STATISTICAL ANALYSIS PLAN

A Multicenter, Double-blind, Randomized, Active-controlled, Parallel-group, Non-inferiority Trial to Evaluate the Efficacy and Safety of OPC-61815 Injection Compared With Tolvaptan 15-mg Tablet in Patients With Congestive Heart Failure

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Otsuka Pharmaceutical Co., Ltd.

Investigational New Drug OPC-61815

Protocol No. 263-102-00003

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
AVP	Arginine vasopressin
BNP	Brain natriuretic peptide
CHF	Congestive heart failure
CRF	Case report form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PT	Preferred Term
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 263-102-00003.

2 Trial Objectives

Primary: To confirm the non-inferiority of OPC-61815 16-mg injection to tolvaptan 15-mg tablet using as the primary endpoint the change in body weight following 5-day intravenous administration of OPC-61815 16-mg injection or 5-day oral administration of tolvaptan 15-mg tablet to congestive heart failure (CHF) patients with volume overload despite having received diuretics other than vasopressin antagonists.

Secondary: To evaluate other efficacy endpoints and the safety, pharmacodynamics, and pharmacokinetics of OPC-61815 16-mg injection in comparison with tolvaptan 15-mg tablet.

3 Trial Design

3.1 Type/Design of Trial

This trial will be conducted in 288 CHF patients with volume overload despite having received diuretics other than vasopressin antagonists. The subjects will be randomly assigned to either of the OPC-61815 16-mg injection group or the tolvaptan 15-mg tablet group (144 patients per group) to confirm the non-inferiority of OPC-61815 16-mg injection to tolvaptan 15-mg tablet in an active control, randomized, double-blind, parallel group, multicenter design.

The 3 days before start of investigational medicinal product (IMP) administration comprise the run-in period, during which the use of diuretics, change in body weight, and congestive symptoms are assessed. After the run-in period, only subjects who meet the inclusion criteria (run-in period) will enter into the treatment period during which the IMP will be administered once daily for 5 days. The doses and dosage regimens of diuretics that have been used since before start of the run-in period must be maintained until the end of the treatment period. The completion assessment will be performed on Day 6 (day after final IMP administration), and the follow-up assessment will be performed at some time between Day 12 and Day 15.

This trial will employ a double-dummy method to maintain blindness. Subjects will receive either of a combination of OPC-61815 16-mg injection and placebo tablet or a combination of placebo injection and tolvaptan 15-mg tablet. Subjects will be

hospitalized from the day before start of the run-in period (Day −4) to the end of the treatment period (Day 6).

3.2 Trial Treatments

The investigator or subinvestigator will instruct subjects to ingest one tolvaptan 15-mg tablet or one placebo tablet with water once daily. Immediately after the intake of the tablet, the investigator or subinvestigator will administer OPC-61815 16-mg injection or placebo injection as a 1-hour (55 to 65 minutes allowable) infusion once daily for 5 days according to the IMP administration procedures specified separately. Subjects will be asked to take breakfast and then urinate to start the measurement of daily urine volume immediately before receiving the administration of IMPs on each of the 5 days. The start time of administration on Day 2 and onward should be within 20 minutes before or after the start time on Day 1, if possible. The investigator or subinvestigator will confirm that administration of the IMPs has been completed, and record the following information in the source document and the eCRF (electronic case report form): the date and time of the start and end of the administration (and the suspension period, if the administration is suspended), and whether or not the entire dose has been administered; and, the date and time of administration for the tablet. The IMPs will also be administered to subjects who do not take breakfast.

3.3 Trial Population

The necessary sample size is 288 subjects (144/group). Subjects are required to be Japanese male and female CHF patients age of 20 to 85 years, inclusive, with volume overload (ie, lower limb edema, pulmonary congestion, and/or jugular venous distension) despite having received diuretics other than vasopressin antagonists, who will be able to be hospitalized from the day before start of the run-in period through the end of the treatment period and take oral tablets.

3.4 Handling of Time Points

Case report form (CRF) Visit values at each time point (run-in period, treatment period, and follow-up) 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.

