# STATISTICAL ANALYSIS PLAN

A Multicenter, Double-blind, Randomized, Active-controlled, Parallel-group Comparison Clinical Pharmacology Trial to Investigate the Dose of OPC-61815 Injection Equivalent to Tolvaptan 15-mg Tablet in Patients With Congestive Heart Failure]

NCT Number: NCT03254108

PRT NO.: 263-102-00001

Version Date: 21 June 2018 (Version 1.0)

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product
OPC-61815

Protocol No. 263-102-00001

# A Multicenter, Double-blind, Randomized, Active-controlled, Parallel-group Comparison Clinical Pharmacology Trial to Investigate the Dose of OPC-61815 Injection Equivalent to Tolvaptan 15-mg Tablet in Patients With Congestive Heart Failure

Statistical Analysis Plan

Version: Final 1.0
Date: June 21, 2018
Protocol Version 2 Date: June 19, 2017

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# List of Abbreviations and Definition of Terms

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| AVP | Arginine vasopressin |
| BNP | Brain natriuretic peptide |
| CHF | Congestive heart failure |
| CRF | Case report form |
| IMP | Investigational medicinal product |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NT-proBNP | N-terminal pro-brain natriuretic peptide |
| NYHA | New York Heart Association |
| TEAE | Treatment-emergent adverse event |

## Pharmacokinetics Parameter Table

| Abbreviation and Term | Unit | Unabbreviated Expression or Definition |
|---|---|---|
| $AUC_{\infty}$ | ng·h/mL | Area under the concentration-time curve from time zero to infinity |
| $AUC_{24h}$ | ng·h/mL | Area under the concentration-time curve from time zero to 24 hours |
| $AUC_t$ | ng·h/mL | Area under the concentration-time curve calculated to the last observable concentration at time t |
| AUC_%Extrap | % | Percentage of AUC due to extrapolation from $t_{last}$ to infinity [$(AUC_{\infty} - AUC_t)/AUC_{\infty} \times 100$] |
| $C_{24h}$ | ng/mL | Concentration of drug in the plasma at 24 hours |
| CL | L/h | Total body clearance of drug from the plasma |
| CL/BW | L/h/kg | CL normalized in body weight |
| CL/F | L/h | Apparent clearance of drug from plasma after extravascular administration |
| CL/F/BW | L/h/kg | CL/F normalized in body weight |
| $C_{max}$ | ng/mL | Maximum (peak) plasma concentration of the drug |
| $\lambda_z$ | $h^{-1}$ | Apparent terminal-phase disposition rate constant (first-order) |
| $R_{5,ac}(C_{24h})$ | | Accumulation ratio of 5th dose to first dose at regular administration for $C_{24h}$ |
| $t_{1/2,z}$ | h | Terminal-phase elimination half-life |
| $t_{last}$ | h | Time of last measurable (positive) concentration |
| $t_{max}$ | h | Time to maximum (peak) plasma concentration |
| $V_z$ | L | Volume of distribution during the terminal ($\lambda_z$) phase |

# 1 Introduction

This statistical analysis plan documents the details of the statistical analysis methodology to be applied in the protocol of Study 263-102-00001.

# 2 Trial Objectives

Primary: To investigate the dose of OPC-61815 injection formulation achieving exposure equivalent to that for tolvaptan 15-mg tablet by 1-hour intravenous administration of OPC-61815 at 2, 4, 8, or 16 mg once daily or oral administration of tolvaptan tablet at 15 mg once daily for 5 days in congestive heart failure (CHF) patients with volume overload despite having received diuretics other than vasopressin antagonists

Secondary: To investigate the efficacy, pharmacokinetics, pharmacodynamics, and safety of OPC-61815 in comparison with tolvaptan tablet by 1-hour intravenous administration of OPC-61815 at 2, 4, 8, or 16 mg once daily or oral administration of tolvaptan tablet at 15 mg once daily for 5 days in CHF patients with volume overload despite having received diuretics other than vasopressin antagonists.

# 3 Trial Design

## 3.1 Type/Design of Trial

This is a multicenter, randomized, double-blind, active-controlled (with tolvaptan tablet), double-dummy, parallel group comparison trial. Fifty CHF patients with volume overload despite having received diuretics other than vasopressin antagonists will be randomly assigned to OPC-61815 injection 2 mg, 4 mg, 8 mg, or 16 mg or tolvaptan tablet 15 mg group (10 per group) to investigate the dose of OPC-61815 injection required to achieve exposure equivalent to tolvaptan 15-mg tablet. To account for withdrawals, 11 patients per group (total 55 patients) will start investigational medicinal product (IMP) administration.

