statistics for Plasma BNP Concentration (pg/mL) (Pharmacodynamic Analysis Set)

PDT-9 Descriptive Statistics for Plasma Renin Activity (ng/mL/hr) (Pharmacodynamic Analysis Set)

PDT-10 Descriptive Statistics for Serum pro BNP Concentration (pg/mL) (Pharmacodynamic Analysis Set)

PDT-11 Descriptive Statistics for Serum Troponin Concentration (pg/mL) (Pharmacodynamic Analysis Set)

PDT-12.1 Descriptive Statistics for Daily Urine Excretion of Sodium (mEq) (Pharmacodynamic Analysis Set)

PDT-12.2.1 Descriptive Statistics for Inteval Urine Excretion of Sodium (mEq) (Pharmacodynamic Analysis Set)

PDT-12.2.2 Descriptive Statistics for Inteval Urine Excretion of Sodium (mEq) by Dose Escalation (Pharmacodynamic Analysis Set)

PDT-12.3.1 Descriptive Statistics for Cumulative Urine Excretion of Sodium (mEq) (Pharmacodynamic Analysis Set)

PDT-12.3.2 Descriptive Statistics for Cumulative Urine Excretion of Sodium (mEq) by Dose Escalation (Pharmacodynamic Analysis Set)

PDT-13.1 Descriptive Statistics for Daily Urine Excretion of Potassium (mEq) (Pharmacodynamic Analysis Set)

PDT-13.2.1 Descriptive Statistics for Interval Urine Excretion of Potassium (mEq) (Pharmacodynamic Analysis Set)

PDT-13.2.2 Descriptive Statistics for Interval Urine Excretion of Potassium (mEq) by Dose Escalation (Pharmacodynamic Analysis Set)

PDT-13.3.1 Descriptive Statistics for Cumulative Urine Excretion of Potassium (mEq) (Pharmacodynamic Analysis Set)

PDT-13.3.2 Descriptive Statistics for Cumulative Urine Excretion of Potassium (mEq) by Dose Escalation (Pharmacodynamic Analysis Set)

PDT-14.1 Descriptive Statistics for Urine Osmolality (mOsm/kg) (Pharmacodynamic Analysis Set)

Appendix 2 List of Subject Data Listings

AE-1	Adverse Events (IMP Administered Subjects)
AE-2	Adverse Events Observed Before Start of Investigational Medicinal Product Administration (IMP Administered Subjects)
DEMOG-1	Demographic and Baseline Characteristics (IMP Administered Subjects)
DREAS-1	Discontinued Subjects and Reason for Discontinuation (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)
LAB-4	Laboratory Test Results - Serum Sodium, K Trial Site (IMP Administered Subjects)
PDEV-1	Protocol Deviations (IMP Administered Subjects)
SMED-1	Investigational Medicinal Product Compliance Injection (IMP Administered Subjects)
SMED-2	Investigational Medicinal Product Compliance Injection (Full Administration / Interruption) (IMP Administered Subjects)
SUBEX-1	Subjects Excluded From Analysis Set (IMP Administered Subjects)
PDATA-1	Study Completion Status and Reason for Discontinuation and Reason for Early Completion (IMP Administered Subjects)
PDATA-2	Inclusion Criteria and Exclusion Criteria Not Met
PDATA-3.1	Medical History and Complications (IMP Administered Subjects)
PDATA-3.2	History of Congestive Heart Failure (IMP Administered Subjects)
PDATA-4.1	Concomitant Medications (IMP Administered Subjects)
PDATA-4.2	Concomitant Therapy Other Than Medication (IMP Administered Subjects)
PDATA-5.1	Vital Signs (IMP Administered Subjects)
PDATA-5.2	Height (IMP Administered Subjects)
PDATA-6.1	Electrocardiogram Results Central ECG Analysis Laboratory (IMP Administered Subjects)

PDATA-6.2	Electrocardiogram Results Trial Site (IMP Administered Subjects)
PDATA-7	Screen Failures
PDATA-8	Physical Examination (IMP Administered Subjects)
PDATA-9	Serum Sodium Concentration, Serum Potassium Concentration (IMP Administered Subjects)
PDATA-10	Serum Osmolality, Plasma AVP Concentration, Plasma BNP Concentration, Plasma Renin Activity (IMP Administered Subjects)
PDATA-11	Serum NT pro BNP Concentration, Serum Troponin Concentration (IMP Administered Subjects)
PDATA-12	Urine Volume, Fluid Intake, Fluid Balance, Urine Sodium Concentration, Urine Osmolality, Urine Potassium Concentration Urine Excretion of Sodium, Urine Excretion of Potassium (IMP Administered Subjects)
PDATA-13	Previous Screened ID (IMP Administered Subjects)
PDATA-14	Post-treatment Follow-up (IMP Administered Subjects)
PDATA-15	Pharmacogenomics (IMP Administered Subjects)
PDATA-16	Dose Increase Assessment (IMP Administered Subjects)
EFF-1	Body Weight (IMP Administered Subjects)
EFF-2	Congestive Symptoms (Lower Limb Edema, Jugular Venous Distension, Hepatomegaly, Pulmonary rales, Third Cardiac Sound) (IMP Administered Subjects)
EFF-3	Chest X-ray (Pulmonary Congestion, Cardiothoracic Ratio) (IMP Administered Subjects)
EFF-4	Dyspnea (Respiratory Rate, Paroxysmal Nocturnal Dyspnea, Orthopnea, and Subject-assessed Dyspnea) (IMP Administered Subjects)
EFF-5	NYHA Classification (IMP Administered Subjects)