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

Table 3.4-1 Handling of Time Points		
Variable	**Baseline[a]**	**Final Administration Time Point**
Body weight	Before IMP administration on Day 1	Day after final IMP administration
Congestive symptoms (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, third cardiac sound)	Run-in period (final measurement)	Day after final IMP administration
Pulmonary congestion, cardiothoracic ratio	Run-in period	Day after final IMP administration
NYHA classification	Run-in period	Day after final IMP administration
Clinical laboratory value	Before IMP administration on Day 1	Day after final IMP administration
Vital signs	Before IMP administration on Day 1	Day after final IMP administration
12-lead ECG	Before IMP administration on Day 1	Day after final IMP administration
Serum sodium concentration, serum potassium concentration, serum osmolality, biomarker	Before IMP administration on Day 1	-
Daily urine volume, daily fluid intake, daily fluid balance, daily urine sodium excretion, daily urine potassium excretion, urine osmolality	Within 24 hours before start of IMP administration on Day1	-

[a]When multiple data are collected during the run-in period, the data closest to Day 1 will be used as baseline.

4 Sample Size

The number of subjects required to confirm the non-inferiority of OPC-61815 16-mg injection to tolvaptan 15-mg tablet for the primary endpoint of change in body weight from baseline (before IMP administration on Day 1) at the time of final IMP administration (day after final IMP administration) was determined.

In the clinical development of tolvaptan for the treatment of cardiac edema, there were 2 placebo-comparison trials conducted for tolvaptan 15-mg tablet: a phase 2 trial (156-03-001) and a phase 3 trial (156-06-002). Regarding the change in body weight (kg) on the morning after Day 5 of treatment (LOCF) in those 2 trials, from an analysis of covariance (ANCOVA) model analysis performed using body weight (kg) at baseline as a covariate, the least-square mean of the difference (treatment difference) between the tolvaptan 15-mg tablet group and the placebo group was respectively −0.99 (95% CI: −1.57 to −0.42) and −0.96 (95% CI: −1.37 to −0.55). Referring to the upper limit of those

CIs, the reliably expected (at 95% probability) minimum difference in body weight decrease (maximum difference in body weight) between the tolvaptan 15-mg tablet group and the placebo group was considered to be in the range of 0.42 to 0.55. The non-inferiority margin for the present trial was therefore set at 0.48, which corresponds to half of the treatment difference of 0.96 between the tolvaptan 15-mg tablet group and the placebo group in the tolvaptan phase 3 trial.

Setting the non-inferiority margin at 0.48, the detection power at 90%, and the significance level at 5%, and using the value for up until the morning after Day 5 of treatment in the tolvaptan 15-mg tablet in the tolvaptan phase 3 trial to set the mean ± SD change in body weight from baseline at time of final administration at −1.30 ± 1.25 for both the tolvaptan 15-mg tablet group and the OPC-61815 16-mg injection group, the number of subjects required for this trial was determined to be 288 (144 subjects per group).

5 Statistical Analysis Datasets

5.1 Full Analysis Set

The full analysis set (FAS) includes all subjects who received at least one dose of IMP and have evaluable post-treatment body weight data.

5.2 Safety Analysis Set

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

5.3 Pharmacodynamic Analysis Set

The pharmacodynamic analysis set includes all subjects who received at least one dose of IMP and have evaluable post-treatment pharmacodynamic data.

5.4 Pharmacokinetic Analysis Set

Of the subjects in the safety analysis set, those with measured plasma drug concentration data will be included in the pharmacokinetic analysis set.

5.5 Handling of Missing Data

If the data at the time of final assessment (on the day after final IMP administration) is missing, the last available data obtained by the day after final IMP administration will be used (efficacy and safety).

6 Primary and Secondary Outcome Variables:

6.1 Primary Outcome Variables

Change in body weight from baseline at time of final IMP administration (day after final IMP administration)

6.2 Secondary Outcome Variables

- Congestive symptoms (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound)
- New York Heart Association (NYHA) classification

7 Disposition and Demographic Analysis

The following will be summarized by treatment group (excluding subjects from whom informed consent was obtained).