The 3-day period prior to IMP administration constitutes the run-in period. The use of diuretics, body weight change, and congestive symptoms are evaluated during the run-in period. Only the patients who meet the criteria for enrollment in the treatment period will be enrolled to undergo treatment. The patients will receive the IMP once a day for 5 days during the treatment period. No change of a diuretic dose or regimen will be allowed throughout the run-in period and until the end-of-trial examination on the day after final administration in the treatment period. End-of-trial examination will be performed on Day 6 (day after final administration) and post-treatment follow-up examination will be performed between Days 12 and 15.

This trial will be conducted using a double-dummy design to maintain blindness. Subjects will receive a combination of either OPC-61815 injection and placebo tablet or placebo injection and tolvaptan 15-mg tablet. As there will be a difference in appearance between the OPC-61815 solution and the placebo solution, the designated non-blinded staff at the trial site will prepare the double-blinded IMP. All enrolled patients will be admitted and remain hospitalized from the day before the start of the run-in period to the end of the treatment period.

## 3.2 Trial Treatments

The investigator or subinvestigator will administer either one tolvaptan 15-mg tablet or placebo tablet once a day with water, immediately followed by intravenous administration of either OPC-61815 injection at 2 mg, 4 mg, 8 mg, or 16 mg or placebo for 1 hour (acceptable range: 55 to 65 minutes) according to a separate written procedure for IMP administration. Each dose should be administered promptly after the patient completes urine sampling (for daily urine volume measurement) after breakfast each day during the 5-day treatment period. The time of administration (start time of administration) on Day 2 and later should be not more than 20 minutes before or after the time of administration (start time of administration) on Day 1. After confirming each dose has been administered, the investigator or subinvestigator documents the start and finish time of administration (for injection) or the date and time of administration (for tablet) in source documents and case report form (CRF). The IMP is to be administered even if the patient fails to eat breakfast that day.

## 3.3 Trial Population

Fifty-five Japanese male or female CHF patients with volume overload (lower limb edema, pulmonary congestion, or jugular venous distension) despite having received diuretics other than vasopressin antagonists, age 20 to 85 years, inclusive, will be enrolled in the trial (11 patients per group to start treatment). All subjects must be available for hospitalization from the day before the start of the run-in period to the end of the treatment period and also be able to swallow the tolvaptan tablet.

## 3.4 Handling of Time Points

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 | 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 | Run-in period | Day after final IMP administration |
| Serum sodium concentration, serum potassium concentration, serum osmolality, biomarker | Before IMP administration on Day 1 | - |
| Daily urinary output, daily fluid intake, daily water balance, daily sodium urinary excretion, daily potassium urinary excretion, urinary osmolality | During 24 hours before start of IMP administration on Day 1 | - |

[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 primary objective of this clinical trial is to compare tolvaptan exposure in order to investigate the dose of OPC-61815 injection required to achieve exposure equivalent to tolvaptan 15-mg tablet for use in conducting phase 3 confirmatory clinical trials of OPC-61815. The number of subjects required for this purpose was determined to be at least 10 subjects per group (50 subjects in total) who complete blood sampling for measurement of plasma drug concentrations up until 24 hours postdose on Day 1. In consideration of the possibility of some subjects withdrawing from the trial prior to 24 hours postdose on Day 1, the approximate target number of subjects for the start of IMP administration is set at 11 subjects per group (55 subjects in total).

# 5 Statistical Analysis Sets

## 5.1 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will include all subjects treated with the IMP at least once and have at least one evaluable plasma drug concentration measurement (other than

Not Analyzed [NA] and Not Determined [ND]) after IMP administration. Subjects who withdrew from the trial or had missing data will also be included. Subjects whose entire data were rejected in Section 102)a) will not be included.

### 5.2 Efficacy Analysis Set

The efficacy analysis set will include all subjects treated with the IMP at least once and have body weight data after IMP administration.

### 5.3 Safety Analysis Set

The safety analysis set will include all subjects treated with the IMP at least once.

### 5.4 Pharmacodynamic Analysis Set

The pharmacodynamic analysis set will include all subjects treated with the IMP at least once and have pharmacodynamic data after IMP administration.

### 5.5 Handling of Missing Data

The last observation before the day after final IMP administration will be carried forward if the measurement of the day after final IMP administration for the evaluation (efficacy and safety) at final administration time point is missing.

## 6 Primary and Secondary Endpoints:

### 6.1 Primary Endpoint

Tolvaptan exposure ($C_{max}$ and $AUC_{24h}$ on Day 1 of treatment period)

### 6.2 Secondary Endpoints

- Pharmacokinetics
  Plasma concentrations and pharmacokinetic parameters of OPC-61815, tolvaptan, DM-4103, and DM-4107
- Pharmacodynamics
  Serum concentrations of sodium and potassium, serum osmolality, biomarkers (plasma concentrations of arginine vasopressin [AVP] and brain natriuretic peptide [BNP], plasma renin activity, and serum concentrations of N-terminal pro-brain natriuretic peptide [NT-proBNP] and troponin), daily urine volume, daily fluid intake, daily fluid balance, daily urine sodium excretion, daily urine potassium excretion, and urine osmolality
- Efficacy
  Body weight, congestive symptoms (lower limb edema, other edema, jugular venous distension, pulmonary congestion confirmed by chest X-ray, pulmonary rales, third

cardiac sound, and hepatomegaly), cardiothoracic ratio, and New York Heart Association (NYHA) classification

# 7 Disposition and Demographic Analysis

The following will be summarized by administration group (including the entire OPC-61815 group).