7.1 Subject Disposition

For subjects from whom informed consent was obtained (screened subjects), the number of subjects and randomized subjects and the numbers and percentages of subjects administered IMP, completed subjects after IMP administration, and discontinued subjects after IMP administration (the denominator indicates the number of randomized subjects) will be summarized. For discontinued subjects after IMP administration, the number and percentage of subjects by reason for discontinuation will be summarized.

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

7.2 Demographic and Baseline Characteristics

For the full analysis set and safety analysis set, descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum, the same applies hereinafter to Chapter 9) or distributions (number of subjects, %, the same applies hereinafter) 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, 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

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 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 (baseline value)	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 (baseline value)	Distribution	Yes, No
Hepatomegaly (cm) (subjects with baseline value)	Descriptive statistics	-
Pulmonary rales	Distribution	Yes, No
Third cardiac sound	Distribution	Yes, No
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
Albumin	Distribution	<3 g/dL, ≥3 g/dL

7.4 Treatment Compliance

Treatment compliance will be summarized for the full analysis set. Distributions for presence or absence of day 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 of deviant duration of IMP administration from the start time to the end time (outside the acceptable range of 55 to 65 minutes) will be calculated. Distributions for days of missing an IMP (tablet) dose will also be calculated.

7.5 Prior and Concomitant Medications

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

Table 7.5-1 Usage of Concomitant Medication on Initial IMP Administration Day

Variable	Level
Use of loop diuretic	Monotherapy with loop diuretic, Loop diuretic + other diuretic
Dose of loop diuretic (Furosemide equivalent*)	<40 mg/day, ≥40 mg/day and <80 mg/day, ≥80 mg/day
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	Yes, No
Anti-aldosterone drug	Yes, No
Drugs for heart failure other than diuretics	Yes, No
Digitalis product	Yes, No
ACE inhibitor	Yes, No
Beta blocker	Yes, No
Angiotensin receptor blocker	Yes, No

*Furosemide equivalent dose of 40 mg is defined as bumetanide, 1 mg; piretanide, 6 mg; azosemide, 60 mg; and torasemide, 8mg

7.6 Protocol Deviations

For randomized subjects, 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 performed in the full analysis set.

8.1 Primary Efficacy Endpoint

The primary endpoint is the change in body weight from baseline (before IMP administration on Day 1) at time of final IMP administration (day after final IMP administration), and the non-inferiority of OPC-61815 16-mg injection to tolvaptan 15-mg tablet in the change from baseline in body weight will be confirmed with a noninferiority margin of 0.48.

8.1.1 Primary Efficacy Analysis

Main analysis is an analysis of the primary endpoint using an ANCOVA model with treatment as a fixed effect factor and baseline body weight as a covariate. The least square mean difference and its two-sided 95% CI (based on the t distribution) between the OPC-61815 16-mg injection group and the tolvaptan 15-mg tablet group will be calculated. The non-inferiority of OPC-61815 16-mg injection to tolvaptan 15-mg tablet will be confirmed when the upper limit of the CI does not exceed 0.48.

At each time point, the measured values, changes, and percent changes in body weight from baseline will be summarized by treatment group using descriptive statistics.

Using the main analysis model excluding baseline body weight, the least-square mean of the difference between the OPC-61815 16-mg injection group and the tolvaptan 15-mg group and its two-sided 95% CI will also be calculated.

For changes in body weight from baseline, a timecourse (mean ± SD) from Day 1 of treatment period to follow-up will be created for each treatment group.

8.1.2 Sensitivity Analyses

No sensitivity analysis will be performed in this trial.

8.1.3 Technical Computational Details for Primary Efficacy Analysis

SAS code is shown below.

```
proc glm data=DATA;
  class TRTP;
  model CHG= TRTP BASE;
```

```
 lsmeans TRTP / cl pdiff=control('CONTROL');
run;
```

8.2 Key Secondary Efficacy Endpoint

Key secondary endpoints are not set.

8.3 Secondary Efficacy Analyses

8.3.1 Lower Limb Edema and Pulmonary Congestion

For lower limb edema and pulmonary congestion, the improvement rate and the resolution rate at the time of final IMP administration will be determined in each group, and the differences and their two-sided 95% CIs (exact) in the rates between the OPC-61815 16-mg injection group and the tolvaptan 15-mg tablet group will be calculated. The improvement rate is defined as the proportion of subjects in whom the symptom is present at baseline and it markedly improved or improved after IMP administration (for the improvement category, see Table 8.3.1-1). The resolution rate is defined as the proportion of subjects in whom the symptom is present at baseline and it resolved after IMP administration. For lower limb edema, the improvement rate will be calculated for each treatment group at each time point and the time course will be plotted.

Shift tables for the severity of the symptoms from baseline at the time of final IMP administration and each time point by treatment group will be prepared.

Table 8.3.1-1 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 1 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 Jugular Venous Distension, Hepatomegaly, and Cardiothoracic Ratio

The changes in jugular venous distension, hepatomegaly, and cardiothoracic ratio from baseline at time of final IMP administration will be analyzed using an ANCOVA model with treatment as a fixed effect factor and baseline body weight as a covariate, and the least-square mean differences and their two-sided 95% CIs (based on the t distribution) between the OPC-61815 16- mg injection group and the tolvaptan 15-mg tablet group

will be calculated. In addition, at each time point, measured values and changes from baseline will be summarized by treatment group using descriptive statistics. For jugular venous distension and hepatomegaly, the time course of changes from baseline to each time point will be plotted (mean ± SD). 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 for subjects with baseline value and the time course will be plotted in the same manner. For the presence/absence of jugular venous distension and hepatomegaly, shift tables in changes from baseline at the final IMP administration and at each timepoint following IMP administration will be prepared by each treatment group.

8.3.3 Pulmonary Rales and Cardiac Third Sound

For the resolution rates of pulmonary rales and cardiac third sound at the time of final IMP administration, the difference and its two-sided 95% CI (exact) between the OPC-61815 16-mg injection group and the tolvaptan 15-mg tablet group will be calculated. The resolution rate is defined as the proportion of patients in whom the symptom is present at baseline and disappeared after IMP administration.

A shift table in changes of the presence of the symptoms from baseline at the time of final IMP administration and each timepoint by treatment group will be prepared.

8.3.4 NYHA Classification

A shift table for the NYHA classification from baseline at the time of final IMP administration and each timepoint by treatment group will be prepared.

For Class II and higher subjects, the proportion of those who have improved from baseline by 1 or more NYHA class at the time of final IMP administration will be calculated for each treatment group to determine the difference between the OPC-61815 16 mg injection group and the tolvaptan 15 mg tablet group and its two-sided 95% CI (exact).

8.4 Subgroup Analyses

For the main analysis of the primary endpoints, subgroup analyses of the following stratified variables will be performed.

Table 8.4-1 Stratified Variables

Variable	Level
Sex	Female, Male
Age	<65, ≥65

Table 8.4-1 Stratified Variables	
Variable	**Level**
NYHA classification	Class I, Class II, Class III and Class IV
Ischemic heart disease	Yes, No
Type of heart failure	Right Heart Failure, Left Heart Failure, Bi-ventricular Failure,
Use of loop diuretic	Monotherapy with loop diuretic, Loop diuretic + other diuretic
Dose of loop diuretic (Furosemide equivalent)	<80 mg/day, ≥80 mg/day
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	Yes, No
Anti-aldosterone drug	Yes, No
Daily urine volume (baseline)	<1500 mL, ≥1500 mL
Creatinine (baseline)	<2 mg/dL, ≥2 mg/dL
Plasma AVP concentration (baseline)	≤3.1 pg/mL, >3.1 pg/mL
Albumin (baseline)	<3 g/dL, ≥3 g/dL

9 Safety Analyses

The following analyses will be conducted on the safety analysis set by treatment group.