## 7.1 Subject Disposition

For subjects from whom informed consent was obtained (screened subjects), the number of subjects and the numbers and percentages of randomized subjects, 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 pharmacokinetic analysis set, the subject population set of the pharmacokinetic analysis set for which at least one primary endpoint was obtained, and safety analysis set, descriptive statistics (number of subjects, mean, standard deviation, 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,<br>30-39,<br>40-49,<br>50-59,<br>60-69,<br>70-79,<br>80-85 |
| | | | < 65,<br>≥ 65 |
| Sex | - | Distribution | Female,<br>Male,<br>Undifferentiated |
| Height (cm) | Screening | Descriptive statistics | - |
| Body weight (kg) | Screening | Descriptive statistics | - |

| Table 7.2-1 Demographic and Other Baseline Characteristics | | | |
|---|---|---|---|
| **Variable** | **Time Point** | **Method** | **Level** |
| BMI (kg/m^2) | Screening | Descriptive statistics | - |
| Country | - | Distribution | JAPAN |
| Race | - | Distribution | Asian |
| Ethnicity | - | Distribution | Not Hispanic or Latino |
| Primary illness (multiple selection)<br>• Ischemic heart disease<br>• Non-ischemic cardiomyopathy<br>• Valvular disease<br>• Hypertensive heart disease<br>• Arrhythmia | Screening | Distribution | Yes,<br>No,<br>Unspecified |
| Type of heart failure | Screening | Distribution | Right Heart Failure,<br>Left Heart Failure,<br>Bi-ventricular Failure,<br>Unspecified |
| Presence of arrhythmia | Screening | Distribution | Yes,<br>No |
| Use of Pacemaker | Screening | Distribution | Yes,<br>No |
| Use of ICD | Screening | Distribution | Yes,<br>No |
| Complication (multiple selection)<br>• Hypertension<br>• Angina pectoris<br>• Diabetes mellitus<br>• Renal impairment | Screening | Distribution | Yes,<br>No |
| Presence of complication | Screening | Distribution | Yes,<br>No |
| Presence of medical history | Screening | Distribution | Yes,<br>No |

## 7.3 Baseline Disease Evaluation

For the pharmacokinetic analysis set, the subject population set of the pharmacokinetic analysis set for which at least one primary endpoint was obtained, 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,<br>Class II,<br>Class III,<br>Class IV |

| Table 7.3-1 Baseline Pathologic Evaluation | | |
|---|---|---|
| **Variable** | **Method** | **Level** |
| Severity of lower limb edema | Distribution | None,<br>Mild,<br>Moderate,<br>Severe |
| Pulmonary congestion | Distribution | None,<br>Mild,<br>Moderate,<br>Severe |
| Presence of jugular venous distension | Distribution | Yes,<br>No |
| Jugular venous distension (cm) | Descriptive statistics | - |
| Presence of hepatomegaly | Distribution | Yes,<br>No |
| Hepatomegaly (cm) | Descriptive statistics | - |
| Pulmonary rales | Distribution | Yes,<br>No |
| Third cardiac sound | Distribution | Yes,<br>No |
| Daily urine volume | Distribution | < 1500 mL,<br>≥ 1500 mL |
| Creatinine | Distribution | < 2 mg/dL,<br>≥ 2 mg/dL |
| Plasma AVP concentration | Distribution | ≤ 3.1 pg/mL,<br>> 3.1 pg/mL |
| Albumin | Distribution | < 3 g/dL,<br>≥ 3 g/dL |

## 7.4 Treatment Compliance

This will be summarized for the pharmacokinetic analysis set, subject population set of the pharmacokinetic analysis set for which at least one primary endpoint was obtained, and safety 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 of missing an IMP (tablet) dose will also be calculated.

## 7.5 Prior and Concomitant Medications

For the pharmacokinetic analysis set, subject population of the pharmacokinetic analysis set for which at least one primary endpoint was obtained, 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<br>Loop diuretic + other diuretic |
| Dose of loop diuretic<br>(Furosemide equivalent[a]) | < 40 mg/day,<br>≥ 40 mg/day and < 80 mg/day,<br>≥ 80 mg/day |
| Category of diuretic<br>*Concomitant use of diuretic drugs other than loop diuretic, thiazide diuretic, and anti-aldosterone drug is not summarized. | Monotherapy with loop diuretic,<br>Loop diuretic + thiazide diuretic,<br>Loop diuretic + anti-aldosterone drug,<br>Loop diuretic + thiazide diuretic + anti-aldosterone drug |
| Thiazide diuretic | Yes,<br>No |
| Anti-aldosterone drug | Yes,<br>No |
| Drugs for heart failure other than diuretics | Yes,<br>No |
| Digitalis product | Yes,<br>No |
| ACE inhibitor | Yes,<br>No |
| Beta blocker | Yes,<br>No |
| Angiotensin receptor blocker | Yes,<br>No |

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

### 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 efficacy analysis set. Each analysis will be exploratory, and multiplicity of testing is not considered.