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.

9.2 Adverse Events

All adverse events (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 discontinuations 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 2% or more of subjects in any group.

9.3 Clinical Laboratory Data

Clinical laboratory data obtained from central measurements will be used.

For hematology, serum chemistry (excluding PAP and TRACP-5b), and urinalysis in the protocol "Table 3.7.3.2-1 Clinical Laboratory Assessments", the following will be summarized.

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 post-treatment time point and at the time of final IMP administration compared with baseline. In addition, for clinical laboratory test parameters other than qualitative urinalysis, measured values will be categorized as below, within, or above the normal range, and shift tables will be prepared at each post-treatment time point and at the time of final IMP administration compared with baseline.

For parameters excluding qualitative urinalysis, a scatter diagram of values after the final administration with comparison to baseline will be created.

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 AST or ALT value of ≥3 times the ULN at any posttreatment time point will be calculated.

9.4 Vital Sign Data

For vital signs, 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 at each time point and at the time of final IMP administration will be summarized using descriptive statistics.

The numbers and percentages of subjects who have a QTc interval (QTcF) of >450, 480, or > 500 msec at any post-treatment 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 post-treatment time point and at the time of final IMP administration will be calculated. Also at baseline and at each post-treatment time point, the numbers and percentages of subjects will be calculated in the same manner as described above.

Shift tables for QTcF interpretation (normal or abnormal) will be prepared at each post-treatment time point and at the time of final IMP administration compared with baseline. Interpretation (normal or abnormal) assessments by the trial site (investigator or subinvestigator) will be used instead of the assessments by the central ECG analysis laboratory.

9.7 Other Safety Data

None.

10 Pharmacokinetic Analyses

10.1 Endpoints

Plasma concentrations of OPC-61815 free form and tolvaptan (OPC-41061)

10.2 Analysis Set

Pharmacokinetic Analysis Set

10.3 Handling of Data

1) Plasma concentrations below lower limit of quantitation that occur prior to and after the first measurable concentration will be imputed to 0 (ng/mL) and missing. Lower limit of quantitation of each analyte is listed in 3.Missing for plasma concentrations will not be imputed.

10.4 Statistical Analyses

The plasma drug concentration data will be summarized using descriptive statistics as follows:

- At each time point, the plasma drug concentration data will be summarized by compound and by treatment group using descriptive statistics.
- The descriptive statistics to be calculated include number of subjects (n), mean, SD, coefficient of variation, minimum, median, and maximum.

11 Pharmacodynamic Analyses

A pharmacodynamic analysis will be conducted on the pharmacodynamic analysis set.

For the following endpoints, measured values and changes from baseline at each time point will be summarized by treatment group using descriptive statistics (n, mean, SD, minimum, median, and maximum). For changes from baseline in daily urine volume, daily fluid intake, and daily fluid balance after IMP administration on Day 1 and after IMP administration on Day 5, the mean difference ([OPC-61815 16-mg injection group] − [tolvaptan 15-mg tablet group]) and its 95% CI (based on the t distribution) will be calculated. For daily urine volume after IMP administration, the mean changes from baseline after IMP administration on Day 1 and after IMP administration on Day 5 and their two-sided 95% CIs (based on the t-distribution) will be calculated.

For daily urine volume, a transition chart of measurements (mean ± SD) from the run-in period to Day 5 will be created in each group. For changes from baseline after IMP administration on Day 1 and after IMP administration on Day 5, a bar graph of the mean (two-sided 95% CI) with the horizontal axis representing treatment groups will also be created.

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Serum sodium concentration, serum potassium concentration
- Serum osmolality
- Biomarkers (plasma arginine vasopressin [AVP] concentration, plasma brain natriuretic peptide [BNP] concentration, plasma renin activity, serum NT-proBNP concentration, and serum troponin I concentration)
- Daily urine sodium excretion
- Daily urine potassium excretion
- Urine osmolality

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

None.

15 References

None.