### 8.1 Body Weight

Analysis of covariance using baseline weight as covariate will be performed on the change from baseline in body weight after final administration to calculate the least-square mean of the difference between each OPC-61815 injection group and tolvaptan 15-mg tablet group and its two-sided 95% confidence interval (based on the t

distribution). At each time point, descriptive statistics of measurement and change and percent change from baseline will be calculated for each group.

For changes in body weight from baseline, a timecourse (mean ± standard deviation) from Day 1 of treatment period to follow-up will be created for each treatment group. For changes in body weight from baseline to the final IMP administration, a bar graph of least square means (two-sided 95% confidence interval) with the horizontal axis representing treatment groups will be created.

## 8.2 Congestive symptoms

### 8.2.1 Lower limb Edema, Other Edema, and Pulmonary Congestion (Chest X-ray)

The proportion of responders (subjects who have congestive symptoms at baseline and have a "markedly improved" or "improved" response evaluated with reference to Table 8.2-1) and the proportion of subjects who achieve resolution (subjects who have congestive symptoms at baseline and in whom the symptoms resolve after IMP administration) of lower limb edema and pulmonary congestion after final administration are calculated for each OPC-61815 injection group, together with the difference in the proportions between each OPC-61815 injection group and tolvaptan 15-mg group with the two-sided 95% confidence intervals (exact) of each difference.

Changes in the severity of each congestive symptom at each time point (from baseline to after each administration and to after final administration) will be summarized for each group in a shift table.

For other edema, analysis will not be performed.

**Table 8.2-1 Response of Lower limb Edema, Other Edema, and Pulmonary Congestion**

| | Response | Description |
|---|---|---|
| 1 | Markedly improved | Resolution of symptom or improvement by 2 grades or more |
| 2 | Improved | Improvement by 1 grade (if the symptom has resolved, an assessment of "markedly improved" is given instead) |
| 3 | No change | No change in symptom, or absence of symptom throughout the trial |
| 4 | Worsened | Worsening by 1 grade or more |

### 8.2.2 Jugular Venous Distension, Hepatomegaly, and Cardiothoracic Ratio

Change from baseline in jugular venous distension and cardiothoracic ratio after final administration will be analyzed using analysis of covariance with baseline value as

covariate to calculate the least square mean of the difference between each OPC-61815 injection group and tolvaptan 15-mg tablet group and its two-sided 95% confidence intervals (based on the t distribution). Descriptive statistics of the measurements and their changes from baseline at each time point for jugular venous distension, hepatomegaly, and cardiothoracic ratio will be calculated for each group.

### 8.2.3 Pulmonary Rales and Third Cardiac Sound

The proportion of subjects who achieve resolution of pulmonary rales and third cardiac sound (subjects who have the sign at baseline and who do not have the sign after IMP administration) will be calculated in each OPC-61815 injection group together with the difference in the proportion between each OPC-61815 injection group and tolvaptan 15-mg group and its two-sided 95% confidence intervals (exact).

Changes in the severity of pulmonary rales and third cardiac sign at each time point (from baseline to after each IMP administration and to after final administration) will be summarized for each group in a shift table.

### 8.2.4 NYHA Classification

Changes in NYHA classification at each time point (from baseline to after each administration and to after final administration) will be summarized for each group in a shift table.

## 8.3 Subgroup Analyses

Subgroup Analyses will not be performed in this trial.

# 9 Safety Analyses

The following analyses will be performed for each group (including the entire OPC-61815 group) in the safety analysis set.

## 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 preferred term (PT) (Medical Dictionary for Regulatory Activities [MedDRA]). The incidence of the following events will be summarized for all events, by SOC, and by PT.

- Treatment-emergent AEs (TEAEs)

- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

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

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

For hematology, serum chemistry (excluding PAP and TRACP-5b), and urinalysis in the protocol "Table 3.7.4.2-1 Clinical Laboratory Assessments" (at the central laboratory), the following will be summarized.

Descriptive statistics of clinical laboratory values (excluding qualitative urinalysis other than pH) as well as of the changes from baseline in values at each time point and after final administration will be calculated. The results of qualitative urinalysis at each postdose time point and after final administration compared with baseline results will be summarized in a shift table. Each clinical laboratory value excluding qualitative urinalysis will be categorized into "within reference range," "below the lower limit of reference range," or "above the upper limit of reference range" using the institutional standard values to generate a shift table summarizing laboratory data at each postdose time point and after final 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 in each group.

For presence or absence of an elevation in AST or ALT that is $\geq 3$ times the upper limit of normal of the institutional standard values as well as an elevation in total bilirubin $\geq 2$ times the upper limit of normal of the institutional standard values at any point after IMP administration, the number and percentage of subjects will be calculated.

## 9.4 Vital Sign Data

Descriptive statistics will be calculated for vital signs together with the changes from baseline at each time point and after final administration.

### 9.5 Electrocardiogram Data

Descriptive statistics of each 12-lead electrocardiogram (ECG) parameter and the changes from baseline in each parameter at each time point and after final administration will be calculated.

The number and percentage of subjects who have a QTc interval (QTcB, QTcF) of "> 450 msec", "> 480 msec", and "> 500 msec" at at least one postdose time point or after final administration will be calculated. In addition, the number and percentage of subjects who show a change of "> 30 msec" and "> 60 msec" in QTc interval from baseline at at least one postdose time point or after final administration will be calculated. The numbers and percentages of subjects will also be calculated at baseline and each postdose time point in the same manner. "Normal" and "abnormal" assessments at each postdose time point and after final administration compared with baseline will be summarized in a shift table. "Normal" and "abnormal" assessments by the trial site (investigator or subinvestigator) will be used instead of the assessments by the central ECG analysis laboratory.

## 10 Pharmacokinetic Analyses

This section describes the pharmacokinetics of primary and secondary endpoints.

1) Endpoints
   a) Primary Endpoint :
   - $C_{max}$ and $AUC_{24h}$ of plasma tolvaptan on Day 1 of treatment period

   b) Secondary Endpoints:
      i) Plasma concentrations of OPC-61815, tolvaptan, DM-4103 and DM-4107
      ii) Plasma pharmacokinetic parameters of OPC-61815, tolvaptan, DM-4103 and DM-4107
      – Day 1 of treatment period: $C_{max}$[a], $AUC_{24h}$[a], $AUC_t$, $AUC_\infty$, $t_{max}$, $\lambda_z$, AUC_%Extrap, $t_{last}$, $t_{1/2,z}$, CL[b], CL/BW[b], $V_z$[b], $V_z$/BW[b], CL/F[c], CL/F/BW[c]
      – Day 1, Day 2, Day 3, Day 4, and Day 5 of treatment period: $C_{24h}$[d]
      – Day 5 of treatment period: $R_{5,ac}$ ($C_{24h}$)

      [a] Excluding tolvaptan

      [b] Calculated only for OPC-61815 after administration of OPC-61815 injection

      [c] Calculated only for tolvaptan after administration of tolvaptan 15-mg tablet

      [d] For calculation of descriptive statistics, $C_{24h}$ will be handled as plasma concentrations.

      iii) Ratio of the AUC of metabolite to that of OPC-61815[e]

      Day 1 of treatment period: $AUC_\infty$, $AUC_{24h}$, and $AUC_t$

      [e] Calculated only for the OPC-61815 injection groups

2) Handling of Data

a) Acceptance or nonacceptance of data will be determined in accordance with Section 3.4 Exclusion From Pharmacokinetic Analysis of the Manual Standard Practice for Noncompartmental Pharmacokinetic Analysis (Version 1.0). In other words, in this trial, data matched to the following conditions will not be used.

- To calculate actual time postdose, the actual start date and time of administration of the active drug (start time of administration for oral tablets and injections may be different).
- For each analyte, if blood sampling is conducted outside the time window for the analyses below, the data will be excluded from the calculation of descriptive statistics for plasma concentrations at that time point. However, it will be used for the calculation of pharmacokinetic parameters, and if the calculation is determined to be unsuitable, the parameter will not be adopted.

**Table 10-1 Acceptable Window for Analysis of OPC-61815**

| Plasma Concentration Sampling Time Point | | Acceptable Window |
|---|---|---|
| Day 1 | Before start of IMP administration | From 2 hours to immediately before start of IMP administration |
| | 1 hour after start of IMP administration | Within 5 minutes after end of IMP administration[a] |
| | 1.5 hours after start of IMP administration | Specified time point ± 5 minutes |
| | 2 hours after start of IMP administration | Specified time point ± 5 minutes |
| | 4 hours after start of IMP administration | Specified time point ± 20 minutes |
| | 6 hours after start of IMP administration | Specified time point ± 30 minutes |
| | 12 hours after start of IMP administration | Specified time point ± 1 hour |
| Day 2 | 24 hours after start of IMP administration on Day 1 (and before administration on Day 2) | 22 to 24 hours after start of administration on Day 1 |
| Day 3 | 24 hours after start of IMP administration on Day 2 (and before administration on Day 3) | 22 to 24 hours after start of administration on Day 2 |
| Day 4 | 24 hours after start of IMP administration on Day 3 (and before administration on Day 4) | 22 to 24 hours after start of administration on Day 3 |
| Day 5 | 24 hours after start of IMP administration on Day 4 (and before administration on Day 5) | 22 to 24 hours after start of administration on Day 4 |
| Day 6 | 24 hours after start of IMP administration on Day 5 | 22 to 24 hours after start of administration on Day 5 |