Appendix 1 List of Summary Tables

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CT-6.13	Disappearance Rate for Pulmonary rales and Third Cardiac Sound at the time of Day After Final IMP Administration (Full Analysis Set)
CT-6.14	Shift Table for Pulmonary rales (Full Analysis Set)
CT-6.15	Shift Table for Third Cardiac Sound (Full Analysis Set)

CT-6.16	Improvement Rate for NYHA Classification at the time of Day After Final IMP Administration (Full Analysis Set)
CT-6.17	Shift Table for NYHA Classification (Full Analysis Set)
CT-7.1	Extent of Exposure to Investigational Medicinal Product (Safety Analysis Set)
CT-7.2	Treatment Compliance (Full Analysis Set)
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% or More of Subjects in Any Treatment Group 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% or More of Subjects in Any Treatment Group 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 (Randomized Subjects)
CT-9.8	Listing of Serious Adverse Events Other Than Death (Randomized Subjects)
CT-9.9	Listing of Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration (Randomized 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 (Randomized Subjects)
CT-10.4.2	Listing of Abnormal Laboratory Findings Potential Drug-Induced Liver Injury (Randomized Subjects)
CT-10.5	Incidence of Potential Drug-Induced Liver Injury (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	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) With Confidence Interval for Treatment Difference (Pharmacodynamic Analysis Set)
PDT-1.2	Mean Change for Daily Urine Volume (mL) With Confidence Interval for Each Treatment Group (Pharmacodynamic Analysis Set)
PDT-2	Descriptive Statistics for Daily Fluid Intake (mL) With Confidence Interval for Treatment Difference (Pharmacodynamic Analysis Set)
PDT-3	Descriptive Statistics for Daily Fluid Balance (mL) With Confidence Interval for Treatment Difference (Pharmacodynamic Analysis Set)
PDT-4	Descriptive Statistics for Serum Sodium Concentration (mEq/L) (Pharmacodynamic Analysis Set)
PDT-5	Descriptive Statistics for Serum Potassium Concentration (mEq/L) (Pharmacodynamic Analysis Set)
PDT-6	Descriptive Statistics for Serum Osmolality (mOsm/kg) (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	Descriptive Statistics for Daily Urine Excretion of Sodium (mEq) (Pharmacodynamic Analysis Set)
PDT-13	Descriptive Statistics for Daily Urine Excretion of Potassium (mEq) (Pharmacodynamic Analysis Set)
PDT-14	Descriptive Statistics for Urine Osmolality (mOsm/kg) (Pharmacodynamic Analysis Set)
CF-1	Transition Diagram for Body Weight (Full Analysis Set)
CF-2	Transition Diagram for Improvement Rate of Lower Limb Edema (Full Analysis Set)
CF-3.1	Transition Diagram for Jugular Venous Distension (cm) (Full Analysis Set)
CF-3.2	Transition Diagram for Jugular Venous Distension (cm) (Subjects With Baseline Value in Full Analysis Set)
CF-4.1	Transition Diagram for Hepatomegaly (cm) (Full Analysis Set)
CF-4.2	Transition Diagram for Hepatomegaly (cm) (Subjects With Baseline Value in Full Analysis Set)
CF-5	Scatter Plot for Clinical Laboratory Tests (Safety Analysis Set)
CF-6	Transition Diagram for Daily Urine Volume (Pharmacodynamic Analysis Set)
CF-7	Bar Graph for Daily Urine Volume (Pharmacodynamic Analysis Set)
PKT-1.X.1.X	Individual and Summary of Plasma Concentration Following Single Intravenous/Oral Administration of OPC-XXX (Pharmacokintic Analysis Set)
PKF-1.X.1.X	Mean Plasma Concentrations Following Single Intravenous/Oral Administration of OPC-XXX (Pharmacokintic Analysis Set)
PKF-1.X.2.X	Median Plasma Concentrations Following Single Intravenous/Oral Administration of OPC-XXX (Pharmacokintic Analysis Set)

PKF-1.X.3.X Plasma Concentrations Following Single Intravenous/Oral Administration of OPC-XXX (Pharmacokintic Analysis Set)