[a]For the tolvaptan 15-mg tablet group, within 1 hour ± 5 minutes after start of IMP administration (= after end of IMP administration)

**Table 10-2 Acceptable Window for Analysis of Analytes other than OPC-61815**

| Plasma Concentration Sampling Time Point | | Acceptable Window |
|---|---|---|
| Day 1 | Before start of IMP administration | From 2 hours to immediately before start of IMP administration |
| | 1 hour after start of IMP administration | Within 6 minutes after end of IMP administration[a] |
| | 1.5 hours after start of IMP administration | Specified time point ± 10 minutes |
| | 2 hours after start of IMP administration | Specified time point ± 10 minutes |
| | 4 hours after start of IMP administration | Specified time point ± 35 minutes |
| | 6 hours after start of IMP administration | Specified time point ± 40 minutes |
| | 12 hours after start of IMP administration | Specified time point ± 1 hour |
| Day 2 | 24 hours after start of IMP administration on Day 1 (and before administration on Day 2) | 22 to 24 hours after start of IMP administration on Day 1 |
| Day 3 | 24 hours after start of IMP administration on Day 2 (and before administration on Day 3) | 22 to 24 hours after start of IMP administration on Day 2 |
| Day 4 | 24 hours after start of IMP administration on Day 3 (and before administration on Day 4) | 22 to 24 hours after start of IMP administration on Day 3 |
| Day 5 | 24 hours after start of IMP administration on Day 4 (and before administration on Day 5) | 22 to 24 hours after start of IMP administration on Day 4 |
| Day 6 | 24 hours after start of IMP administration on Day 5 | 22 to 24 hours after start of IMP administration on Day 5 |

[a]For the tolvaptan 15-mg tablet group, within 1 hour ± 6 minutes after start of IMP administration (= after end of IMP administration)

- If a subject in the tolvaptan 15-mg tablet group experiences vomiting within 8 hours (twice the median $t_{max}$ [4 hours[1]]) after IMP administration, none of the postdose plasma concentration data on that day will be used for the calculation of descriptive statistics. Of the parameters calculated with data including plasma concentrations excluded from descriptive statistics, the parameters determined to be unsuitable for the calculations will not be adopted.
- None of the plasma concentrations after use of drugs or food (see Protocol Version 2 Table 4.1-3) which may inhibit or induce CYP3A4 activity will be used (This also applies to plasma concentrations of the following day or later). Of the parameters calculated with data including plasma concentrations excluded from descriptive statistics, the parameters determined to be unsuitable for the calculations will not be adopted.
- If the administration method specified in the protocol (see below) is not applied to administer the IMP, the instructions listed below will be followed.

  a) Tolvaptan 15-mg tablet group: One tablet is taken with water once daily.

  - For the tolvaptan 15-mg tablet group, in the event of overdosing or missing a dose, plasma concentration at predose on that day will be used, but none of the plasma concentrations after that time point (including the plasma concentrations after administration on the following day or later) will be used for the calculation of descriptive statistics.

b) OPC-61815 injection 2 mg, 4 mg, 8 mg, and 16 mg groups: The assigned dose is administered intravenously for 1 hour (acceptable range: 55 to 65 minutes) once daily.

- For OPC-61815 injection 2 mg, 4 mg, 8 mg, and 16 mg groups, in the event of insufficient dose administration, overdosing, or missing a dose, plasma concentration at predose on that day will be used, but the plasma concentrations after that time point (including the plasma concentrations after administration on the following day or later) will not be used for the calculation of descriptive statistics. In the event of full dose administration but outside the acceptable window because of interruption, etc or full dose administration with an unknown administration time, plasma concentrations after administration on that day will not be used (plasma concentrations at predose on the following day and after administration on the following day or later will be used).

Of the parameters calculated with data including plasma concentrations excluded from descriptive statistics, the parameters determined to be unsuitable for the calculations will not be adopted.

- For each analyte, if a quantitative value is obtained at predose on Day 1, and the value exceeds 5 % or more of the highest value of the period between 1 hour and 24 hours after administration on Day 1, the plasma concentrations for that analyte at predose and thereafter will be excluded from the calculation of descriptive statistics. Parameters of the analyte with all of the plasma concentrations excluded from the calculation of descriptive statistics will not be adopted.

b) 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 Appendix 3.

c) Concentrations reported as Not Analyzed (NA) or Not Determined (ND) are regarded as missing values.

3) Statistical Analysis Method

a) Primary Endpoint

i) For primary endpoint, analysis will be performed for the subject population set of the pharmacokinetic analysis set for which at least one primary endpoint was obtained.

ii) For "1)a) Primary Endpoint," descriptive statistics will be calculated for each parameter by treatment group.

iii) For "1)a) Primary Endpoint," logarithm converted value (natural logarithm) will be used to calculate the mean difference (each OPC-61815 injection group − tolvaptan 15-mg tablet group) and the 95% confidence interval of the difference.

b) Secondary Endpoints

i) For secondary endpoints, analyses will be conducted for the pharmacokinetic analysis set.

ii) For "1)b) Secondary Endpoints i)," descriptive statistics at each blood sampling point will be calculated by administration date, analyte, and treatment group.

iii) For "1)b) Secondary Endpoints ii)" (excluding $\lambda_z$, $\lambda_z$(lower), $\lambda_z$(upper), $\lambda_z$(point) and $\lambda_z$(Rsq)), descriptive statistics of each parameter will be calculated by administration date, analyte, and treatment group.

iv) For "1)b) Secondary Endpoints iii)," descriptive statistics of each parameter will be calculated by analyte and treatment group.

c) Descriptive Statistics

Descriptive statistics to be calculated for plasma drug concentration will be number of analyzed subjects, number of subjects for which concentrations data were obtained (excluding missing data or unadopted data), arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum. However, descriptive statistics will be calculated only at the time point when the number of subjects for which data were obtained (excluding missing data or unadopted data) exceeds half of the number of analyzed subjects in each group.

For variables other than plasma drug concentration, descriptive statistics to be calculated will be number of analyzed subjects, number of subjects for which data were obtained (excluding incalculable data or unadopted data), arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum. However, descriptive statistics will be calculated only when the number of subjects for which data were obtained (excluding Not Determined (ND) or unadopted data) exceeds half of the number of analyzed subjects in each group.

# 11 Pharmacodynamic Analyses

Analyses will be performed in the pharmacodynamic analysis set.

For each of the endpoints listed below, descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) of the measurement and the change from baseline will be calculated for each group at each time point. For daily urine volume, daily fluid intake, and daily fluid balance after IMP administration on Day 1 and after IMP administration on Day 5, the difference (each OPC-61815 injection group − tolvaptan 15-mg tablet) in mean change from baseline and its 95% confidence interval (based on t distribution) will be calculated.

For daily urine output, a transition chart of measurements (mean ± standard deviation) 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% confidence interval) with the horizontal axis representing treatment groups will also be created.

- Serum sodium concentration, serum potassium concentration (at the central laboratory)
- Serum osmolality
- Biomarkers (plasma AVP concentration, plasma BNP concentration, plasma renin activity, serum NT-proBNP, serum troponin concentration)
- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- 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

- For further clarification, handling of discontinued subjects and subjects with missing data was added to Protocol 6.1.1. Pharmacokinetic Analysis Set.
- For erroneous entry, "V" described in Protocol 6.1.2 (1) (b) Secondary endpoints 2) was changed to "$V_{z.}$" Since "$V_z$/BW" was erroneously omitted, it was added.
- For omission in entry, an explanatory note on treating $C_{24h}$ as the plasma concentration for the calculation of descriptive statistics was added.
- For omission in entry, a note considering IMP administration methods in addition to the manual on data handling was added.
- In Protocol 6.1.2 (3) Analytical Method 2), the analysis set for primary endpoints was added for clarification.
- In Protocol 6.1.2 (3) Analytical Method 2), the calculation method in "6.1.2 (1) (b) Secondary endpoints 3)" was added because it was erroneously omitted.
- For erroneous entry, "after final administration" described in Protocol 6.2 Pharmacodynamics was changed to "after administration on Day 5."
- For erroneous entry, "Analysis of covariance using baseline weight as covariate will be performed on the change (absolute change and percent change)" described in

Protocol 7.4.1 Body Weight was changed to “Analysis of covariance using baseline weight as covariate will be performed on the change.”

- Because the evaluation of multiple sections all together is difficult, it was decided not to summarize for other edema described in Protocol 7.4.2.1.
- Because of the low number of applicable subjects, hepatomegaly described in Protocol 7.4.2.2. was eliminated from the list for analysis of covariance

# 15 References

[1] Package insert for Samsca tablet (tolvaptan tablet) 7.5 mg, 15 mg, 30 mg

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PKF-1.2.7.4 Median DM-4107 Plasma Trough Concentrations Following Oral Administration of OPC-41061

PKF-1.2.8.1 Mean OPC-41061 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

PKF-1.2.8.2 Mean OPC-61815 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

PKF-1.2.8.3 Mean DM-4103 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

PKF-1.2.8.4 Mean DM-4107 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

PKF-1.2.9.1 Median OPC-41061 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

PKF-1.2.9.2 Median OPC-61815 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