Appendix 2 List of Subject Data Listings

AE-1	Adverse Events (Randomized Subjects)
AE-2	Adverse Events Observed Before Start of Investigational Medicinal Product Administration (Randomized Subjects)
DEMOG-1	Demographic and Baseline Characteristics (Randomized Subjects)
DREAS-1	Discontinued Subjects and Reason for Discontinuation (Randomized Subjects)
LAB-1	Laboratory Test Results - Serum Chemistry (Randomized Subjects)
LAB-2	Laboratory Test Results - Hematology (Randomized Subjects)
LAB-3	Laboratory Test Results - Urinalysis (Randomized Subjects)
LAB-4	Laboratory Test Results - Serum Sodium Trial Site (Randomized Subjects)
PDEV-1	Protocol Deviations (Randomized Subjects)
SMED-1	Investigational Medicinal Product Compliance Injection (Randomized Subjects)
SMED-2	Investigational Medicinal Product Compliance Injection (Full Administration / Interruption) (Randomized Subjects)
SMED-3	Investigational Medicinal Product Compliance Tablet (Randomized Subjects)
SUBEX-1	Subjects Excluded From Analysis Set (Randomized Subjects)
PDATA-1	Study Completion Status and Reason for Discontinuation (Randomized Subjects)
PDATA-2	Inclusion Criteria and Exclusion Criteria Not Met
PDATA-3.1	Medical History and Complications (Randomized Subjects)
PDATA-3.2	History of Congestive Heart Failure (Randomized Subjects)
PDATA-4.1	Concomitant Medications (Randomized Subjects)
PDATA-4.2	Concomitant Therapy Other Than Medication (Randomized Subjects)
PDATA-5.1	Vital Signs (Randomized Subjects)
PDATA-5.2	Height (Randomized Subjects)

PDATA-6.1	Electrocardiogram Results Central ECG Analysis Laboratory (Randomized Subjects)
PDATA-6.2	Electrocardiogram Results Trial Site (Randomized Subjects)
PDATA-7	Pharmacokinetic Blood Draw Time (Randomized Subjects)
PDATA-8	Screen Failures
PDATA-9	Physical Examination (Randomized Subjects)
PDATA-10	Serum Sodium Concentration, Serum Potassium Concentration (Randomized Subjects)
PDATA-11	Serum Osmolality, Plasma AVP Concentration, Plasma BNP Concentration, Plasma Renin Activity (Randomized Subjects)
PDATA-12	Serum NT pro BNP Concentration, Serum Troponin Concentration (Randomized Subjects)
PDATA-13	Daily Urine Volume, Daily Fluid Intake, Daily Fluid Balance, Urine Sodium Concentration, Urine Osmolality, Urine Potassium Concentration Daily Urine Excretion of Sodium, Daily Urine Excretion of Potassium (Randomized Subjects)
PDATA-14	Previous Screened ID (Randomized Subjects)
PDATA-15	Post-treatment Follow-up (Randomized Subjects)
PDATA-16	Pharmacogenomics (Randomized Subjects)
EFF-1	Body Weight (Randomized Subjects)
EFF-2	Congestive Symptoms (Lower Limb Edema, Jugular Venous Distension, Hepatomegaly, Pulmonary rales, Third Cardiac Sound) (Randomized Subjects)
EFF-3	Chest X-ray (Pulmonary Congestion, Cardiothoracic Ratio) (Randomized Subjects)
EFF-4	NYHA Classification (Randomized Subjects)

Appendix 3 Molecular Weight and Lower Limit of Quantification for Plasma Drug Concentrations

Compound	Molecular Weight[a]	Lower Limit of Quantification (ng/mL)[b]
OPC-61815	572.88 (disodium salt)	Not applicable
	528.92 (free form)	2.00
OPC-41061	448.94	2.00

[a]Molecular Weight Information, Issued on 1 Apr 2016

[b]Study Protocol (Study No. PBC016-244, Issued on 15 Nov 2019)