PKF-1.2.9.3 Median DM-4103 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

PKF-1.2.9.4 Median DM-4107 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

PKF-1.2.10.1 OPC-41061 Plasma Concentrations Following Multiple Oral Administration of OPC-41061

PKF-1.2.10.2 OPC-61815 Plasma Concentrations Following Multiple Oral Administration of OPC-41061

PKF-1.2.10.3 DM-4103 Plasma Concentrations Following Multiple Oral Administration of OPC-41061

PKF-1.2.10.4 DM-4107 Plasma Concentrations Following Multiple Oral Administration of OPC-41061

PKF-1.2.11.1 OPC-41061 Plasma Trough Concentrations Following Oral Administration of OPC-41061

PKF-1.2.11.2 OPC-61815 Plasma Trough Concentrations Following Oral Administration of OPC-41061

PKF-1.2.11.3 DM-4103 Plasma Trough Concentrations Following Oral Administration of OPC-41061

PKF-1.2.11.4 DM-4107 Plasma Trough Concentrations Following Oral Administration of OPC-41061

PKF-1.2.12.1 OPC-41061 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

PKF-1.2.12.2 OPC-61815 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

PKF-1.2.12.3 DM-4103 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

PKF-1.2.12.4 DM-4107 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-41061

## Appendix 2 List of Subject Data

| | |
|---|---|
| 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-1.1 | Laboratory Test Results - Serum Chemistry (Randomized Subjects) |
| LAB-1.2 | Laboratory Test Results - Serum Chemistry (from ADaM) (Randomized Subjects) |
| LAB-2.1 | Laboratory Test Results - Hematology (Randomized Subjects) |
| LAB-2.2 | Laboratory Test Results - Hematology (from ADaM) (Randomized Subjects) |
| LAB-3.1 | Laboratory Test Results - Urinalysis (Randomized Subjects) |
| LAB-3.2 | Laboratory Test Results - Urinalysis (from ADaM) (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 (Randomized Subjects) |

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-5.1.1 Vital Signs (Randomized Subjects)

PDATA-5.1.2 Vital Signs (from ADaM) (Randomized Subjects)

PDATA-5.2 Body Weight and Height (Randomized Subjects)

PDATA-6.1.1 Electrocardiogram Results Central ECG Analysis Laboratory (Randomized Subjects)

PDATA-6.1.2 Electrocardiogram Results Central ECG Analysis Laboratory (from ADaM) (Randomized Subjects)

PDATA-6.2.1 Electrocardiogram Results Trial Site (Randomized Subjects)

PDATA-6.2.2 Electrocardiogram Results Trial Site (from ADaM) (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, Urine Sodium Concentration, Urine Osmolality and Urine Potassium Concentration (Randomized Subjects)

PDATA-14 Daily Fluid Intake (Randomized Subjects)

PDATA-15 Previous Screened ID and Previous Enrolled Trial (Randomized Subjects)

PDATA-16 Post-treatment Follow-up (Randomized Subjects)

PDATA-17 Pharmacogenomics (Randomized Subjects)

| | |
|---|---|
| PDATA-18 | Informed Consent (Randomized Subjects) |
| EFF-1 | Body Weight (from ADaM) (Randomized Subjects) |
| EFF-2.1 | Congestive Symptoms (Lower Limb Edema, Other Edema, Juglar Venous Distension, Hepatomegaly, Pulmonary rales, Third Cardiac Sound) (Randomized Subjects) |
| EFF-2.2 | Congestive Symptoms (Lower Limb Edema, Juglar Venous Distension, Hepatomegaly, Pulmonary rales, Third Cardiac Sound) (from ADaM) (Randomized Subjects) |
| EFF-3.1 | Chest X-ray (Pulmonary Congestion, Cardiothoracic Ratio) (Randomized Subjects) |
| EFF-3.2 | Chest X-ray (Pulmonary Congestion, Cardiothoracic Ratio) (Randomized Subjects) (from ADaM) |
| EFF-4.1 | NYHA Classification (Randomized Subjects) |
| EFF-4.2 | NYHA Classification (from ADaM) (Randomized Subjects) |
| EFF-5 | Pharmacodynamics Parameter (from ADaM) (Randomized Subjects) |

## Appendix 3 Molecular Weight and Quantitation Limit of Plasma Drug Concentration

| Analyte | Molecular Weight[a)] | Lower Limit of Quantitation (ng/mL)[b)] |
|---|---|---|
| OPC-61815 | 572.88 (sodium salt) | Not Appreciable |
| | 528.92 (free base) | 2.00 |
| OPC-41061 | 448.94 | 2.00 |
| DM-4103 | 478.92 | 2.00 |
| DM-4107 | 480.94 | 2.00 |

a): Molecular Weight Information, Issued on 1 Apr 2016
b): Study Protocol (Study No. P17-21515, Issued on 9 Feb 2018)